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## **Desmopressin use for minimising perioperative blood transfusion (Review)**

Desborough MJ, Oakland K, Brierley C, Bennett S, Doree C, Trivella M, Hopewell S, Stanworth SJ, Estcourt LJ

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# Desmopressin use for minimising perioperative blood transfusion

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## ABSTRACT

### Background

Blood transfusion is administered during many types of surgery, but its efficacy and safety are increasingly questioned. Evaluation of the efficacy of agents, such as desmopressin (DDAVP; 1-deamino-8-D-arginine-vasopressin), that may reduce perioperative blood loss is needed.

### Objectives

To examine the evidence for the efficacy of DDAVP in reducing perioperative blood loss and the need for red cell transfusion in people who do not have inherited bleeding disorders.

### Search methods

We searched for randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (2017, issue 3) in the Cochrane Library, MEDLINE (from 1946), Embase (from 1974), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (from 1937), the Transfusion Evidence Library (from 1980), and ongoing trial databases (all searches to 3 April 2017).

### Selection criteria

We included randomised controlled trials comparing DDAVP to placebo or an active comparator (e.g. tranexamic acid, aprotinin) before, during, or immediately after surgery or after invasive procedures in adults or children.

### Data collection and analysis

We used the standard methodological procedures expected by Cochrane.

## Main results

We identified 65 completed trials (3874 participants) and four ongoing trials. Of the 65 completed trials, 39 focused on adult cardiac surgery, three on paediatric cardiac surgery, 12 on orthopaedic surgery, two on plastic surgery, and two on vascular surgery; seven studies were conducted in surgery for other conditions. These trials were conducted between 1986 and 2016, and 11 were funded by pharmaceutical companies or by a party with a commercial interest in the outcome of the trial.

The GRADE quality of evidence was very low to moderate across all outcomes. No trial reported quality of life.

### DDAVP versus placebo or no treatment

Trial results showed considerable heterogeneity between surgical settings for total volume of red cells transfused (*low-quality evidence*) and for total blood loss (*very low-quality evidence*) due to large differences in baseline blood loss. Consequently, these outcomes were not pooled and were reported in subgroups.

Compared with placebo, DDAVP may slightly decrease the total volume of red cells transfused in adult cardiac surgery (mean difference (MD) -0.52 units, 95% confidence interval (CI) -0.96 to -0.08 units; 14 trials, 957 participants), but may lead to little or no difference in orthopaedic surgery (MD -0.02, 95% CI -0.67 to 0.64 units; 6 trials, 303 participants), vascular surgery (MD 0.06, 95% CI -0.60 to 0.73 units; 2 trials, 135 participants), or hepatic surgery (MD -0.47, 95% CI -1.27 to 0.33 units; 1 trial, 59 participants).

DDAVP probably leads to little or no difference in the total number of participants transfused with blood (risk ratio (RR) 0.96, 95% CI 0.86 to 1.06; 25 trials; 1806 participants) (*moderate-quality evidence*).

Whether DDAVP decreases total blood loss in adult cardiac surgery (MD -135.24 mL, 95% CI -210.80 mL to -59.68 mL; 22 trials, 1358 participants), orthopaedic surgery (MD -285.76 mL, 95% CI -514.99 mL to -56.53 mL; 5 trials, 241 participants), or vascular surgery (MD -582.00 mL, 95% CI -1264.07 mL to 100.07 mL; 1 trial, 44 participants) is uncertain because the quality of evidence is very low.

DDAVP probably leads to little or no difference in all-cause mortality (Peto odds ratio (pOR) 1.09, 95% CI 0.51 to 2.34; 22 trials, 1631 participants) or in thrombotic events (pOR 1.36, 95% CI, 0.85 to 2.16; 29 trials, 1984 participants) (*both low-quality evidence*).

### DDAVP versus placebo or no treatment for people with platelet dysfunction

Compared with placebo, DDAVP may lead to a reduction in the total volume of red cells transfused (MD -0.65 units, 95% CI -1.16 to -0.13 units; 6 trials, 388 participants) (*low-quality evidence*) and in total blood loss (MD -253.93 mL, 95% CI -408.01 mL to -99.85 mL; 7 trials, 422 participants) (*low-quality evidence*).

DDAVP probably leads to little or no difference in the total number of participants receiving a red cell transfusion (RR 0.83, 95% CI 0.66 to 1.04; 5 trials, 258 participants) (*moderate-quality evidence*).

Whether DDAVP leads to a difference in all-cause mortality (pOR 0.72, 95% CI 0.12 to 4.22; 7 trials; 422 participants) or in thrombotic events (pOR 1.58, 95% CI 0.60 to 4.17; 7 trials, 422 participants) is uncertain because the quality of evidence is very low.

### DDAVP versus tranexamic acid

Compared with tranexamic acid, DDAVP may increase the volume of blood transfused (MD 0.6 units, 95% CI 0.09 to 1.11 units; 1 trial, 40 participants) and total blood loss (MD 142.81 mL, 95% CI 79.78 mL to 205.84 mL; 2 trials, 115 participants) (*both low-quality evidence*).

Whether DDAVP increases or decreases the total number of participants transfused with blood is uncertain because the quality of evidence is very low (RR 2.42, 95% CI 1.04 to 5.64; 3 trials, 135 participants).

No trial reported all-cause mortality.

Whether DDAVP leads to a difference in thrombotic events is uncertain because the quality of evidence is very low (pOR 2.92, 95% CI 0.32 to 26.83; 2 trials, 115 participants).

### DDAVP versus aprotinin

Compared with aprotinin, DDAVP probably increases the total number of participants transfused with blood (RR 2.41, 95% CI 1.45 to 4.02; 1 trial, 99 participants) (*moderate-quality evidence*).

No trials reported volume of blood transfused or total blood loss and the single trial that included mortality as an outcome reported no deaths.

Whether DDAVP leads to a difference in thrombotic events is uncertain because the quality of evidence is very low (pOR 0.98, 95% CI 0.06 to 15.89; 2 trials, 152 participants).

### **Authors' conclusions**

Most of the evidence derived by comparing DDAVP versus placebo was obtained in cardiac surgery, where DDAVP was administered after cardiopulmonary bypass. In adults undergoing cardiac surgery, the reduction in volume of red cells transfused and total blood loss was small and was unlikely to be clinically important. It is less clear whether DDAVP may be of benefit for children and for those undergoing non-cardiac surgery. A key area for researchers is examining the effects of DDAVP for people with platelet dysfunction. Few trials have compared DDAVP versus tranexamic acid or aprotinin; consequently, we are uncertain of the relative efficacy of these interventions.

## **PLAIN LANGUAGE SUMMARY**

### **Desmopressin use for reducing the need for blood transfusion for people having an operation**

#### **Review question**

Could desmopressin (a medicine that can be used to prevent bleeding) reduce the need for blood transfusion when people have surgery?

#### **Background**

Blood loss is common during major surgery. Blood transfusions can replace blood that has been lost. Risks associated with blood transfusion include reactions against the blood, and - particularly in low- and middle-income countries - infection.

Desmopressin is a medicine commonly known as DDAVP (an abbreviation of its chemical name: 1-deamino-8-D-arginine vasopressin). It is used for people born with problems that put them at risk of bleeding, and may help people who do not have bleeding disorders. DDAVP may have side effects; for instance, it might increase risk of heart attack or stroke, or cause low blood pressure when it is given.

#### **Study characteristics**

We investigated whether giving DDAVP reduced the need for blood transfusion in people having surgery.

We searched the medical literature to 3 April 2017. We identified 65 relevant trials with 3874 participants (adults and children). All trials assessed the effects of giving DDAVP before, during, or immediately after surgery or more minor procedures like biopsies. Most trials focused on adult heart surgery, or bone and joint surgery. Fewer trials focused on heart surgery for children, plastic surgery, surgery on blood vessels, or liver surgery. The trials were conducted between 1986 and 2016. Eleven were funded by pharmaceutical companies or by a party with a commercial interest in the trial's outcome.

#### **Key results**

Compared with placebo (an inactive substance that looks the same as the substance being tested, i.e. DDAVP) or no treatment, DDAVP may slightly reduce the amount of blood transfused in adult heart surgery. DDAVP may lead to little or no difference in the amount of blood transfused in heart surgery for children, bone and joint surgery, surgery on major blood vessels, or liver surgery. DDAVP probably leads to little or no difference in the total number of people who receive a blood transfusion. Whether DDAVP increases or reduces total blood loss is uncertain because the quality of evidence is very low. DDAVP may lead to little or no difference in the risk of death, heart attack, or stroke.

For people who are more vulnerable to bleeding because they are taking an antiplatelet medicine that stops their blood from clotting normally, DDAVP may lead to a reduction in the total volume of red cells transfused and in total blood loss. It probably leads to little or no difference in the number of people receiving a red cell transfusion. Whether DDAVP increases or reduces the risk of death, heart attack, or stroke is uncertain because the quality of evidence is very low.

Compared with tranexamic acid (a medication used to treat or prevent excessive blood loss) DDAVP may be less effective in reducing the volume of blood transfused and total blood loss. Whether DDAVP increases or reduces the number of people who receive a blood transfusion, or risk of death, heart attack, or stroke is uncertain because the quality of evidence is very low.

Compared with aprotinin (another medication used to reduce bleeding) DDAVP probably increases the number of people who receive a blood transfusion. Whether it increases or decreases the risk of a heart attack or stroke is uncertain because the quality of evidence is very low. No trials comparing DDAVP against aprotinin reported the volume of blood transfused, total blood loss, or risk of death.

None of the 65 trials assessed quality of life.

### **Quality of the evidence**

We rated the quality of evidence as very low to moderate for the outcomes above. We considered many of the trials to be at high risk of bias and noted inconsistency and imprecision in their results.

### **Conclusion**

Overall, differences in transfusion and blood loss when people were treated with DDAVP or placebo were small and unlikely to be clinically important. It is possible that people who are more vulnerable to bleeding, such as those taking antiplatelet agents, may gain more benefit from DDAVP. Few trials compared DDAVP against tranexamic acid or aprotinin; consequently, we are uncertain whether DDAVP is better or worse than these agents.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

| Participant or population: participants undergoing surgery      |   |                           |                        |                          |                                   |  |          |
|---|---|---------------------------|------------------------|--------------------------|-----------------------------------|--|----------|
| Intervention: desmopressin                                      |   |                           |                        |                          |                                   |  |          |
| Comparison: placebo or standard care                            |   |                           |                        |                          |                                   |  |          |
| Outcomes  | Anticipated absolute effects* (95% CI)  |                           |                        | Relative effect (95% CI) | No. of participants (studies)     | Quality of the evidence (GRADE)  | Comments |
|   | Risk with placebo   | Risk with desmo-pressin   |                        |                          |                                   |  |          |
| Red cell volume trans-fused (total)                             | Adult cardiac surgery: red cell volume transfused in the desmopressin group was 0.52 units less (0.96 fewer to 0.08 fewer units, 14 RCTs, 957 participants) |                           |                        | 1454 (23 RCTs)           | ⊕⊕○○<br>LOW <sup>a,b</sup>        | Data not pooled due to clinical heterogeneity and reported as sub-groups   |          |
|   | Orthopaedic surgery: red cell volume transfused in the desmopressin group was 0.02 units less (0.67 less to 0.64 more units, 6 RCTs, 303 participants)      |                           |                        |                          |                                   |  |          |
|   | Vascular surgery: red cell volume transfused in the desmopressin group was 0.06 units more (0.60 less to 0.73 more units, 2 RCTs, 135 participants)         |                           |                        |                          |                                   |  |          |
|   | Hepatic surgery: red cell volume transfused in the desmopressin group was 0.47 units less (1.27 less to 0.33 more units, 1 RCT, 59 participants)            |                           |                        |                          |                                   |  |          |
| Number of participants receiving a red cell transfusion (total) | 450 per 1000  | 436 per 1000 (400 to 476) | RR 0.96 (0.86 to 1.06) | 1806 (25 RCTs)           | ⊕⊕⊕○<br>MODERATE <sup>a</sup>     |  |          |
| Blood loss (total)  | Cardiac surgery: total blood loss in the desmopressin group was 135.24 mL less (210.8 mL to 59.68 mL less, 22 RCTs, 1358 participants)                      |                           |                        | 1643 (28 RCTs)           | ⊕○○○<br>VERY LOW <sup>a,c,d</sup> | Data not pooled owing to clinical heterogeneity and reported as sub-groups |          |

|  |   |                           |                            |                   |                            |
|--|---|---------------------------|----------------------------|-------------------|----------------------------|
|  | <b>Orthopaedic surgery:</b> total blood loss in the desmopressin group was 285.76 mL less (514.99 mL to 56.53 mL less, 5 RCTs, 241 participants)<br><b>Vascular surgery:</b> total blood loss in the desmopressin group was 582 mL less (1264.07 mL less to 100.07 mL more, 1 RCT, 44 participants) |                           |                            |                   |                            |
| <b>All-cause mortality</b>   | 16 per 1000   | 17 per 1000<br>(7 to 41)  | pOR 1.09<br>(0.51 to 2.34) | 1631<br>(22 RCTs) | ⊕⊕○○<br>LOW <sup>a,e</sup> |
| <b>All thrombotic events<br/>(including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)</b> | 34 per 1000   | 44 per 1000<br>(28 to 67) | pOR 1.36<br>(0.85 to 2.16) | 1984<br>(29 RCTs) | ⊕⊕○○<br>LOW <sup>a,e</sup> |
| <b>Quality of life</b>   | Not reported  |                           | -                          | (No studies)      | -                          |

\*The risk in the intervention group (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; pOR: Peto odds ratio; RCT: randomised controlled trial; RR: risk ratio

#### GRADE Working Group grades of evidence

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>a</sup>Downgraded one level due to risk of bias: inadequate reporting of blinding and incomplete outcome data

<sup>b</sup>Downgraded one level for inconsistency:  $I^2 = 66\%$

<sup>c</sup>Downgraded one level for inconsistency:  $I^2 = 73\%$  and sensitivity analysis unable to determine cause of heterogeneity

<sup>d</sup>Downgraded one level for suspected publication bias

<sup>e</sup>Downgraded one level due to imprecision, as confidence intervals include both clinically important benefit and clinically important harm

## BACKGROUND

Red cell transfusion is common in the perioperative period for major surgery. Anaemia is known to be an independent predictor of poor outcomes following surgery (Carson 2002), but studies examining restrictive or liberal use of red cells in this setting have not found a clear beneficial effect for red cell transfusion (Holst 2015). Red cell transfusions are a biological product associated with risks such as infectious transmission and transfusion reactions (Delaney 2016). Consequently, agents that could reduce blood loss and the need for red cell transfusion are needed. Recent work has demonstrated the importance of alternative agents such as tranexamic acid, which reduces red cell transfusion requirements and mortality without increasing the risk of thrombotic events when administered perioperatively (Ker 2012). Desmopressin (also known as DDAVP, or 1-deamino-8-D-arginine vasopressin) has a potential role in this setting.

## Description of the condition

### Surgery

In 2014, people undergoing surgical procedures received 26.7% of the red cell units (12,318 units) transfused in the UK. The largest volumes of blood were transfused in cardiac surgery (6%; 2756 units), trauma (4.8%; 2193 units), orthopaedic surgery (3.9%; 1811 units), gastrointestinal surgery (3.8%; 1764 units), and vascular surgery (2.4%; 1091 units) (Tingate 2016), with the remaining 5.8% transfused in surgery for other conditions. Blood loss is associated with increased mortality among people undergoing surgery and is associated with surgical complexity. The mortality risk of routine elective surgery is approximately 0.1%, rising to 1% to 2% for cardiac surgery and to 5% to 8% for vascular surgery (NICE 2014). Between 5% and 7% of people undergoing cardiac surgery lose more than two litres of blood, and 3.6% to 4.2% of people require a second operation (reoperation) to arrest the bleeding (NICE 2014). The need for reoperation is associated with a 4.5-fold increase in risk of mortality (Mehta 2009), and blood loss of more than two litres is associated with an eight-fold increase in risk of death (NICE 2014). Several key points apply in surgical operations for which an intervention such as DDAVP can be administered to prevent bleeding.

- Anaesthetic induction: this involves the administration of a general anaesthetic or regional anaesthesia such as a spinal or epidural block and occurs before the operation.
  - First incision in the skin: the start of the operation.
  - Important time points during different types of operations.
    - Cardiac surgery: once the chest has been opened and the mediastinum accessed, cardiopulmonary bypass (CPB) is initiated. This diverts blood from the heart and lungs, allowing them to be operated on. Patients are given heparin (an anticoagulant drug), which reduces the risk of blood clot

formation while patients are on the bypass machine but renders them vulnerable to bleeding. When the procedure is finished, heparin is reversed with protamine, and normal circulation is restored.

- Vascular surgery: for some procedures, large vessels such as the aorta are cross-clamped to allow visualisation of the operative field. When the clamps are removed and normal circulation restored, patients are at risk of blood loss from the newly perfused vessel and tributaries.

- Orthopaedic surgery and plastic surgery: the blood supply to the limbs can be reduced temporarily by a tourniquet applied proximal to the area being operated on. Once the tourniquet is removed, normal blood flow returns, and this may lead to bleeding at the operative site.

- Closure of the skin.
- Postoperative recovery in an intensive care unit or a postoperative recovery ward depending on the type of surgery and any complications that may have arisen.

## Interventional procedures

Risk of bleeding is much lower for interventional procedures such as liver or kidney biopsy than for surgical operations. For example, risk of bleeding following a transjugular liver biopsy is approximately 0.07% and risk of death is 0.09% (Kalambokis 2007). For these procedures, bleeding is not expected, and the aim of treatment with a drug such as DDAVP is to prevent bleeding, rather than to reduce the volume of blood loss. These procedures may be performed with imaging (such as ultrasound) used to guide the procedure or with the use of anatomical landmarks. Bleeding may be difficult to detect, or it may occur at a site where it cannot be easily arrested, and where mechanical compression cannot be applied. The short duration of these procedures means that drugs such as DDAVP are administered before the procedure is started.

## Characteristics of people undergoing surgery that may make them vulnerable to bleeding

Particular challenges in preventing blood loss are associated with people with platelet dysfunction (e.g. those taking antiplatelet drugs such as aspirin, which inhibits the function of platelets and so makes these individuals more vulnerable to bleeding). Often antiplatelet agents cannot be stopped before an operation is performed because the procedure is urgent, or the risk of stopping the drug is considered too high (e.g. for those with a recent drug-eluting coronary artery stent). Other patients who are vulnerable to bleeding include those with low platelet counts or abnormal blood clotting, and those taking anticoagulant drugs such as warfarin.

## Description of the intervention

Desmopressin is a synthetic version of the naturally occurring hormone vasopressin. It is used most commonly for treatment of people with inherited bleeding disorders such as haemophilia A or von Willebrand disease, for whom it is administered at a dose of 0.3 µg/kg subcutaneously or intravenously. Desmopressin has been in use for more than 40 years and is a relatively inexpensive drug to administer. Increases in von Willebrand factor (vWF) and in factor VIII have the potential to increase the risk of arterial or venous thrombotic events; this is an important safety consideration (Franchini 2007). DDAVP also results in release of nitric oxide from endothelial cells, which can cause vasodilation with symptoms of facial flushing, tachycardia, and hypotension (Kaufmann 2003). In rare cases, DDAVP administration may be associated with hyponatraemia and seizures, particularly when it is administered to young children (Smith 1989).

### DDAVP in clinical guidelines

DDAVP is commonly used for treatment of people with mild to moderate haemophilia A and von Willebrand disease and is recommended for treatment of some individuals with inherited platelet disorders (Estcourt 2017; Keeling 2008; Laffan 2014). Outside the setting of inherited bleeding disorders, DDAVP is recommended by the following guidelines.

- European guideline on management of major bleeding and coagulopathy following trauma: “We suggest that desmopressin (0.3 µg/kg) be administered in patients treated with platelet-inhibiting drugs or with von Willebrand disease. We do not suggest that desmopressin be used routinely in the bleeding trauma patient” (Rossaint 2016).
- American Society of Anesthesiologists (ASA): “Both the consultants and ASA members agree that, in patients with excessive bleeding and platelet dysfunction, consider the use of desmopressin” (American Society of Anesthesiologists 2015).
- European Society of Anaesthesiology: “Following discontinuation of CPB, patients with severe aortic stenosis or drug- or CPB-induced platelet dysfunction may benefit from desmopressin” (Kozek-Langenecker 2013).
- Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines: “Use of 1-deamino-8-D-arginine vasopressin (DDAVP) may be reasonable to attenuate excessive bleeding and transfusion in certain patients with demonstrable and specific platelet dysfunction known to respond to this agent (e.g. uraemic or CPB-induced platelet dysfunction, type I von Willebrand’s disease)” (Society of Thoracic Surgeons 2011).

### How the intervention might work

Desmopressin stimulates the release of vWF from endothelial cells (Kaufmann 2003). vWF is essential for forming normal blood clots through platelet adhesion and aggregation following endothelial

injury (Mannucci 2004). Increasing vWF levels for people undergoing surgery or invasive procedures may reduce the volume of blood that they lose (or may prevent them from losing blood), and consequently may reduce the need for red cell transfusion. vWF levels often rise naturally in response to stressful stimuli such as surgery, and the benefits of increasing vWF levels with DDAVP may vary according to baseline vWF levels. DDAVP takes approximately 30 minutes to reach peak effectiveness, and this effect lasts up to six to eight hours (Franchini 2007). Consequently, the timing of its administration in clinical trials assessing its efficacy is of key significance. Release of vWF also results in an increase in procoagulant factor VIII levels, as vWF prolongs the half-life of factor VIII (Svensson 2014), which may promote haemostasis or thrombosis. Tissue plasminogen activator, a key promotor of fibrinolysis, is released from Weibel-Palade bodies at the same time as vWF (Kaufmann 2003), and co-administration of an antifibrinolytic agent may increase the efficacy of DDAVP.

### Why it is important to do this review

The need to identify effective agents for reduction of blood loss and improvement of surgical outcomes is ongoing. This review is an update of a previous review (Carless 2004), and builds on the results of previous systematic reviews (Cattaneo 1995; Crescenzi 2008; Fremes 1994; Henry 1998; Laupacis 1997; Levi 1999). Desmopressin is a cheap drug that may provide particular benefit in countries where risk of infection or other adverse events from blood transfusion is high (Desborough 2016a). Currently, blood is not screened for transfusion-transmitted infection in 39 countries, and only 47% of transfusions from low-income countries are tested in laboratories with quality assurance. The risk of infection following transfusion in low-income countries is higher than in high-income countries: Recent figures show risk of 0.85% for HIV infection in low-income countries compared with 0.002% in high-income countries; similarly, 3.59% versus 0.02% for hepatitis B, and 1.07% versus 0.02% for hepatitis C (World Health Organization 2015). Other agents such as tranexamic acid are used increasingly to reduce surgical blood loss (Padhi 2015). Therefore, we will also examine trials that compared these agents directly with DDAVP to assess their relative efficacy. See [Published notes](#) for prespecified changes to this review that were made prior to this update.

## OBJECTIVES

To examine the evidence for the efficacy of DDAVP in reducing perioperative blood loss and the need for red cell transfusion in people who do not have inherited bleeding disorders.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled trials (RCTs) with no restriction on language or publication status.

#### Types of participants

We included adults or children undergoing any type of surgery or interventional procedure. We excluded trials that included participants with inherited bleeding disorders such as haemophilia A or von Willebrand disease. However we identified no randomised controlled trials that met our inclusion criteria in people with inherited bleeding disorders.

#### Types of interventions

We included trials that investigated subcutaneous or intravenous DDAVP. We did not include studies on intranasal DDAVP because this route of administration has much lower bioavailability and produces a reduced effect (Köhler 1988).

We considered:

- trials that compared subcutaneous or intravenous DDAVP versus placebo or no active comparator; and
- trials that compared subcutaneous or intravenous DDAVP versus an active comparator (such as tranexamic acid or aprotinin).

#### Types of outcome measures

##### Primary outcomes

- Numbers of participants transfused with blood (during the procedure and within 30 days of the procedure)
- Volume of blood transfused (expressed as total units of blood, or millilitres per kilogram for children) (during the procedure and within 30 days of the procedure)
- Blood loss in millilitres per adult participant, or blood loss in millilitres per kilogram for children (during the procedure and within 30 days of the procedure)

##### Justification for timing of assessment

We anticipated that the timing of DDAVP administration would vary between trials, with some administering it preoperatively and others administering it during or after the operation. DDAVP has a relatively short duration of action and may provide greatest benefit during times when blood loss is greatest (e.g. intraoperatively). Consequently, we considered this to be a key time point.

We anticipated that most trials would not specify the timing of their assessments for each of the primary outcomes, so we allowed a broad period for reporting. We reported the timing of this outcome assessment in the results section and in [Table 1](#); assessment was performed most commonly up to 48 hours, and up to 72 hours in all but one case.

##### Secondary outcomes

- Reoperation due to bleeding
- Numbers of participants with any bleeding during the procedure and with any blood loss within 30 days of the procedure (low-risk procedures only, such as drain insertions or biopsies). These data are reported separately from the other bleeding analyses because blood loss is not expected from these procedures, and consequently the outcome is dichotomous
- All-cause mortality within 30 days of the procedure
- Risk of thrombotic events (arterial or venous):
  - myocardial infarction up to 30 days post infusion
  - stroke up to 30 days post infusion
  - venous thromboembolism up to 30 days post infusion
- Serious adverse events (clinically important hypotension) within 30 days of the procedure
- Quality of life

### Search methods for identification of studies

The Systematic Review Initiative Information Specialist (CD) formulated new search strategies in collaboration with the Cochrane Injuries Review Group. We created a new search strategy ([Appendix 1](#)), rather than updating the search strategy used in the previous review (Carless 2004).

#### Electronic searches

We searched for RCTs in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 3) in the Cochrane Library;
- MEDLINE (OvidSP, 1946 to 3 April 2017);
- PubMed (epublications only, to 3 April 2017);
- Embase (OvidSP, 1974 to 3 April 2017);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost, 1937 to 3 April 2017);
- UK Blood Transfusion Services/Systematic Review Initiative (UKBTS/SRI) Transfusion Evidence Library ([www.transfusionevidencelibrary.com](http://www.transfusionevidencelibrary.com)) (1950 to 3 April 2017);
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to 3 April 2017);
- Latin American Caribbean Health Sciences Literature (LILACS) (BIREME/PAHO/WHO, 1982 to 3 April 2017);
- IndMed (ICMR-NIC, 1985 to 3 April 2017);
- KoreaMed (KAMJE, 1997 to 3 April 2017);

- PakMediNet (2001 to 3 April 2017).

We combined searches in MEDLINE, Embase, and CINAHL with adaptations of the Cochrane RCT search filters, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We also searched ClinicalTrials.gov ([clinicaltrials.gov](http://clinicaltrials.gov)), the World Health Organization (WHO) International Clinical Trials Registry (ICTRP - [apps.who.int/trialsearch](http://apps.who.int/trialsearch)), and the Hong Kong University Clinical Trials Register ([www.hkuctr.com](http://www.hkuctr.com)), to identify ongoing trials. We included the new search strategy in [Appendix 1](#).

### Searching other resources

We searched the bibliographies of eligible trials, review articles, and reports for further potentially relevant studies.

### Data collection and analysis

Two review authors screened all electronically derived citations and abstracts of papers identified by the review search strategy. Two review authors assessed risk of bias in the included studies and extracted data independently.

### Selection of studies

Two independent review authors (MD, LE) initially screened all electronically derived citations and abstracts of papers identified by the review search strategy for relevance. At this stage, we excluded studies that were clearly irrelevant. Two independent review authors (MD, LE) then formally assessed the full texts of all potentially relevant trials for eligibility against the criteria outlined above. We resolved all disagreements by discussion without the need to consult a third review author (SS). We used an article abstraction form to extract information regarding randomisation criteria, study methods, presence of a transfusion protocol, type of surgery, treatment outcomes, and general comments. We recorded the reasons why potentially relevant studies failed to meet the eligibility criteria.

### Data extraction and management

We performed a new data extraction for all trials in this update of the review. Any two of the five review authors (MD, KO, CB, SB, LE) extracted data according to Cochrane guidelines ([Higgins 2011a](#)). Review authors resolved disagreements by consensus and were not blinded to names of study authors, institutions, journals, or trial outcomes. Papers not published in English were translated in their entirety, then data extracted in the usual way ([Aida 1991a](#); [Aida 1991b](#); [Marczinski 2007](#)). We discussed unclear data or entries directly with the translators. We extracted data from studies in duplicate using an online systematic review management tool

(Covidence; [www.covidence.org](http://www.covidence.org)), then entered the data into Review Manager 5 ([RevMan 2014](#)). We collected the following data:

- type of study (study design, number of arms, single centre or multicentre);
- inclusion and exclusion criteria;
- participants (number of participants randomised, number of participants analysed, age, gender, antiplatelet agents, anticoagulants, coagulopathy, thrombocytopenia, use of tranexamic acid);
- details of surgery (type of surgery, duration of surgery, duration of cardiopulmonary bypass (if applicable), emergency or elective, use of cell salvage, use of a transfusion protocol);
- interventions (DDAVP dose, route of administration, diluent, speed of administration, timing of administration);
- comparators (type of comparator, route of administration, speed of administration, timing of administration);
- outcomes (number of participants exposed to blood transfusion (expressed as whole blood or packed red cells), blood loss, reoperation for bleeding, number of participants experiencing postoperative complications (thrombosis, myocardial infarction, stroke), mortality, number of participants requiring reoperation due to bleeding, quality of life);
- risk of bias (see [Assessment of risk of bias in included studies](#)).

When the standard error of the mean was reported, we derived the standard deviation.

### Assessment of risk of bias in included studies

We performed an assessment of all RCTs using the Cochrane 'Risk of bias' tool according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). Any two of the five review authors (MD, KO, CB, SB, LE) worked independently to assess each element of potential bias listed below as 'high', 'low', or 'unclear risk of bias'. We considered a trial to be at low risk of bias overall if we judged it to have no high-risk domains, and if we judged at least half of the domains to be at low risk of bias. In the [Characteristics of included studies](#) table we provided a brief description of the judgement statements upon which review authors assessed potential bias. We ensured that we reached consensus on the degree of risk of bias by comparing review authors' statements and, when necessary, by consulting with a third review author. The Cochrane tool for assessing risk of bias includes the following domains:

- selection bias: random sequence generation and allocation concealment;
- performance bias: blinding of participants and personnel;
- detection bias: blinding of outcome assessment;
- attrition bias: incomplete outcome data;
- reporting bias: selective reporting;
- other bias.

## Measures of treatment effect

- For continuous outcomes, we recorded the mean, standard deviation, and total numbers of participants in both treatment and control groups. For dichotomous outcomes, we recorded numbers of events and total numbers of participants in both treatment and control groups.
- For continuous outcomes, using the same scale, we performed analyses based on the mean difference (MD) with 95% confidence intervals (CIs).
- For dichotomous outcomes, we reported the pooled risk ratio (RR) with 95% CI. When the number of observed events was small (< 5% of sample per group), and when trials included balanced treatment groups, we reported Peto's odds ratio (pOR) with 95% CI (Deeks 2011).
- When data allowed, we undertook quantitative assessments using Review Manager 5 (RevMan 2014).
- When we could not report available data in any of the formats described above, we provided a narrative report and, when appropriate, presented the data in tables.

## Unit of analysis issues

We treated trials with three or more arms in accordance with advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). For studies with multiple treatment groups, two review authors excluded subgroups that were considered irrelevant to the analysis. We tabulated all subgroups in the [Characteristics of included studies](#) section. When appropriate, we combined groups to create a single pair-wise comparison. When this was not possible, we selected the most appropriate pair of interventions and excluded the others (Higgins 2011c). We identified no cross-over trials, but for future updates, if we identify them, we plan to establish whether assessment of outcome measures occurred before the cross-over, and we will include outcomes assessed after the cross-over if they are not biased by treatment provided before the cross-over. We will examine each trial individually to determine this eventuality. We did not find any relevant cluster-randomised trials, but for future updates of this review, we plan to analyse cluster-randomised trials at the individual participant level, accounting for the cluster design, and to seek statistical advice.

## Dealing with missing data

When data were identified as missing or unclear in published literature, we contacted study authors directly. This practice was limited to contacting authors of studies published in the past ten years. We recorded the number of participants lost to follow-up for each study and analysed data on an intention-to-treat (ITT) basis (Higgins 2011c).

## Assessment of heterogeneity

When we considered studies to be sufficiently homogenous in study design, we conducted meta-analysis and assessed statistical heterogeneity of treatment effects between trials by using a Chi<sup>2</sup> test with a significance level at  $P < 0.1$  (Deeks 2011). We used the I<sup>2</sup> statistic to quantify possible heterogeneity (I<sup>2</sup> > 50% moderate heterogeneity, I<sup>2</sup> > 80% considerable heterogeneity). When necessary, we explored potential causes of heterogeneity by conducting sensitivity and subgroup analyses.

## Assessment of reporting biases

We explored potential publication bias (small-trial bias) by generating a funnel plot and by using a modified Harbord test for dichotomous outcomes (Harbord 2006), and an Egger's test for continuous outcomes (Egger 1997). We considered a P value < 0.1 as statistically significant for this test (Sterne 2011).

## Data synthesis

We performed analyses according to recommendations provided in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using aggregated data for analysis (Deeks 2011). For statistical analysis, we entered data into Review Manager 5 software (RevMan 2014). One review author (MD) entered the data, and a second (KO) checked the data for accuracy. When meta-analysis was feasible, we used the random-effects model for pooling data. We used the Mantel-Haenszel method for dichotomous outcomes, and the inverse variance method (or standardised mean difference as necessary) for continuous outcomes. In cases for which events were rare and appropriate conditions were satisfied, we used Peto's odds method. We converted transfused blood volume expressed in millilitres (mL) to units by assuming 300 mL to be equivalent to one unit of blood (Walters 2016), as was done in the previous review (Carless 2004).

## Trial sequential analysis (TSA)

We provided a sample size estimate showing how many participants needed to be included in a meta-analysis for it to produce reliable results. We used trial sequential methods to explore all treatment effects attained before the required sample size was reached, by using TSA v0.9 software (TSA 2011). We sequenced trials by first publication date of the full articles. This provided the required information size (the total number of participants) necessary to detect a statistically significant underlying effect. We applied trial sequential analysis to the following outcomes:

- total volume of blood transfused (analysed in subgroups only);
- number of participants transfused with blood;
- total blood loss (analysed in subgroups only).

We estimated total volume of blood transfused and total blood lost by calculating the mean across the control arms of the trials. We

calculated transfusion requirements in this population using the proportion of participants in the control group who were transfused. We calculated the information size necessary for a relative risk reduction of 15%, equivalent to the minimum clinically relevant effect size described for prophylactic use of tranexamic acid before surgery (Henry 2011; Ker 2012). When calculated cumulative Z-curves crossed trial sequential monitoring boundaries, we determined that statistical significance had been reached and the overall type I error rate had been maintained. We produced futility boundaries such that if the cumulative Z-curve crossed the futility threshold, evidence showed that the two treatments did not differ more than the anticipated effect size. We used the O'Brien Fleming alpha-spending function with an overall type I error rate of 5% and with 80% statistical power to derive two-sided sequential monitoring and futility boundaries. We adjusted estimates according to calculated diversity ( $D^2$ ). We calculated variance empirically and used a model variance-based heterogeneity correction. We performed TSA only for outcomes reported by two or more trials.

### Subgroup analysis and investigation of heterogeneity

When clinical and methodological characteristics of individual studies were sufficiently homogeneous, we combined the data to perform a meta-analysis. We assessed statistical heterogeneity of treatment effects between studies using a  $\chi^2$  test with a statistical significance level at  $P < 0.1$ . We used the  $I^2$  statistic to quantify the degree of potential heterogeneity and classified heterogeneity as moderate if  $I^2$  was greater than 50%, and as considerable if  $I^2$  exceeded 80%. We assessed potential causes of heterogeneity by conducting sensitivity and subgroup analyses (Deeks 2011). We performed subgroup analyses for each of the following categories to assess effects on heterogeneity:

- type of surgery or procedure;
- age of participant (paediatric cardiac surgery defined as a separate subgroup);
  - preoperative administration of DDAVP;
  - inclusion of 75% or more participants with platelet dysfunction (measured by bleeding time or platelet function analyser 100) or taking antiplatelet agents, or both;
  - inclusion of 75% or more participants taking an antifibrinolytic agent.

We intended to investigate subgroups of participants with liver disease or kidney disease with uraemia, but the trials included in this review did not report these subgroups.

### Sensitivity analysis

We assessed the robustness of our findings by performing the following sensitivity analyses when data were sufficient. We included only those trials:

- with a 'low risk of bias' (defined as trials with no high risk of bias domains and at least half of the remaining domains considered to be at low risk of bias);
- that used autologous cell salvage (red cell transfusion and bleeding outcomes only);
- with a transfusion protocol;
- published as full-text papers;
- with less than 20% dropout; and
- that had been prospectively registered in a trial database, if the study was published during 2010 or more recently.

### Summary of findings

We used the GRADE approach to create a 'Summary of findings' table, as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We used the GRADE approach to rate the quality of evidence as 'high', 'moderate', 'low', or 'very low', according to the following five GRADE considerations:

- risk of bias: serious or very serious;
- inconsistency: serious or very serious;
- indirectness: serious or very serious;
- imprecision: serious or very serious; and
- publication bias: likely or very likely.

Outcomes included were:

- total volume of blood transfused;
- total number of participants transfused with blood;
- total blood loss;
- overall mortality up to 30 days post infusion;
- risk of thrombotic events (arterial or venous); and
- quality of life.

## RESULTS

### Description of studies

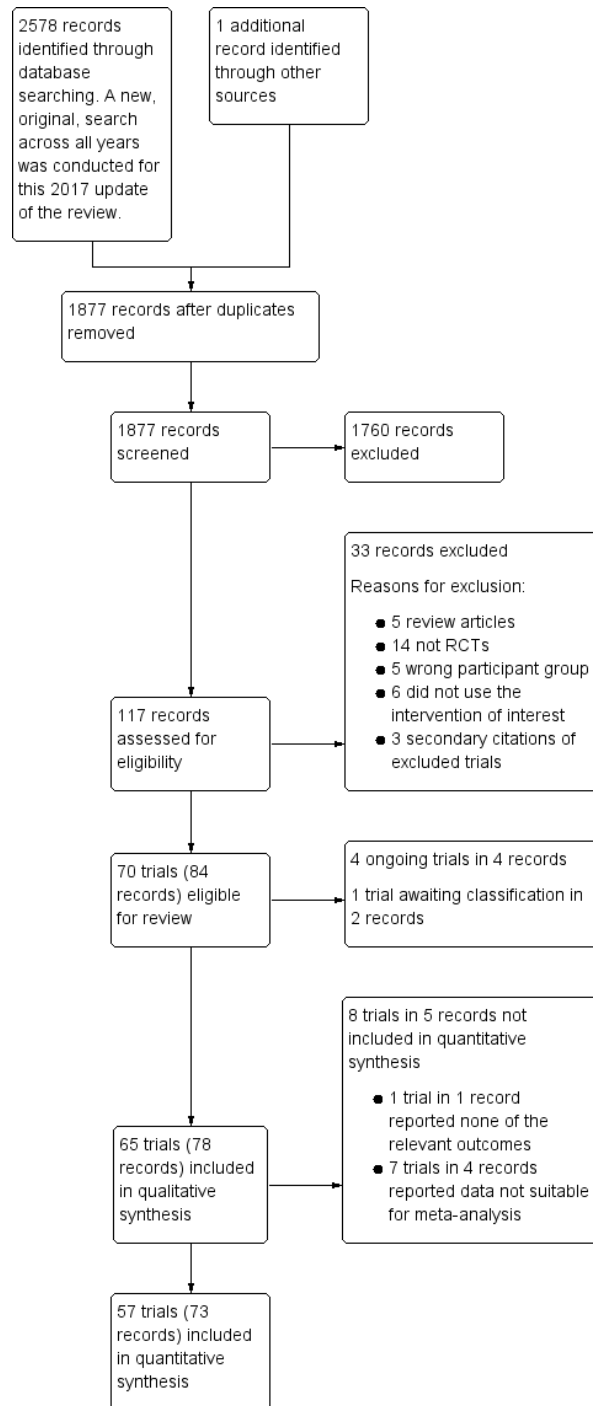
See [Characteristics of included studies](#); [Characteristics of excluded studies](#); and [Characteristics of ongoing studies](#).

### Results of the search

Database searches for the 2017 update identified 2578 records, and searching the references of other records revealed one additional record. We reduced these to 1877 after removing duplicates. Two review authors (MD, LE) screened these records according to the criteria defined above and excluded 1760 records that were not RCTs or were clearly outside the scope of this review (see PRISMA diagram; Figure 1). We obtained the full text of the remaining 117 records and excluded 33 of them. We divided multi-arm trials into separate trials, which yielded 70

studies with 84 records: 65 completed trials (Aida 1991a; Aida 1991b; Alanay 1999; Andersson 1990; Ansell 1992; Bignami 2016; Brown 1989; Casas 1995; Chuang 1993; Clagett 1995; de Prost 1992; Despotis 1999; Dilthey 1993; Ellis 2001; Flordal 1991; Flordal 1992; Frankville 1991; Gratz 1992; Guay 1992; Guyuron 1996; Hackmann 1989; Hajjar 2007; Hedderich 1990; Hemş inli 2012a; Hemş inli 2012b; Hemş inli 2012c; Horrow 1991a; Horrow 1991b; Horrow 1991c; Jin 2015; Karnezis 1994a; Karnezis 1994b; Kobrinsky 1987; Kuitunen 1992; Lazarchick 1995; Lee 2010; Leino 2010; Lethagen 1991; Letts 1998; Manno 2011; Marczynski 2007; Marquez 1992; Mongan 1992a; Mongan 1992b; Oliver 2000; Ozkisacik 2001; Pley 2004; Reich 1991; Reynolds 1993; Rocha 1988; Rocha 1994; Salmenpera 1991; Salzman 1986; Schott 1995; Seear 1989; Shao 2015; Sheridan 1994; Splyt 1990; Steinlechner 2011; Temeck 1994; Theroux 1997; Wingate 1992a; Wingate 1992b; Wong 2003; Zohar 2001); four ongoing trials (ISRCTN12845429; NCT00885924; NCT01982760; NCT02084342); and one trial awaiting classification (Jahangirifard 2017).

**Figure 1. Study flow diagram.**



## Included studies

See [Characteristics of included studies](#) for full details of each study.

## Design

We included 65 completed trials in the qualitative synthesis.

- Sixty trials were published as full-text articles, four were reported in abstract form only ([Hajjar 2007](#); [Hem§ inli 2012a](#); [Hem§ inli 2012b](#); [Hem§ inli 2012c](#)), and one was published as full text but, despite a worldwide search, the original text could not be found, so we extracted data from the abstract ([Chuang 1993](#)).
- Trials were published between 1986 and 2016.
- Two trials were published in Japanese ([Aida 1991a](#); [Aida 1991b](#)), one in Chinese ([Chuang 1993](#)), and one in Dutch ([Marczinski 2007](#)). The remaining 61 trials were published in English.
- One three-arm trial compared DDAVP versus placebo and aprotinin ([Casas 1995](#)), and another compared DDAVP versus placebo and tranexamic acid ([Ellis 2001](#)): DDAVP was compared with each comparator in separate analyses. Two trials compared two different doses of DDAVP versus placebo ([Leino 2010](#); [Marquez 1992](#)): for these trials, the dose closest to a single intravenous dose of 0.3 µg/kg was used for DDAVP versus placebo analyses. One four-arm trial compared two doses of DDAVP versus placebo and aprotinin ([Rocha 1994](#)): the dose closest to a single intravenous dose of 0.3 µg/kg was used for DDAVP versus placebo and DDAVP versus aprotinin analyses. Four four-arm trials were split into two, two-arm trials, each comparing DDAVP versus placebo ([Aida 1991a](#); [Aida 1991b](#); [Karnezis 1994a](#); [Karnezis 1994b](#); [Mongan 1992a](#); [Mongan 1992b](#); [Wingate 1992a](#); [Wingate 1992b](#)). Two four-arm trials compared DDAVP versus placebo, tranexamic acid, and a combination of tranexamic acid and DDAVP. These were split into the following comparisons:
  - DDAVP versus placebo ([Hem§ inli 2012a](#); [Horrow 1991a](#)), and DDAVP plus tranexamic acid versus tranexamic acid ([Hem§ inli 2012b](#); [Horrow 1991b](#)); all analysed in the DDAVP versus placebo comparison, as the only difference between arms was the presence, or absence, of DDAVP).
  - DDAVP versus tranexamic acid ([Hem§ inli 2012c](#); [Horrow 1991c](#)).
- The remaining 46 trials were parallel-group two-arm trials.
- Two trials were multi-centre trials ([Ansell 1992](#); [Bignami 2016](#)), and whether four other trials were single-centred or multi-centred remains unclear ([Hajjar 2007](#); [Hedderich 1990](#); [Letts 1998](#); [Pleym 2004](#)). The remaining 59 trials were single-centre studies.

## Sample sizes

The trials included 3874 participants, with numbers ranging from nine participants in [Aida 1991a](#) to 162 in [Manno 2011](#).

## Setting

In [Table 1](#) we summarised full details of the countries where the trials were performed: 24 trials were conducted in the USA; six in Canada; five in Sweden; five in Turkey; three in China; three in Finland; three in Spain; two in Israel; two in Japan; two in Italy; and one each in Austria, Brazil, France, Germany, Hong Kong, the Netherlands, Norway, South Korea, and the UK.

## Participants

We outlined characteristics of trial participants in [Table 1](#).

- Settings: 39 trials were in cardiac surgery; 12 in orthopaedic surgery; three in paediatric cardiac surgery; two in plastic surgery; two in vascular surgery; and one each in dialysis catheter insertion, hepatic surgery, kidney biopsy, maxillofacial surgery, and sinus surgery. One trial included a combination of participants undergoing orthopaedic, breast, and abdominal surgery, and one trial did not report the types of surgery included.
- Fifty-four trials reported elective surgery or procedures; three trials reported emergency surgery; and eight trials provided insufficient information to reveal whether surgery was elective or emergency in nature.
- We had access to unpublished data from one trial and were able to extract data for a subgroup with platelet dysfunction ([Bignami 2016](#)). Seventeen trials did not include participants with platelet dysfunction; four trials included 0.1% to 25% of participants with platelet dysfunction; three trials included 25.1% to 50% with platelet dysfunction; one trial included 50.1% to 75% with platelet dysfunction; and 12 trials included 75.1% to 100% with platelet dysfunction. Twenty-eight trials provided no information on the number of participants with platelet dysfunction.
- Thirty trials did not include participants taking an anticoagulant drug; two trials included up to 10% of participants taking anticoagulants; no trials included more than 10% of participants taking an anticoagulant drug. Thirty-three trials provided no information about the number of participants taking anticoagulant drugs.
- Twenty-two trials did not include participants with a coagulopathy, and one trial reported a single participant with a coagulopathy in each arm. Forty-two trials provided no information about the number of participants with coagulopathies.

- Sixteen trials did not include participants with thrombocytopenia, and 49 trials provided no information on the number of participants with thrombocytopenia.

- Three trials included no participants who received an antifibrinolytic agent; three included 0.1% to 25% of participants taking antifibrinolytic agents; one included 25.1% to 50% taking antifibrinolytic agents; one included 50.1% to 75% taking antifibrinolytic agents; and four included more than 75% of participants taking antifibrinolytic agents. Six trials compared DDAVP directly with an antifibrinolytic agent, and in these trials, no participants in the DDAVP arm received an antifibrinolytic agent. Forty-seven trials provided no information about whether participants received an antifibrinolytic agent.

- Two trials did not use autologous cell salvage; 13 trials used autologous cell salvage for all participants; and 50 trials did not report whether autologous cell salvage was used.

- Two trials did not use a transfusion protocol, and transfusion decisions were made at the discretion of the treating physician; 26 used a transfusion protocol to guide transfusion decisions; and 37 trials did not report whether a transfusion protocol was used to guide transfusion decisions.

- Seven trials included only children (Guay 1992; Kobrinsky 1987; Letts 1998; Oliver 2000; Reynolds 1993; Sear 1989; Theroux 1997); and in six trials it was unclear whether participants were children or adults (Guyuron 1996; Hajjar 2007; Lazarchick 1995; Temeck 1994; Wingate 1992a; Wingate 1992b). The remaining 52 trials included only adults.

## Interventions

We reported full details of interventions for each trial in [Characteristics of included studies](#) and summarised these details in [Table 2](#).

- Fifty-two trials used a single dose of 0.3 µg/kg DDAVP intravenously; one trial used a single dose of 0.4 µg/kg DDAVP intravenously; four trials administered two doses of 0.3 µg/kg DDAVP intravenously six hours apart; one trial included two different doses of intravenous DDAVP (0.2 µg/kg and 0.4 µg/kg); four trials administered one dose of 10 µg/m<sup>2</sup> body surface area DDAVP intravenously; two trials administered 20 µg DDAVP intravenously to all participants; and one trial administered a single dose of 15 µg to 45 µg DDAVP intravenously (depending on body weight).

- Timing of administration varied between trials, with 20 trials administering DDAVP preoperatively; 39 trials administered DDAVP shortly before the end of the operation; two administered DDAVP postoperatively; and one administered it shortly before the end of the operation, or postoperatively in the event of excessive bleeding. Three trials did not report when DDAVP was administered.

## Comparators

We reported full details of comparators for each trial in [Characteristics of included studies](#) and summarised these details in [Table 2](#).

- Fifty-four two-arm trials used a matching placebo as a comparator, most commonly 0.9% saline.

- One trial compared DDAVP versus tranexamic acid.

- One three-arm trial compared two different doses of DDAVP versus placebo.

- One three-arm trial compared DDAVP versus tranexamic acid and placebo.

- One three-arm trial compared DDAVP versus aprotinin and placebo.

- One four-arm trial compared two different doses of DDAVP versus aprotinin or standard care.

- Two four-arm trials (each split into three two-arm trials) compared DDAVP versus tranexamic acid, placebo, and a combination of DDAVP and tranexamic acid.

## Outcomes

We included full details of trial outcomes in [Characteristics of included studies](#). No trial reported all outcomes of interest. One trial did not report any outcomes of interest for this review (Lazarchick 1995).

- Eleven trials reported volume of blood transfused intraoperatively.

- Forty-one trials reported total volume of blood transfused.

- Six trials reported the number of participants transfused with blood intraoperatively.

- Twenty-eight trials reported the total number of participants transfused with blood.

- Seventeen trials reported intraoperative blood loss.

- Fifty-two trials reported total blood loss.

- One trial reported the number of participants undergoing interventional procedures with intraoperative bleeding.

- One trial reported the number of participants undergoing interventional procedures with any bleeding.

- Twenty-four trials reported the number of participants undergoing reoperation due to bleeding.

- Twenty-two trials reported overall mortality.

- Thirty-one trials reported thrombotic disease (arterial or venous).

- Eighteen trials reported clinically important hypotension.

- No trials reported quality of life.

## Baseline level of bleeding and red cell transfusion

The baseline total volume of red cell transfusion varied between trials, with a range in the placebo arms of 0.7 units in [Wong 2003](#), to 6.6 units in [Chuang 1993](#). Likewise, the proportion of participants who received a red cell transfusion ranged from 0% in

Manno 2011, to 100% in Gratz 1992, and volume of total blood loss varied between 310 mL in Horrow 1991a, and 3130 mL in Guay 1992.

#### Timing of outcome assessments for total volume of blood transfused and total blood loss

We reported full details of the timing of outcome assessments in Table 1. Fifty trials reported total volume of blood transfused and total blood loss within 48 hours of drug administration; seven trials reported these outcomes over a longer time; three reported these outcomes only intraoperatively; and five did not report sufficient detail to reveal the timing of this assessment.

#### Excluded studies

We excluded 33 records from the review (see Characteristics of excluded studies for details).

- Five records were review articles (Gandhi 2014; Hansen 1980; Mannucci 1994; Myrvang 2011; Zotz 2009).
- Fourteen studies were not RCTs (EudraCT Number: 2009-017265-33; Flordal 1993; Forero 2003; Hooghiemstra 2012; Johnson 1990; Karger 2012; Keyl 2011; Kim 2015; Lozano 1999; NCT01606072; NCT01623206; Palaia 2001; Spiro 1982; Weinberg 2015).
- Five were trials that included an ineligible participant group (Haith 1993; NCT00835211; NCT01382134; Nilsen 1984; Zielske 2003).

- Six did not use the intervention of interest (IRCT2013092114728N1; IRCT201409304345N3; Mirmansoori 2016; NCT01218074; Oza 2002; Stanca 2010).
- Three records were secondary citations of excluded trials.

#### Ongoing studies

We identified four ongoing studies (see Characteristics of ongoing studies) (ISRCTN12845429; NCT00885924; NCT01982760; NCT02084342). Three of these trials have been completed but have not yet been published (NCT00885924; NCT01982760; NCT02084342). We will monitor the progress of these trials, and on publication (assuming eligibility), we will include them in future updates of this review. All four of the ongoing studies compare DDAVP versus placebo. One is assessing DDAVP before interventional procedures for thrombocytopenic patients (ISRCTN12845429), one involves cardiac surgery (NCT00885924), one orthopaedic surgery (NCT02084342), and one rhinoplasty (NCT01982760). These trials are planning to include approximately 147 participants in total.

#### Risk of bias in included studies

See the 'Risk of bias' tables within Characteristics of included studies for details of our assessment for each study, and Figure 2 for a tabular summary.

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

|                   | Sequence Generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessors | Incomplete outcome data | Selective outcome reporting | Other sources of bias |
|-------------------|---------------------|------------------------|--|-------------------------------|-------------------------|-----------------------------|-----------------------|
| Aida 1991a        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Aida 1991b        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Alanay 1999       | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Andersson 1990    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Ansell 1992       | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Bignami 2016      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Brown 1989        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Casas 1995        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Chuang 1993       | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Claggett 1995     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| de Prost 1992     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Despotis 1999     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Dilthey 1993      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Ellis 2001        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Flordal 1991      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Flordal 1992      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Frankville 1991   | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Gratz 1992        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Guay 1992         | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Guyuron 1996      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Hackmann 1989     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Hajjar 2007       | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Hedderich 1990    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Hemşinli 2012a    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Hemşinli 2012b    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Hemşinli 2012c    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Horrow 1991a      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Horrow 1991b      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Horrow 1991c      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Jin 2015          | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Karnezis 1994a    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Karnezis 1994b    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Kobrinisky 1987   | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Kuitunen 1992     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Lazarchick 1995   | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Lee 2010          | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Leino 2010        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Lethagen 1991     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Letts 1998        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Manno 2011        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Marczinski 2007   | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Marquez 1992      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Mongan 1992a      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Mongan 1992b      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Oliver 2000       | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Ozkisacik 2001    | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Pleym 2004        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Reich 1991        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Reynolds 1993     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Rocha 1988        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Rocha 1994        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Salmenpera 1991   | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Salzman 1986      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Schott 1995       | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Seear 1989        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Shao 2015         | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Sheridan 1994     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Spyt 1990         | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Steinlechner 2011 | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Terneck 1994      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Theroux 1997      | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Wingate 1992a     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Wingate 1992b     | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Wong 2003         | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |
| Zohar 2001        | ?                   | ?                      | ?                                      | ?                             | ?                       | ?                           | ?                     |

## Allocation

### Sequence generation

- Twenty-one trials were at low risk of bias for sequence generation because they used either:
  - a table of random numbers (Horrow 1991a; Horrow 1991b; Horrow 1991c; Karnezis 1994a; Karnezis 1994b; Leino 2010; Manno 2011; Oliver 2000; Wingate 1992a; Wingate 1992b); or
  - computer-generated random numbers (Ansell 1992; Bignami 2016; Despotis 1999; Ellis 2001; Hedderich 1990; Mongan 1992a; Mongan 1992b; Pleym 2004; Shao 2015; Steinlechner 2011; Zohar 2001).
- The remaining 44 trials were at unclear risk of bias because they did not report details of the randomisation sequence.

### Concealment of treatment allocation

- Eleven trials were at low risk for concealment of treatment allocation because they used sealed envelopes (Bignami 2016; Clagett 1995; Frankville 1991; Horrow 1991a; Horrow 1991b; Horrow 1991c; Leino 2010; Salzman 1986; Seear 1989; Steinlechner 2011; Wong 2003).
- The remaining 54 trials were at unclear risk of bias because they did not report details of treatment allocation.

### Blinding

- Twenty-five trials were at low risk of bias with adequate blinding of participants, personnel, and analysts because:
  - they used identical vials of DDAVP and placebo (Frankville 1991; Spyrt 1990; Temeck 1994; Theroux 1997);
  - a pharmacist who was not otherwise involved in the trial prepared the DDAVP or matching placebo (Casas 1995; Clagett 1995; Gratz 1992; Horrow 1991a; Horrow 1991b; Horrow 1991c; Karnezis 1994a; Karnezis 1994b; Leino 2010; Marczynski 2007; Oliver 2000; Reynolds 1993; Seear 1989; Wingate 1992a; Wingate 1992b); or
  - a member of the study team who was not involved in determining outcomes prepared the DDAVP or matching placebo, while all other members of the study team and outcome assessors were blinded (Alanay 1999; Bignami 2016; Guay 1992; Hackmann 1989; Steinlechner 2011; Wong 2003).
- Two trials were at low risk of bias for blinding of participants and personnel but were at unclear risk for blinding analysts (Despotis 1999; Diltz 1993).
- Four trials were at unclear risk for blinding of participants and personnel and at low risk for blinding of analysts (Guyuron 1996; Manno 2011; Pleym 2004; Salzman 1986).

- Two trials were at high risk for blinding of participants and personnel but at low risk of bias for blinding of analysts (Ellis 2001; Zohar 2001).
- Five trials were at high risk of bias for blinding of participants, personnel, and study analysts because:
  - they were open label (Hedderich 1990; Hemş inli 2012a; Lee 2010; Rocha 1994); or
  - the rapid rate of desmopressin infusion induced clinically important hypotension which is likely to have resulted in unblinding (Brown 1989).
- The remaining 27 trials did not report sufficient information to permit us to determine risk of bias from blinding.

### Incomplete outcome data

- We considered 35 trials to be at low risk of bias for incomplete outcome data because participants were analysed on an ITT basis (Aida 1991a; Aida 1991b; Alanay 1999; Ansell 1992; Bignami 2016; Brown 1989; Clagett 1995; Despotis 1999; Ellis 2001; Flordal 1991; Flordal 1992; Frankville 1991; Gratz 1992; Guay 1992; Guyuron 1996; Jin 2015; Kobrinsky 1987; Lee 2010; Manno 2011; Marczynski 2007; Mongan 1992a; Mongan 1992b; Oliver 2000; Ozkisacik 2001; Reich 1991; Rocha 1988; Salmenpera 1991; Salzman 1986; Schott 1995; Seear 1989; Shao 2015; Sheridan 1994; Theroux 1997; Wingate 1992a; Wingate 1992b).
- We considered 16 trials to be at high risk of bias because of:
  - exclusion of participants with severe bleeding or complications post randomisation (Casas 1995; de Prost 1992; Diltz 1993; Hackmann 1989; Hedderich 1990; Kuitunen 1992; Lethagen 1991; Marquez 1992; Pleym 2004; Reynolds 1993; Wong 2003); or
  - high or unbalanced participant dropout (Andersson 1990; Karnezis 1994a; Karnezis 1994b; Rocha 1994; Temeck 1994).
- We considered the remaining 14 trials to be at unclear risk of bias, as investigators reported insufficient information to allow us to make a judgement about this domain.

### Selective reporting

- We considered three trials to be at low risk of bias because they were prospectively registered and reported all prespecified outcomes (Bignami 2016; Marczynski 2007; Shao 2015).
- We considered five trials to be at high risk of bias because they did not report a prespecified outcome (Hemş inli 2012a; Hemş inli 2012b; Hemş inli 2012c; Lethagen 1991; Temeck 1994).

- We considered the remaining 57 trials to be at unclear risk of bias because they published no protocol or prospective trial registration.

### Other potential sources of bias

- We considered 18 trials to be at high risk of bias because they:
  - were funded by a drug manufacturer or other party with a commercial interest in the outcome of the trial (Andersson 1990; Ansell 1992; Casas 1995; de Prost 1992; Despotis 1999; Flordal 1991; Gratz 1992; Reynolds 1993; Schott 1995; Sheridan 1994; Spyt 1990);
  - had an imbalance in baseline characteristics (Aida 1991a; Aida 1991b);
  - had an imbalance in co-interventions (Temeck 1994);
  - included re-randomised participants (Alanay 1999);
  - were discontinued prematurely without appropriate rationale (Marquez 1992; Marczinski 2007); or

- were a subgroup of a larger trial, and the larger trial was never published (Salmenpera 1991).

- We considered 14 trials to be at low risk of other bias (Bignami 2016; Hackmann 1989; Horrow 1991a; Horrow 1991b; Horrow 1991c; Karnezis 1994a; Karnezis 1994b; Kuitunen 1992; Lee 2010; Lethagen 1991; Manno 2011; Salzman 1986; Seear 1989; Shao 2015).

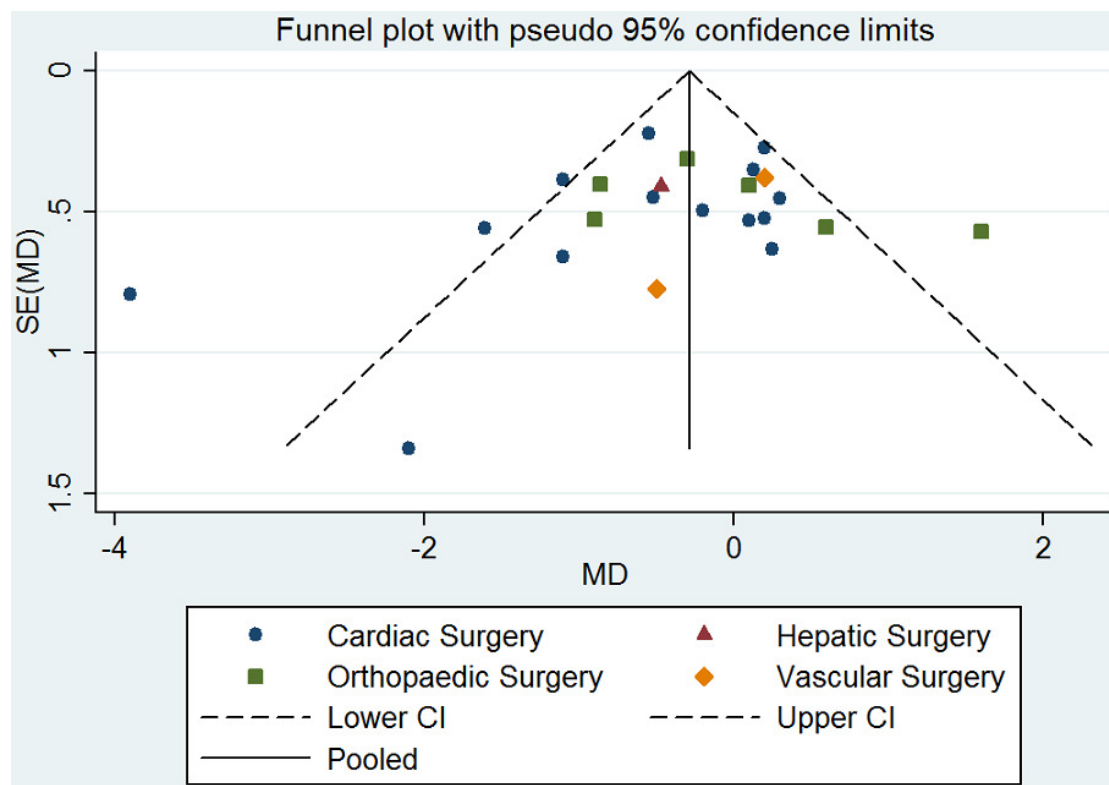
- We considered the remaining 33 trials to be at unclear risk of other bias.

### Publication bias

#### Total volume of red cells transfused

We performed Egger's test: bias coefficient 0.93 ( $P = 0.38$ ). Trials were spread equally around the regression line and did not favour one treatment. Egger's test is known to be sensitive to small-study effects. Consequently, we consider this result to be indicative, but not conclusive, of a lack of publication bias for this outcome (Figure 3).

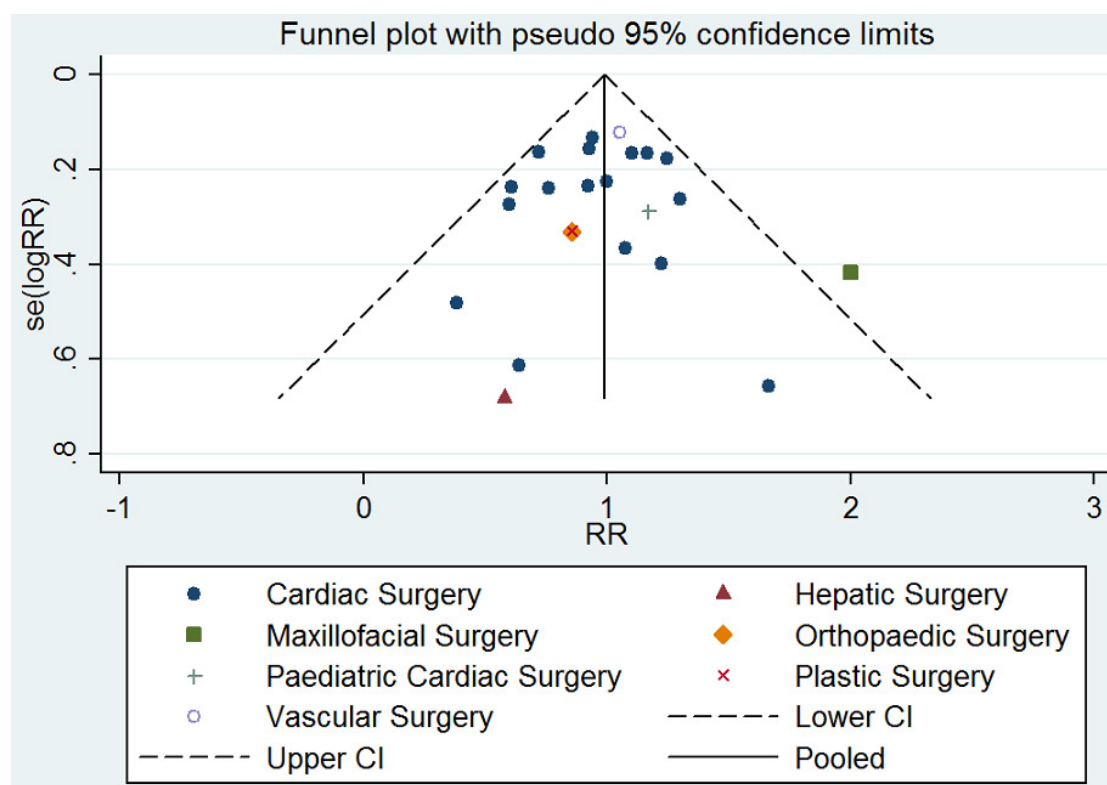
**Figure 3. Funnel plot of comparison: desmopressin vs placebo: total red cell volume transfused. CI: confidence interval; MD: mean difference; SE: standard error.**



### Total number of participants transfused with red cells

We performed a modified Harbord test: bias coefficient -0.26 ( $P = 0.67$ ). Trials were spread equally around the regression line and did not favour one treatment. Consequently, we consider this result to be indicative, but not conclusive, of a lack of publication bias for this outcome (Figure 4).

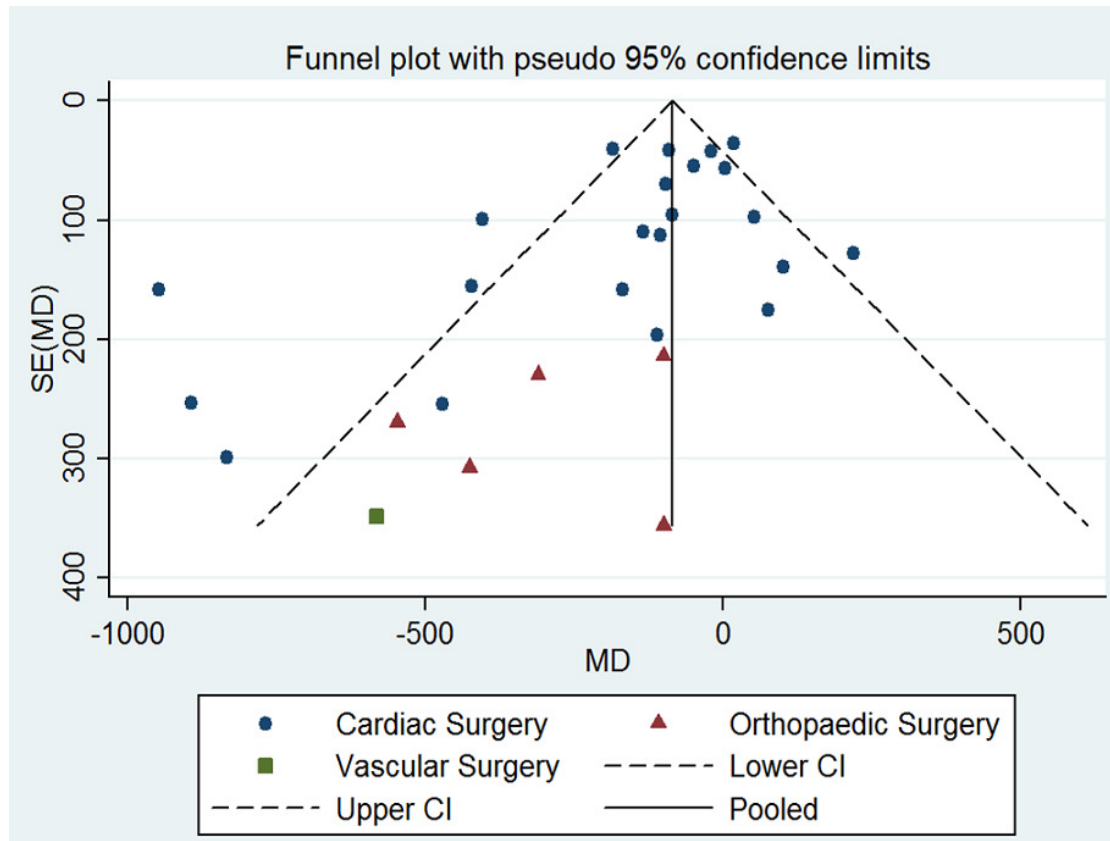
**Figure 4. Funnel plot of comparison: desmopressin vs placebo: number of participants receiving a red cell transfusion. CI: confidence interval; RR: relative risk.**



### Total blood loss

We performed Egger's test: bias coefficient 1.49 ( $P = 0.01$ ). Trials were spread unequally around the regression line with bias favouring DDAVP. Consequently, we consider this result to demonstrate publication bias for this domain. Egger's test is known to be sensitive to small-study effects, but for this domain the small  $P$  value suggests publication bias (Figure 5).

**Figure 5. Funnel plot of comparison: desmopressin vs placebo: total blood loss. CI: confidence interval; MD: mean difference; SE: standard error.**



## Effects of interventions

See: [Summary of findings for the main comparison DDAVP vs placebo or standard care](#); [Summary of findings 2 DDAVP vs placebo or standard care: platelet dysfunction subgroup](#); [Summary of findings 3 DDAVP vs tranexamic acid](#); [Summary of findings 4 DDAVP vs aprotinin](#)

- Sixty-two trials with 3672 participants compared DDAVP versus placebo or standard care (see [Summary of findings for the main comparison](#)).
- Eleven trials with 606 participants compared DDAVP versus placebo in the platelet dysfunction subgroup (see [Summary of findings 2](#))
- Four trials with 163 participants compared DDAVP versus tranexamic acid (see [Summary of findings 3](#))
- Two trials with 154 participants compared DDAVP versus aprotinin (see [Summary of findings 4](#))

• Multi-arm trials were not combined and the separate arms were compared in pair-wise analyses ([Casas 1995](#); [Ellis 2001](#); [Leino 2010](#); [Marquez 1992](#); [Rocha 1994](#)). For trials including arms with different doses of DDAVP, we selected the regimen closest to a single intravenous dose of 0.3 µg/kg for inclusion in the analysis of DDAVP versus placebo or standard care ([Marquez 1992](#); [Rocha 1994](#)). We included trials that compared tranexamic acid versus tranexamic acid and DDAVP in the DDAVP versus placebo or standard care analysis, as the characteristics of groups were matched, with the exception of administration of DDAVP or placebo ([Hemşinli 2012b](#); [Horrow 1991b](#)).

## DDAVP versus placebo or standard care

### Primary outcomes

### Volume of blood transfused intraoperatively

Ten trials (388 participants) reported the volume of blood transfused intraoperatively (Brown 1989; Guay 1992; Kobrinsky 1987; Leino 2010; Letts 1998; Lethagen 1991; Oliver 2000; Schott 1995; Theroux 1997; Wingate 1992a). Results showed considerable variation in volume of transfusion between types of surgery, so this outcome is reported in subgroups only (Analysis 1.1). Analysis revealed no evidence of a difference between subgroups ( $\chi^2 = 4.39$ , degrees of freedom (df) = 4 ( $P = 0.36$ );  $I^2 = 8.8\%$ ).

### Adult cardiac surgery

Owing to the small number of participants, we are uncertain whether results showed a difference in the volume of blood transfused (intraoperatively) for participants treated with DDAVP compared with placebo (MD -0.1 units, 95% CI -1.22 to 1.02 units; 1 trial, 19 participants; Analysis 1.1).

### Paediatric cardiac surgery

Owing to the small number of participants, we are uncertain whether results showed a difference in the volume of blood transfused (intraoperatively) for participants treated with DDAVP compared with placebo (MD 0.40 units, 95% CI -0.87 to 1.67 units; 1 trial, 60 participants; Analysis 1.1).

### Orthopaedic surgery

Six trials (242 participants) reported intraoperative blood loss for orthopaedic surgery (Guay 1992; Kobrinsky 1987; Leino 2010; Letts 1998; Schott 1995; Theroux 1997), but three of these trials did not report this outcome in a way that could be incorporated into meta-analysis and so are reported narratively in Table 3. Results show a reduction in the volume of red cells transfused intraoperatively in those treated with DDAVP compared with placebo (MD -0.50 units, 95% CI -0.89 to -0.11;  $I^2 = 0\%$ ; 3 trials, 144 participants; Analysis 1.1). Restricting the analysis to trials at low risk of bias reduced the effect size (MD -0.20 units, 95% CI -1.74 to 1.34 units; 1 trial, 30 participants; analysis not shown) (Guay 1992). Restricting the analysis to studies with a transfusion protocol did not change the effect estimate (MD -0.38 units, 95% CI -0.84 to 0.07 units;  $I^2 = 0\%$ ; 2 trials, 109 participants; analysis not shown) (Guay 1992; Schott 1995).

### Vascular surgery

Owing to the small number of participants, we are uncertain whether results showed a difference in the volume of blood transfused (intraoperatively) for participants treated with DDAVP

compared with placebo (MD -1.2 units, 95% CI -2.55 to 0.15 units; 1 trial, 44 participants; Analysis 1.1).

### Plastic surgery

Results showed a reduction in the volume of red cells transfused intraoperatively for those treated with DDAVP compared with placebo (MD -0.75 units, 95% CI -1.23 to -0.27 units; 2 trials, 44 participants; Analysis 1.1).

### Total volume of blood transfused

Thirty-nine trials (2324 participants) reported the total volume of blood transfused (Aida 1991a; Aida 1991b; Alanay 1999; Ansell 1992; Bignami 2016; Brown 1989; Chuang 1993; Clagett 1995; de Prost 1992; Despotis 1999; Diltthey 1993; Ellis 2001; Flordal 1992; Frankville 1991; Gratz 1992; Guyuron 1996; Hackmann 1989; Hajjar 2007; Hedderich 1990; Karnezis 1994a; Karnezis 1994b; Kobrinsky 1987; Kuitunen 1992; Leino 2010; Lethagen 1991; Marquez 1992; Mongan 1992a; Mongan 1992b; Ozkiscak 2001; Reich 1991; Reynolds 1993; Rocha 1988; Rocha 1994; Salzman 1986; Schott 1995; Spyt 1990; Steinlechner 2011; Theroux 1997; Wong 2003). Results showed considerable variation in the volume of transfusion between types of surgery, so we reported this outcome in subgroups only (Analysis 1.2). Analysis revealed no evidence of a difference between subgroups ( $\chi^2 = 2.97$ , df = 3 ( $P = 0.40$ );  $I^2 = 0\%$ ).

### Adult cardiac surgery

Twenty-six trials (1674 participants) reported total volume of red cells transfused for adult cardiac surgery; 12 trials did not report this outcome in a way that allowed inclusion in meta-analysis, and so we reported these results narratively in Table 4. The total volume of blood transfused was less for those treated with DDAVP compared with placebo (MD -0.52 units, 95% CI -0.96 to -0.08 units;  $I^2 = 70\%$ ; 14 trials, 957 participants; Analysis 1.2). We noted no change to the effect estimate or to heterogeneity when we restricted the analysis to:

- trials with a low risk of bias (MD -0.54 units, 95% CI -1.40 to 0.31 units;  $I^2 = 16\%$ ; 2 trials, 113 participants; analysis not shown) (Salzman 1986; Steinlechner 2011);
- trials that used autologous cell salvage (MD -0.62 units; 95% CI -1.26 to 0.01 units;  $I^2 = 52\%$ ; 5 trials, 243 participants; analysis not shown) (Brown 1989; Despotis 1999; Diltthey 1993; Gratz 1992; Reich 1991); or
- trials with a transfusion protocol (MD -0.52 units; 95% CI -1.12 to 0.08 units;  $I^2 = 51\%$ ; 4 trials, 240 participants; analysis not shown) (de Prost 1992; Diltthey 1993; Ozkiscak 2001; Steinlechner 2011).

Restricting the analysis to trials published as full-text papers resulted in reduced effect estimate and heterogeneity (MD -0.30 units; 95% CI -0.63 to 0.04 units;  $I^2 = 49\%$ ; 12 trials, 759 participants; analysis not shown) (Ansell 1992; Brown 1989; de Prost 1992; Despotis 1999; Dilthey 1993; Gratz 1992; Hedderich 1990; Ozkisacik 2001; Reich 1991; Rocha 1988; Salzman 1986; Steinlechner 2011).

TSA showed accrual of 68.5% of the information size so far to detect or reject a 15% (0.52 unit) relative risk reduction based on an estimated mean transfusion volume of 3.45 units in study control arms ( $D^2 = 75\%$ ). When we restricted TSA to trials at low risk of bias, results showed that 18.0% of the information size had been accrued so far.

### **Orthopaedic surgery**

Eight trials (344 participants) reported total volume of red cells transfused for orthopaedic surgery, but two trials (41 participants) did not report this outcome in a way that allowed inclusion in meta-analysis, and so we reported these results narratively in Table 4. Results showed no difference in the total volume of blood transfused for those treated with DDAVP compared with placebo (MD -0.02 units, 95% CI -0.67 to 0.64 units;  $I^2 = 71\%$ ; 6 trials, 303 participants; Analysis 1.2).

Restricting the analysis to trials with:

- a low risk of bias increased the effect size but not to clinical significance (MD -0.90 units, 95% CI -1.93 to 0.13 units; 1 trial, 47 participants; analysis not shown) (Leino 2010);
- a transfusion protocol did not alter the effect estimate or heterogeneity (MD 0.33 units, 95% CI -0.63 to 1.28 units;  $I^2 = 72\%$ ; 4 trials, 218 participants; analysis not shown) (Karnezis 1994a; Karnezis 1994b; Leino 2010; Schott 1995).

TSA showed accrual of 30.8% of the information size so far to detect or reject a 15% (0.52 unit) relative risk reduction based on an estimated mean transfusion volume of 3.48 units in study control arms ( $D^2 = 73\%$ ). When we restricted TSA to trials at low risk of bias, results showed that 16.6% of the information size had been accrued so far.

### **Vascular surgery**

Owing to the small number of participants, we are uncertain whether results showed a difference in the total volume of blood transfused for participants treated with DDAVP compared with placebo (MD 0.06 units, 95% CI -0.60 to 0.73 units; 2 trials, 135 participants; Analysis 1.2). TSA showed accrual of 9.3% of the information size so far to detect or reject a 15% (0.29 unit) relative risk reduction based on an estimated mean transfusion volume of 1.94 units in the study control arms ( $D^2 = 0\%$ ). When we restricted TSA to trials at low risk of bias, results showed that 7.7% of the information size had been accrued so far.

### **Hepatic surgery**

Owing to the small number of participants, we are uncertain whether results showed a difference in total volume of blood transfused for participants treated with DDAVP compared with placebo (MD -0.47 units, 95% CI -1.27 to 0.33 units; 1 trial, 59 participants; Analysis 1.2).

### **Maxillofacial surgery**

One trial (20 participants) reported total volume of red cells transfused in maxillofacial surgery but did not report this outcome in a way that allowed inclusion in meta-analysis; so we reported these findings narratively in Table 4.

### **Paediatric cardiac surgery**

Owing to the small number of participants, we are uncertain whether results showed a difference in the total volume of blood transfused for participants treated with DDAVP compared with placebo (MD 1 mL/kg, 95% CI -17.10 to 19.10 mL/kg; 1 trial, 95 participants; Analysis 1.3).

### **Number of participants transfused with blood intraoperatively**

Six trials (349 participants) reported the number of participants transfused with blood intraoperatively, and all six contributed data towards the final pooled estimate (Manno 2011; Marcziński 2007; Mongan 1992a; Mongan 1992b; Wingate 1992a; Wingate 1992b). Results showed no difference in the number of participants transfused with blood intraoperatively between those treated with DDAVP and those not treated with DDAVP (RR 0.74 units, 95% CI 0.50 to 1.09 units;  $I^2 = 0\%$ ; 6 trials, 349 participants; Analysis 1.4). Analysis revealed no evidence of a difference between subgroups ( $\text{Chi}^2 = 0.30$ ,  $\text{df} = 1$  ( $P = 0.58$ );  $I^2 = 0\%$ ). Results showed no change in the effect estimate when analysis was restricted to trials:

- at low risk of bias (RR 0.86, 95% CI 0.45 to 1.64; 3 trials, 206 participants; analysis not shown) (Manno 2011; Wingate 1992a; Wingate 1992b); or
- with a transfusion protocol (RR 0.68, 95% CI 0.43 to 1.10; 2 trials, 115 participants; analysis not shown) (Mongan 1992a; Mongan 1992b).

### **Cardiac surgery**

Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants transfused with blood intraoperatively between those treated with

DDAVP and those given placebo (RR 0.68, 95% CI 0.43 to 1.10 units; 2 trials, 45 participants; [Analysis 1.4](#)).

### **Plastic surgery**

Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants transfused with blood intraoperatively between those treated with DDAVP and those given placebo (RR 0.86, 95% CI 0.45 to 1.64 units; 2 trials, 44 participants; [Analysis 1.4](#)).

### **Kidney biopsy**

One trial in this subgroup reported the number of participants transfused with blood intraoperatively. However, researchers reported no events in either arm of the trial ([Manno 2011](#)).

### **Other types of surgery**

One trial in this subgroup reported the number of participants transfused with blood intraoperatively. However, researchers reported no events in either arm of the trial ([Marczinski 2007](#)).

## **Total number of participants transfused with blood**

Twenty-six trials (1866 participants) reported the total number of participants transfused with blood ([Ansell 1992](#); [Bignami 2016](#); [Casas 1995](#); [Clagett 1995](#); [Dilthey 1993](#); [Ellis 2001](#); [Frankville 1991](#); [Gratz 1992](#); [Guyuron 1996](#); [Hackmann 1989](#); [Horrow 1991a](#); [Horrow 1991b](#); [Jin 2015](#); [Manno 2011](#); [Marquez 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Oliver 2000](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Sheridan 1994](#); [Spyt 1990](#); [Temeck 1994](#); [Wingate 1992a](#); [Wingate 1992b](#); [Wong 2003](#)). We excluded one trial from the final analysis because every participant in both arms of the trial received a red cell transfusion ([Gratz 1992](#)). We found no evidence showing a difference in the total number of participants transfused with blood between those treated with DDAVP and those given placebo (RR 0.96, 95% CI 0.86 to 1.06;  $I^2 = 17\%$ ; 25 trials, 1806 participants; *moderate-quality evidence*; [Analysis 1.5](#)). Analysis revealed no evidence of a difference between subgroups ( $\text{Chi}^2 = 3.02$ ,  $\text{df} = 2$  ( $P = 0.22$ ),  $I^2 = 33.7\%$ ). The effect estimate was similar to results of the main analysis when we restricted the analysis to trials:

- at low risk of bias (RR 1.06, 95% CI 0.90 to 1.25;  $I^2 = 2\%$ ; 9 trials, 691 participants; analysis not shown) ([Bignami 2016](#); [Clagett 1995](#); [Frankville 1991](#); [Horrow 1991a](#); [Horrow 1991b](#); [Manno 2011](#); [Oliver 2000](#); [Wingate 1992a](#); [Wingate 1992b](#));
- that used a transfusion protocol (RR 0.91, 95% CI 0.79 to 1.05; 13 trials, 928 participants; analysis not shown) ([Bignami 2016](#); [Casas 1995](#); [Dilthey 1993](#); [Ellis 2001](#); [Horrow 1991a](#);

[Horrow 1991b](#); [Marquez 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Spyt 1990](#); [Wong 2003](#));

- that used autologous cell salvage (RR 1.02, 95% CI 0.82 to 1.26;  $I^2 = 20\%$ ; 6 trials, 532 participants; analysis not shown) ([Clagett 1995](#); [Frankville 1991](#); [Hackmann 1989](#); [Horrow 1991a](#); [Horrow 1991b](#); [Pleym 2004](#)); or
- published before 2010 plus those registered prospectively and published after 2010 (RR 0.96, 95% CI 0.86 to 1.07;  $I^2 = 19\%$ ; 23 trials, 1543 participants; analysis not shown) ([Ansell 1992](#); [Bignami 2016](#); [Casas 1995](#); [Clagett 1995](#); [Dilthey 1993](#); [Ellis 2001](#); [Frankville 1991](#); [Guyuron 1996](#); [Hackmann 1989](#); [Horrow 1991a](#); [Horrow 1991b](#); [Marquez 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Oliver 2000](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Sheridan 1994](#); [Spyt 1990](#); [Temeck 1994](#); [Wingate 1992a](#); [Wingate 1992b](#); [Wong 2003](#)).

TSA showed accrual of 70% of the information size so far to detect or reject a 15% relative risk reduction based on 43.1% of participants in the study control arms receiving a transfusion ( $D^2 = 18\%$ ). This estimate crossed the futility boundary, suggesting that no evidence shows a difference between desmopressin and placebo for this outcome, and that further trial data are unlikely to alter this estimate. When we restricted TSA to trials at low risk of bias, results showed that 19.4% of the information size had been accrued so far.

### **Cardiac surgery**

We found no evidence showing a difference in the total number of participants transfused with blood between those treated with DDAVP and those given placebo (RR 0.93, 95% CI 0.82 to 1.06;  $I^2 = 25\%$ ; 17 trials, 1350 participants; [Analysis 1.5](#)). The effect estimate was similar to results of the main analysis when we restricted the analysis to trials:

- at low risk of bias (RR 1.03, 95% CI 0.66 to 1.59;  $I^2 = 47\%$ ; 4 trials, 334 participants; analysis not shown) ([Bignami 2016](#); [Frankville 1991](#); [Horrow 1991a](#); [Horrow 1991b](#));
- that used a transfusion protocol (RR 0.90, 95% CI 0.77 to 1.05; 11 trials, 848 participants; analysis not shown) ([Bignami 2016](#); [Casas 1995](#); [Dilthey 1993](#); [Horrow 1991a](#); [Horrow 1991b](#); [Marquez 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Spyt 1990](#));
- that used autologous cell salvage (RR 0.99, 95% CI 0.70 to 1.41;  $I^2 = 34\%$ ; 5 trials, 441 participants; analysis not shown) ([Frankville 1991](#); [Hackmann 1989](#); [Horrow 1991a](#); [Horrow 1991b](#); [Pleym 2004](#)); or
- published before 2010 plus those registered prospectively and published after 2010 (RR 0.94, 95% CI 0.82 to 1.06;  $I^2 = 29\%$ ; 16 trials, 1248 participants; analysis not shown) ([Ansell 1992](#); [Bignami 2016](#); [Casas 1995](#); [Dilthey 1993](#); [Frankville 1991](#); [Hackmann 1989](#); [Horrow 1991a](#); [Horrow 1991b](#));

Marquez 1992; Mongan 1992a; Mongan 1992b; Ozkisacik 2001; Pleym 2004; Sheridan 1994; Spyt 1990; Temeck 1994).

### ***Orthopaedic surgery***

Owing to the small number of participants, we are uncertain whether results showed a difference in the total number of participants transfused with blood when treated with DDAVP versus placebo (RR 0.86, 95% CI 0.45 to 1.64; 1 trial, 13 participants; [Analysis 1.5](#)).

### ***Vascular surgery***

Owing to the small number of participants, we are uncertain whether results showed a difference in the total number of participants transfused with blood when treated with DDAVP versus placebo (RR 1.05, 95% CI 0.83 to 1.34; 1 trial, 68 participants; [Analysis 1.5](#)).

### ***Paediatric cardiac surgery***

Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants transfused with blood when treated with DDAVP versus placebo (RR 1.17, 95% CI 0.66 to 2.06; 1 trial, 27 participants; [Analysis 1.5](#)).

### ***Plastic surgery***

Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants transfused with blood when treated with DDAVP versus placebo (RR 0.86, 95% CI 0.45 to 1.64; 2 trials, 44 participants; [Analysis 1.5](#)).

### ***Hepatic surgery***

Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants transfused with blood when treated with DDAVP versus placebo (RR 0.58, 95% CI 0.15 to 2.21; 1 trial, 59 participants; [Analysis 1.5](#)).

### ***Kidney biopsy***

One trial in this subgroup reported the total number of participants transfused with blood. However, researchers reported no events in either arm of the trial ([Analysis 1.5](#)).

### ***Maxillofacial surgery***

Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants transfused with blood when treated with DDAVP versus placebo (RR 2.00, 95% CI 0.88 to 4.54; 1 trial, 20 participants; [Analysis 1.5](#)).

### ***Intraoperative blood loss***

Seventeen trials (933 participants) reported intraoperative blood loss (Brown 1989; Flordal 1992; Guay 1992; Hackmann 1989; Kobrinsky 1987; Leino 2010; Lethagen 1991; Letts 1998; Marcziński 2007; Oliver 2000; Rocha 1988; Salzman 1986; Schott 1995; Shao 2015; Wingate 1992a; Wingate 1992b; Wong 2003). Clinical heterogeneity due to differences in baseline blood loss meant that it was not possible to calculate a pooled estimate for the whole population, and we performed analyses in subgroups according to type of surgery ([Analysis 1.6](#)). We found no evidence of a difference between subgroups ( $\text{Chi}^2 = 4.10$ ,  $\text{df} = 4$  ( $P = 0.39$ ),  $I^2 = 2.5\%$ ).

### ***Adult cardiac surgery***

Four trials (337 participants) reported intraoperative blood loss for adult cardiac surgery (Brown 1989; Hackmann 1989; Rocha 1988; Salzman 1986), but two trials (250 participants) did not report this outcome in a way that allowed inclusion in meta-analysis, and so we reported this information narratively in [Table 5](#). We found no evidence of a difference in intraoperative blood loss for participants treated with DDAVP versus placebo (MD -138.2 mL, 95% CI -623.4 mL to 347.01 mL;  $I^2 = 85\%$ ; 2 trials, 87 participants; [Analysis 1.6](#)).

### ***Paediatric cardiac surgery***

One trial reported intraoperative blood loss for paediatric cardiac surgery, but did not report this outcome in a way that allowed inclusion in meta-analysis, and so we reported this information narratively in [Table 5](#).

### ***Orthopaedic surgery***

Six trials (271 participants) reported intraoperative blood loss for orthopaedic surgery (Flordal 1992; Guay 1992; Kobrinsky 1987; Leino 2010; Letts 1998; Schott 1995), but one trial (47 participants) did not report this outcome in a way that allowed inclusion in meta-analysis, and so we reported this information narratively in [Table 5](#). We found no evidence of a difference in intraoperative blood loss for participants treated with DDAVP versus placebo (MD -118.24 mL, 95% CI -278.43 mL to 41.95 mL;  $I^2 = 6\%$ ;

5 trials, 224 participants; [Analysis 1.6](#)). The mean difference was similar when we restricted the analysis to trials:

- at low risk of bias (MD -126 mL, 95% CI -766.22 to 514.22 mL; 1 trial, 30 participants; analysis not shown) ([Guay 1992](#)); or
- with a transfusion protocol (MD -103.87 mL, 95% CI -350.88 to 143.14 mL;  $I^2 = 0\%$ ; 2 trials, 109 participants; analysis not shown) ([Guay 1992](#); [Schott 1995](#)).

### *Vascular surgery*

Owing to the small number of participants, we are uncertain whether results showed a difference in intraoperative blood loss for participants treated with DDAVP versus placebo (MD -525.00 mL, 95% CI -1177.34 to 127.34 mL; 1 trial, 44 participants; [Analysis 1.6](#)).

### *Sinus surgery*

Intraoperative blood loss was less for those treated with DDAVP than placebo (MD -28 mL, 95% CI -31.70 to -24.30 mL; 1 trial, 90 participants; [Analysis 1.6](#)).

### *Plastic surgery*

Owing to the small number of participants, we are uncertain whether results showed a difference in total blood loss for participants treated with DDAVP versus placebo (MD -146.02 mL, 95% CI -487.86 to 195.83 mL;  $I^2 = 83\%$ ; 2 trials, 44 participants; [Analysis 1.6](#)).

### *Hepatic surgery*

One trial (59 participants) reported intraoperative blood loss for hepatic surgery but did not report this outcome in a format that allowed inclusion in meta-analysis, and so we reported this information narratively in [Table 5](#).

### *Other types of surgery*

One trial (28 participants) reported intraoperative blood loss for other types of surgery but did not report this outcome in a format that allowed inclusion in meta-analysis, and so we reported this information narratively in [Table 5](#).

## **Total blood loss**

Forty-eight trials (2808 participants) reported total blood loss ([Aida 1991a](#); [Aida 1991b](#); [Alanay 1999](#); [Andersson 1990](#); [Ansell 1992](#); [Bignami 2016](#); [Brown 1989](#); [Casas 1995](#); [Chuang 1993](#); [de Prost 1992](#); [Despotis 1999](#); [Dilthey 1993](#); [Flordal 1991](#); [Flordal 1992](#); [Frankville 1991](#); [Gratz 1992](#); [Guay 1992](#); [Guyuron 1996](#); [Hackmann 1989](#); [Hajjar 2007](#); [Hedderich 1990](#); [Hemş inli 2012a](#); [Hemş inli 2012b](#); [Horrow 1991a](#); [Horrow 1991b](#); [Jin 2015](#); [Kobrinisky 1987](#); [Kuitunen 1992](#); [Leino 2010](#); [Lethagen 1991](#); [Marquez 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Reich 1991](#); [Reynolds 1993](#); [Rocha 1988](#); [Rocha 1994](#); [Salmenpera 1991](#); [Salzman 1986](#); [Schott 1995](#); [Seear 1989](#); [Sheridan 1994](#); [Spyt 1990](#); [Steinlechner 2011](#); [Temeck 1994](#); [Theroux 1997](#)). Clinical heterogeneity due to differences in baseline blood loss meant that it was not possible to obtain a pooled estimate for the whole population, and so we performed analyses in subgroups according to type of surgery ([Analysis 1.7](#); [Analysis 1.8](#)). We found no evidence of a difference between subgroups ( $\text{Chi}^2 = 3.02$ ,  $\text{df} = 2$  ( $P = 0.22$ );  $I^2 = 33.7\%$ ).

### *Adult cardiac surgery*

Thirty-seven trials (2354 participants) reported total blood loss for adult cardiac surgery ([Aida 1991a](#); [Aida 1991b](#); [Alanay 1999](#); [Andersson 1990](#); [Ansell 1992](#); [Bignami 2016](#); [Brown 1989](#); [Casas 1995](#); [Chuang 1993](#); [de Prost 1992](#); [Despotis 1999](#); [Dilthey 1993](#); [Frankville 1991](#); [Gratz 1992](#); [Hackmann 1989](#); [Hajjar 2007](#); [Hedderich 1990](#); [Hemş inli 2012a](#); [Hemş inli 2012b](#); [Horrow 1991a](#); [Horrow 1991b](#); [Jin 2015](#); [Kuitunen 1992](#); [Marquez 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Reich 1991](#); [Rocha 1988](#); [Rocha 1994](#); [Salmenpera 1991](#); [Salzman 1986](#); [Sheridan 1994](#); [Spyt 1990](#); [Steinlechner 2011](#); [Temeck 1994](#)), but 15 trials (996 participants) did not report this outcome in a way that allowed inclusion in meta-analysis, and so we reported this information narratively in [Table 6](#).

Total blood loss for participants undergoing cardiac surgery was less for participants treated with DDAVP than placebo (MD -135.24 mL, 95% CI -210.8 to -59.68 mL;  $I^2 = 78\%$ ; 22 trials, 1358 participants; [Analysis 1.7](#)). Sensitivity analyses could not account for the level of heterogeneity observed. Heterogeneity was not improved by restricting the analysis to trials:

- at low risk of bias (MD -89.77 mL, 95% CI -227.72 to 48.19 mL;  $I^2 = 85\%$ ; 5 trials, 312 participants; analysis not shown) ([Frankville 1991](#); [Horrow 1991a](#); [Horrow 1991b](#); [Salzman 1986](#); [Steinlechner 2011](#)); or
- published as full-text papers (MD -98.96 mL, 95% CI -163.75 to -34.17 mL;  $I^2 = 68\%$ ; 21 trials, 1310 participants; analysis not shown) ([Andersson 1990](#); [Ansell 1992](#); [Brown 1989](#); [Despotis 1999](#); [Frankville 1991](#); [Gratz 1992](#); [Hedderich 1990](#); [Horrow 1991a](#); [Horrow 1991b](#); [Jin 2015](#); [Kuitunen 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Ozkisacik 2001](#); [Pleym 2004](#);

Reich 1991; Salzman 1986; Sheridan 1994; Spyt 1990; Steinlechner 2011; Temeck 1994).

Restricting the analysis to trials:

- with a transfusion protocol did not reduce the effect estimate and heterogeneity (MD -17.12 mL, 95% CI -84.61 to 50.36 mL;  $I^2 = 35\%$ ; 7 trials, 394 participants; analysis not shown) (Brown 1989; Frankville 1991; Gratz 1992; Horrow 1991a; Horrow 1991b; Pleym 2004; Reich 1991);
- published before 2010 plus those registered prospectively and published after 2010 did not alter the effect estimate and heterogeneity (MD -143.99 mL, 95% CI -225.09 to -62.90 mL;  $I^2 = 78\%$ ; 21 trials, 1256 participants; analysis not shown) (Andersson 1990; Ansell 1992; Brown 1989; Chuang 1993; Despotis 1999; Frankville 1991; Gratz 1992; Hedderich 1990; Horrow 1991a; Horrow 1991b; Kuitunen 1992; Mongan 1992a; Mongan 1992b; Ozkisacik 2001; Pleym 2004; Reich 1991; Salzman 1986; Sheridan 1994; Spyt 1990; Steinlechner 2011; Temeck 1994).

TSA showed accrual of 157% of the information size so far to detect or reject a 15% (150.5 mL) reduction in blood loss based on an estimated mean blood loss of 1003.3 mL in study control arms ( $D^2 = 84\%$ ). This crossed the 5% O'Brien-Fleming boundary, suggesting that DDAVP results in a statistically significant reduction in blood loss and that further trial data are unlikely to change this estimate. However, this result included many trials that we assessed as being at high risk of bias, and results show risk of systematic error. When we restricted TSA to trials at low risk of bias, results showed that 23.6% of the information size had been accrued so far.

### Orthopaedic surgery

Seven trials (274 participants) reported total blood loss for orthopaedic surgery (Flordal 1991; Flordal 1992; Guay 1992; Kobrinsky 1987; Leino 2010; Schott 1995; Theroux 1997), but two trials (33 participants) did not report this outcome in a way that allowed inclusion in meta-analysis, and so we reported this information narratively in Table 6. Among participants undergoing orthopaedic surgery, total blood loss was less for those treated with DDAVP than placebo (MD -285.76 mL, 95% CI -514.99 mL to -56.53 mL;  $I^2 = 0\%$ ; 5 trials, 241 participants; Analysis 1.7). Restricting the analysis to trials:

- at low risk of bias did not alter the estimate (MD -285.63 mL, 95% CI -741.88 to 170.63 mL;  $I^2 = 0\%$ ; 2 trials, 77 participants; analysis not shown) (Guay 1992; Leino 2010);
- with a transfusion protocol did not affect the effect estimate (MD -277.23 mL, 95% CI -543.75 to -10.71 mL;  $I^2 = 0\%$ ; 4 trials, 191 participants; analysis not shown) (Guay 1992; Kobrinsky 1987; Leino 2010; Schott 1995);
- published before 2010 plus those registered prospectively and published after 2010 did not alter the effect estimate (MD -

262.24, 95% CI -510.07 to -14.40;  $I^2 = 0\%$ ; 4 trials, 194 participants; analysis not shown) (Flordal 1992; Guay 1992; Kobrinsky 1987; Schott 1995).

TSA showed that 99.2% of the information size required to detect or reject a 15% (326.8 mL) reduction in blood loss based on an estimated mean blood loss of 2178.7 mL in study control arms ( $D^2 = 0\%$ ) had been accrued so far. This crossed the 5% O'Brien-Fleming boundary, suggesting that DDAVP results in a statistically significant reduction in blood loss and that further trial data are unlikely to change this estimate. However, this result included many trials that we assessed as being at high risk of bias, and so results show risk of systematic error. When we restricted TSA to trials at low risk of bias, results showed that 14.4% of the information size had been accrued so far.

### Vascular surgery

Total blood loss for participants undergoing vascular surgery was less for participants treated with DDAVP than placebo (MD -582.00 mL, 95% CI -1264.07 to 100.07 mL; 1 study, 44 participants; Analysis 1.7). TSA showed that 8.3% of the information size required to detect or reject a 15% (281.6 mL) reduction in blood loss based on an estimated mean blood loss of 1877 mL in study control arms ( $D^2 = 0\%$ ) had been accrued so far.

### Paediatric cardiac surgery

Owing to the small number of participants, we are uncertain whether results showed a difference in total blood loss for paediatric participants undergoing cardiac surgery among those treated with DDAVP versus placebo (MD 1.11 mL/kg, 95% CI -12.92 mL/kg to 15.15 mL/kg;  $I^2 = 35\%$ ; 2 studies, 155 participants; Analysis 1.8). TSA showed that 6.0% of the information size had been accrued so far to detect or reject a 15% (4.9 mL/m<sup>2</sup>) reduction in blood loss based on an estimated mean blood loss of 33.1 mL/m<sup>2</sup> in study control arms ( $D^2 = 38\%$ ). When we restricted TSA to trials at low risk of bias, results showed that 1.3% of the information size had been accrued so far.

### Secondary outcomes

#### Number of participants with intraoperative bleeding (interventional procedures only)

One trial (48 participants) reported the number of participants undergoing interventional procedures with intraoperative bleeding (Lee 2010). Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants who had an intraoperative bleed in the DDAVP

arm versus the placebo arm (RR 0.29, 95% CI 0.07 to 1.24; 1 trial, 48 participants; [Analysis 1.9](#)).

### Number of participants with any bleeding (interventional procedures only)

One trial (162 participants) reported the number of participants undergoing interventional procedures with any bleeding ([Manno 2011](#)). Fewer participants had an intraoperative bleed in the DDAVP arm compared to the placebo arm (RR 0.45, 95% CI 0.24 to 0.85; 1 trial, 162 participants; [Analysis 1.10](#)).

### Reoperation due to bleeding

Twenty-three trials (1783 participants) reported the number of participants undergoing reoperation due to bleeding, and all 23 contributed data towards the final pooled estimate ([Ansell 1992](#); [Bignami 2016](#); [Brown 1989](#); [Casas 1995](#); [de Prost 1992](#); [Despotis 1999](#); [Frankville 1991](#); [Guay 1992](#); [Hackmann 1989](#); [Hedderich 1990](#); [Horror 1991a](#); [Horror 1991b](#); [Lee 2010](#); [Manno 2011](#); [Mongan 1992a](#); [Mongan 1992b](#); [Oliver 2000](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Rocha 1988](#); [Rocha 1994](#); [Salzman 1986](#); [Steinlechner 2011](#)). Results showed no difference in the number of participants who required reoperation due to bleeding between those treated with DDAVP versus placebo (pOR 0.66, 95% CI 0.40 to 1.09;  $I^2 = 33\%$ ; 23 trials, 1783 participants; [Analysis 1.11](#)). We found no evidence of a difference between subgroups ( $\text{Chi}^2 = 1.40$ ,  $\text{df} = 1$  ( $P = 0.24$ ),  $I^2 = 28.6\%$ ). When we restricted analysis to trials:

- at low risk of bias, the effect estimate was similar (pOR 0.75, 95% CI 0.35 to 1.59;  $I^2 = 14\%$ ; 9 trials, 699 participants; analysis not shown) ([Bignami 2016](#); [Frankville 1991](#); [Guay 1992](#); [Horror 1991a](#); [Horror 1991b](#); [Manno 2011](#); [Oliver 2000](#); [Salzman 1986](#); [Steinlechner 2011](#));
- published before 2010 plus those registered prospectively and published after 2010, the effect estimate was unchanged (pOR 0.66, 95% CI 0.40 to 1.09;  $I^2 = 33\%$ ; 22 trials, 1599 participants; analysis not shown) ([Ansell 1992](#); [Bignami 2016](#); [Brown 1989](#); [Casas 1995](#); [de Prost 1992](#); [Despotis 1999](#); [Frankville 1991](#); [Guay 1992](#); [Hackmann 1989](#); [Hedderich 1990](#); [Horror 1991a](#); [Horror 1991b](#); [Lee 2010](#); [Mongan 1992a](#); [Mongan 1992b](#); [Oliver 2000](#); [Ozkisacik 2001](#); [Pleym 2004](#); [Rocha 1988](#); [Rocha 1994](#); [Salzman 1986](#); [Steinlechner 2011](#)).

### Cardiac surgery

We found no evidence of a difference in reoperation due to bleeding (pOR 0.64, 95% CI 0.38 to 1.05;  $I^2 = 33\%$ ; 19 trials, 1483 participants; [Analysis 1.11](#)). When we restricted analysis to trials:

- at low risk of bias, the effect estimate was similar (RR 0.69, 95% CI 0.32 to 1.48;  $I^2 = 12\%$ ; 6 trials, 447 participants;

analysis not shown) ([Bignami 2016](#); [Frankville 1991](#); [Horror 1991a](#); [Horror 1991b](#); [Salzman 1986](#); [Steinlechner 2011](#));

- using autologous cell salvage, the direction of effect was reversed, although this finding did not reach statistical significance (RR 1.36, 95% CI 0.50 to 3.68;  $I^2 = 34\%$ ; 5 trials, 424 participants; analysis not shown) ([Brown 1989](#); [Hackmann 1989](#); [Horror 1991a](#); [Horror 1991b](#); [Pleym 2004](#)).

### Orthopaedic surgery

One trial in this subgroup reported reoperation due to bleeding. However, no participants in either arm of the trial returned to theatre with bleeding ([Guay 1992](#)).

### Paediatric cardiac surgery

Owing to the small number of participants, we are uncertain if results showed a difference in the number of participants undergoing reoperation due to bleeding after treatment with DDAVP versus placebo (pOR 6.93, 95% CI 0.14 to 349.88; 1 trial, 60 participants; [Analysis 1.11](#)) ([Oliver 2000](#)).

### Dialysis catheter insertion

One trial in this subgroup reported reoperation due to bleeding. However, no participants in either arm of the trial returned to theatre with bleeding ([Lee 2010](#)).

### Kidney biopsy

One trial in this subgroup reported reoperation due to bleeding. However, no participants in either arm of the trial returned to theatre with bleeding ([Manno 2011](#)).

### All-cause mortality

Twenty-two trials (1631 participants) reported all-cause mortality, and all 22 contributed data towards the final pooled estimate ([Ansell 1992](#); [Bignami 2016](#); [Clagett 1995](#); [Despotis 1999](#); [Gratz 1992](#); [Hackmann 1989](#); [Hedderich 1990](#); [Jin 2015](#); [Karnezis 1994a](#); [Karnezis 1994b](#); [Kuitunen 1992](#); [Mongan 1992a](#); [Mongan 1992b](#); [Oliver 2000](#); [Pleym 2004](#); [Rocha 1988](#); [Rocha 1994](#); [Salzman 1986](#); [Schott 1995](#); [Seear 1989](#); [Sheridan 1994](#); [Steinlechner 2011](#)). We found no evidence of a difference in all-cause mortality between participants treated with DDAVP versus placebo (pOR 1.09, 95% CI 0.51 to 2.34;  $I^2 = 3\%$ ; 22 trials, 1631 participants; [Analysis 1.12](#)). We found no evidence of a difference between subgroups ( $\text{Chi}^2 = 4.29$ ,  $\text{df} = 2$  ( $P = 0.12$ );  $I^2 = 53.4\%$ ). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 1.16, 95% CI 0.41 to 3.25;  $I^2 = 31\%$ ; 6 trials, 469 participants; analysis not shown) (Bignami 2016; Clagett 1995; Oliver 2000; Salzman 1986; Seear 1989; Steinlechner 2011);
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 1.09, 95% CI 0.51 to 2.34;  $I^2 = 3\%$ ; 21 trials, 1529 participants; analysis not shown) (Ansell 1992; Bignami 2016; Clagett 1995; Despotis 1999; Gratz 1992; Hackmann 1989; Hedderich 1990; Karnezis 1994a; Karnezis 1994b; Kuitunen 1992; Mongan 1992a; Mongan 1992b; Oliver 2000; Pleym 2004; Rocha 1988; Rocha 1994; Salzman 1986; Schott 1995; Seear 1989; Sheridan 1994; Steinlechner 2011).

### *Cardiac surgery*

We found no evidence of a difference in all-cause mortality for participants treated with DDAVP versus placebo (pOR 1.09, 95% CI 0.48 to 2.51;  $I^2 = 0\%$ ; 16 trials, 1239 participants; Analysis 1.12). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 1.20, 95% CI 0.36 to 4.02;  $I^2 = 0\%$ ; 3 trials, 248 participants; analysis not shown) (Bignami 2016; Salzman 1986; Steinlechner 2011);
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 1.09, 95% CI 0.48 to 2.51;  $I^2 = 0\%$ ; 15 trials, 1137 participants; analysis not shown) (Ansell 1992; Bignami 2016; Despotis 1999; Gratz 1992; Hackmann 1989; Hedderich 1990; Kuitunen 1992; Mongan 1992a; Mongan 1992b; Pleym 2004; Rocha 1988; Rocha 1994; Salzman 1986; Sheridan 1994; Steinlechner 2011).

### *Orthopaedic surgery*

Three trials in this subgroup reported all-cause mortality as an outcome, however, no deaths occurred during these trials (Karnezis 1994a; Karnezis 1994b; Schott 1995).

### *Vascular surgery*

Owing to the small number of participants, we are uncertain if results showed a difference in all-cause mortality between participants treated with DDAVP versus placebo (pOR 8.50, 95% CI 0.52 to 138.60; 1 trial, 91 participants; Analysis 1.12).

### *Paediatric cardiac surgery*

Owing to the small number of participants, we are uncertain if results showed a difference in all-cause mortality between participants treated with DDAVP versus placebo (pOR 0.13, 95% CI 0.01 to 2.14; 2 trials, 130 participants; Analysis 1.12).

### **All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)**

Twenty-nine trials (1984 participants) reported thrombotic events, and all 29 contributed data towards the final pooled estimate (Ansell 1992; Bignami 2016; Brown 1989; Casas 1995; Clagett 1995; Despotis 1999; Flordal 1991; Flordal 1992; Gratz 1992; Hedderich 1990; Horrow 1991a; Horrow 1991b; Jin 2015; Karnezis 1994a; Karnezis 1994b; Leino 2010; Lethagen 1991; Manno 2011; Marquez 1992; Mongan 1992a; Mongan 1992b; Pleym 2004; Rocha 1994; Salmenpera 1991; Salzman 1986; Schott 1995; Shao 2015; Sheridan 1994; Steinlechner 2011). We found no evidence of a difference in thrombotic events between participants treated with DDAVP versus placebo (pOR 1.36, 95% CI 0.85 to 2.16;  $I^2 = 0\%$ ; 29 trials, 1984 participants; Analysis 1.13). We found no evidence of a difference between subgroups ( $\text{Chi}^2 = 1.60$ ,  $\text{df} = 2$  ( $P = 0.45$ );  $I^2 = 0\%$ ). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 1.14, 95% CI 0.51 to 2.58;  $I^2 = 0\%$ ; 9 trials, 497 participants; analysis not shown) (Bignami 2016; Clagett 1995; Horrow 1991a; Horrow 1991b; Leino 2010; Manno 2011; Salzman 1986; Shao 2015; Steinlechner 2011);
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 1.36, 95% CI 0.85 to 2.16;  $I^2 = 0\%$ ; 26 trials, 1528 participants; analysis not shown) (Ansell 1992; Bignami 2016; Brown 1989; Casas 1995; Clagett 1995; Despotis 1999; Flordal 1991; Flordal 1992; Gratz 1992; Hedderich 1990; Horrow 1991a; Horrow 1991b; Karnezis 1994a; Karnezis 1994b; Leino 2010; Lethagen 1991; Marquez 1992; Mongan 1992a; Mongan 1992b; Pleym 2004; Rocha 1994; Salmenpera 1991; Salzman 1986; Schott 1995; Sheridan 1994; Steinlechner 2011).

### *Cardiac surgery*

We found no evidence of a difference in thrombotic events for cardiac surgery between participants treated with DDAVP versus placebo (pOR 1.46, 95% CI 0.88 to 2.42;  $I^2 = 0\%$ ; 19 trials, 1311 participants; Analysis 1.13). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 1.58, 95% CI 0.52 to 4.77;  $I^2 = 0\%$ ; 5 trials, 407 participants; analysis not shown) (Bignami 2016; Horrow 1991a; Horrow 1991b; Salzman 1986; Steinlechner 2011);

- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 1.46, 95% CI 0.88 to 2.42;  $I^2 = 0\%$ ; 18 trials, 1209 participants; analysis not shown) (Ansell 1992; Bignami 2016; Brown 1989; Casas 1995; Despotis 1999; Gratz 1992; Hedderich 1990; Horrow 1991a; Horrow 1991b; Marquez 1992; Mongan 1992a; Mongan 1992b; Pley 2004; Rocha 1994; Salmenpera 1991; Salzman 1986; Sheridan 1994; Steinlechner 2011).

### **Orthopaedic surgery**

Six trials in the orthopaedic surgery subgroup reported thrombotic events as an outcome, however, these trials reported only a single thrombotic event between them (Analysis 1.13).

### **Vascular surgery**

Owing to the small number of participants, we are uncertain whether results showed a difference in thrombotic events for vascular surgery between participants treated with DDAVP versus placebo (pOR 0.77, 95% CI 0.23 to 2.60; 2 trials, 141 participants; Analysis 1.13) (Clagett 1995; Lethagen 1991).

### **Sinus surgery**

One trial in this subgroup reported thrombotic events as an outcome, however, neither arm of this trial reported any thrombotic events (Shao 2015).

### **Renal biopsy**

One trial in this subgroup reported thrombotic events as an outcome, however, neither arm of this trial reported any thrombotic events (Manno 2011).

### **Myocardial infarction**

Twenty-six trials (1704 participants) reported myocardial infarction, and all 26 contributed data towards the final pooled estimate (Ansell 1992; Brown 1989; Casas 1995; Clagett 1995; Flordal 1991; Flordal 1992; Gratz 1992; Hedderich 1990; Horrow 1991a; Horrow 1991b; Jin 2015; Karnezis 1994a; Karnezis 1994b; Leino 2010; Lethagen 1991; Manno 2011; Marquez 1992; Mongan 1992a; Mongan 1992b; Pley 2004; Rocha 1994; Salmenpera 1991; Salzman 1986; Schott 1995; Shao 2015; Steinlechner 2011). We found no evidence of a difference in myocardial infarction between participants treated with DDAVP versus placebo (pOR 1.32, 95% CI 0.70 to 2.46;  $I^2 = 0\%$ ; 26 trials, 1704 participants; Analysis 1.14). We found no evidence of a difference

between subgroups ( $\text{Chi}^2 = 1.24$ ,  $\text{df} = 1$  ( $P = 0.27$ );  $I^2 = 19.3\%$ ). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 0.65, 95% CI 0.16 to 2.67;  $I^2 = 0\%$ ; 8 trials, 662 participants; analysis not shown) (Clagett 1995; Horrow 1991a; Horrow 1991b; Leino 2010; Manno 2011; Salzman 1986; Shao 2015; Steinlechner 2011);
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 1.32, 95% CI 0.70 to 2.46;  $I^2 = 0\%$ ; 24 trials, 1512 participants; analysis not shown) (Ansell 1992; Brown 1989; Casas 1995; Clagett 1995; Flordal 1991; Flordal 1992; Gratz 1992; Hedderich 1990; Horrow 1991a; Horrow 1991b; Karnezis 1994a; Karnezis 1994b; Leino 2010; Lethagen 1991; Marquez 1992; Mongan 1992a; Mongan 1992b; Pley 2004; Rocha 1994; Salmenpera 1991; Salzman 1986; Schott 1995; Shao 2015; Steinlechner 2011).

### **Cardiac surgery**

We found no evidence of a difference in myocardial infarction between participants treated with DDAVP versus placebo (pOR 1.52, 95% CI 0.77 to 3.00;  $I^2 = 0\%$ ; 16 trials, 1031 participants; Analysis 1.14). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 1.00, 95% CI 0.06 to 16.32;  $I^2 = 0\%$ ; 4 trials, 272 participants; analysis not shown) (Horrow 1991a; Horrow 1991b; Salzman 1986; Steinlechner 2011);
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 1.52, 95% CI 0.77 to 3.00;  $I^2 = 0\%$ ; 15 trials, 929 participants; analysis not shown) (Ansell 1992; Brown 1989; Casas 1995; Gratz 1992; Hedderich 1990; Horrow 1991a; Horrow 1991b; Marquez 1992; Mongan 1992a; Mongan 1992b; Pley 2004; Rocha 1994; Salmenpera 1991; Salzman 1986; Steinlechner 2011).

### **Orthopaedic surgery**

Six trials in this subgroup reported myocardial infarction as an outcome, however, no myocardial infarctions occurred during these trials (Flordal 1991; Flordal 1992; Karnezis 1994a; Karnezis 1994b; Leino 2010; Schott 1995).

### **Vascular surgery**

Owing to the small number of participants, we are uncertain whether results showed a difference in myocardial infarction between participants treated with DDAVP versus placebo (pOR

0.55, 95% CI 0.11 to 2.88; 2 trials, 141 participants; [Analysis 1.14](#)).

### ***Sinus surgery***

One trial in this subgroup reported myocardial infarction as an outcome, however, no myocardial infarctions occurred in either arm of this trial ([Shao 2015](#)).

### ***Renal biopsy***

One trial in this subgroup reported myocardial infarction as an outcome, however, no myocardial infarctions occurred in either arm of this trial ([Manno 2011](#)).

### **Stroke**

Nineteen trials (1277 participants) reported stroke, and all 19 contributed data towards the final pooled estimate ([Ansell 1992](#); [Brown 1989](#); [Casas 1995](#); [Clagett 1995](#); [Flordal 1991](#); [Flordal 1992](#); [Gratz 1992](#); [Horrow 1991a](#); [Horrow 1991b](#); [Jin 2015](#); [Karnezis 1994a](#); [Karnezis 1994b](#); [Leino 2010](#); [Manno 2011](#); [Marquez 1992](#); [Rocha 1994](#); [Salzman 1986](#); [Shao 2015](#); [Sheridan 1994](#)). We found no evidence of a difference in stroke for participants treated with DDAVP versus placebo (pOR 2.95, 95% CI 0.94 to 9.24;  $I^2 = 0\%$ ; 19 trials, 1277 participants; [Analysis 1.15](#)). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 4.09, 95% CI 0.81 to 20.59;  $I^2 = 0\%$ ; 7 trials, 619 participants; analysis not shown) ([Clagett 1995](#); [Horrow 1991a](#); [Horrow 1991b](#); [Leino 2010](#); [Manno 2011](#); [Salzman 1986](#); [Shao 2015](#));
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (RR 2.07, 95% CI 0.69 to 6.25;  $I^2 = 0\%$ ; 16 trials, 923 participants; analysis not shown) ([Ansell 1992](#); [Brown 1989](#); [Casas 1995](#); [Clagett 1995](#); [Flordal 1991](#); [Flordal 1992](#); [Gratz 1992](#); [Horrow 1991a](#); [Horrow 1991b](#); [Karnezis 1994a](#); [Karnezis 1994b](#); [Leino 2010](#); [Marquez 1992](#); [Rocha 1994](#); [Salzman 1986](#); [Sheridan 1994](#)).

### ***Cardiac surgery***

We found no evidence of a difference in stroke between participants treated with DDAVP versus placebo (pOR 2.95, 95% CI 0.94 to 9.24;  $I^2 = 0\%$ ; 11 trials, 733 participants; [Analysis 1.15](#)). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 4.09, 95% CI 0.81 to 20.59;  $I^2 = 0\%$ ; 3 trials, 229 participants; analysis not shown) ([Horrow 1991a](#); [Horrow 1991b](#); [Salzman 1986](#));

- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 2.95, 95% CI 0.94 to 9.24;  $I^2 = 0\%$ ; 10 trials, 631 participants; analysis not shown) ([Ansell 1992](#); [Brown 1989](#); [Casas 1995](#); [Gratz 1992](#); [Horrow 1991a](#); [Horrow 1991b](#); [Marquez 1992](#); [Rocha 1994](#); [Salzman 1986](#); [Sheridan 1994](#)).

### ***Orthopaedic surgery***

Five trials in this subgroup reported stroke as an outcome, however, no strokes occurred during these trials ([Flordal 1991](#); [Flordal 1992](#); [Karnezis 1994a](#); [Karnezis 1994b](#); [Leino 2010](#)).

### ***Vascular surgery***

One trial in this subgroup reported stroke as an outcome, however, no strokes occurred in either arm of this trial ([Clagett 1995](#)).

### ***Sinus surgery***

One trial in this subgroup reported stroke as an outcome, however, no strokes occurred in either arm of this trial ([Shao 2015](#)).

### ***Renal biopsy***

One trial in this subgroup reported stroke as an outcome, however, no strokes occurred in either arm of this trial ([Manno 2011](#)).

### **Venous thromboembolism**

Twenty trials (1377 participants) reported venous thromboembolism, and all 20 contributed data towards the final pooled estimate ([Ansell 1992](#); [Brown 1989](#); [Casas 1995](#); [Clagett 1995](#); [Flordal 1991](#); [Flordal 1992](#); [Gratz 1992](#); [Horrow 1991a](#); [Horrow 1991b](#); [Jin 2015](#); [Karnezis 1994a](#); [Karnezis 1994b](#); [Leino 2010](#); [Manno 2011](#); [Marquez 1992](#); [Pleym 2004](#); [Rocha 1994](#); [Schott 1995](#); [Shao 2015](#); [Steinlechner 2011](#)). We found no evidence of a difference in venous thromboembolism between participants treated with DDAVP versus placebo (pOR 0.77, 95% CI 0.17 to 3.38;  $I^2 = 0\%$ ; 20 trials, 1377 participants; [Analysis 1.16](#)). We found no evidence of a difference between subgroups ( $\text{Chi}^2 = 1.47$ ,  $\text{df} = 1$  ( $P = 0.23$ );  $I^2 = 31.8\%$ ). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 0.14, 95% CI 0.01 to 2.23;  $I^2 = 0\%$ ; 7 trials, 592 participants; analysis not shown) ([Clagett 1995](#); [Horrow 1991a](#); [Horrow 1991b](#); [Leino 2010](#); [Manno 2011](#); [Shao 2015](#); [Steinlechner 2011](#));
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was

not altered (pOR 0.77, 95% CI 0.17 to 3.38;  $I^2 = 0\%$ ; 17 trials, 1023 participants; analysis not shown) (Ansell 1992; Brown 1989; Casas 1995; Clagett 1995; Flordal 1991; Flordal 1992; Gratz 1992; Horrow 1991a; Horrow 1991b; Karnezis 1994a; Karnezis 1994b; Leino 2010; Marquez 1992; Pleym 2004; Rocha 1994; Schott 1995; Steinlechner 2011).

### *Cardiac surgery*

We found no evidence of a difference in venous thromboembolism for participants treated with DDAVP versus placebo (pOR 0.53, 95% CI 0.11 to 2.62;  $I^2 = 0\%$ ; 11 trials, 754 participants; Analysis 1.16). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (pOR 0.14, 95% CI 0.01 to 2.23;  $I^2 = 0\%$ ; 3 trials, 202 participants; analysis not shown) (Horrow 1991a; Horrow 1991b; Steinlechner 2011);
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was not altered (pOR 0.53, 95% CI 0.11 to 2.62;  $I^2 = 0\%$ ; 10 trials, 652 participants; analysis not shown) (Ansell 1992; Brown 1989; Casas 1995; Gratz 1992; Horrow 1991a; Horrow 1991b; Marquez 1992; Pleym 2004; Rocha 1994; Steinlechner 2011).

### *Orthopaedic surgery*

Six trials in this subgroup reported venous thromboembolism as an outcome, however, no venous thromboembolic events occurred during these trials (Flordal 1991; Flordal 1992; Karnezis 1994a; Karnezis 1994b; Leino 2010; Schott 1995).

### *Vascular surgery*

One trial in this subgroup reported venous thromboembolism as an outcome, however, no venous thromboembolic events occurred in either arm of this trial (Clagett 1995).

### *Sinus surgery*

One trial in this subgroup reported venous thromboembolism as an outcome, however, no venous thromboembolic events occurred in either arm of this trial (Shao 2015).

### *Renal biopsy*

One trial in this subgroup reported venous thromboembolism as an outcome, however, no venous thromboembolic events occurred in either arm of this trial (Manno 2011).

### **Clinically important hypotension**

Eighteen trials (1183 participants) reported clinically important hypotension, and all 18 contributed data towards the final pooled estimate (Bignami 2016; Brown 1989; Despotis 1999; Diltthey 1993; Frankville 1991; Letts 1998; Manno 2011; Marquez 1992; Mongan 1992a; Mongan 1992b; Oliver 2000; Pleym 2004; Reich 1991; Rocha 1994; Salmenpera 1991; Salzman 1986; Schott 1995; Shao 2015). Clinically important hypotension was more frequent for participants treated with DDAVP than for those given placebo (RR 2.32, 95% CI 1.37 to 3.91;  $I^2 = 0\%$ ; 18 trials, 1183 participants; Analysis 1.17). We found no evidence of a difference between subgroups ( $\text{Chi}^2 = 0.83$ ,  $\text{df} = 2$  ( $P = 0.66$ );  $I^2 = 0\%$ ). When we restricted the analysis to:

- trials at low risk of bias, the effect estimate was similar (RR 2.34, 95% CI 0.71 to 7.69;  $I^2 = 0\%$ ; 7 trials, 587 participants; analysis not shown) (Bignami 2016; Despotis 1999; Frankville 1991; Manno 2011; Oliver 2000; Salzman 1986; Shao 2015);
- trials published before 2010 plus those registered prospectively and published after 2010, the effect estimate was altered (RR 2.32, 95% CI 1.37 to 3.91;  $I^2 = 0\%$ ; 16 trials, 931 participants; analysis not shown) (Brown 1989; Despotis 1999; Diltthey 1993; Frankville 1991; Letts 1998; Manno 2011; Marquez 1992; Mongan 1992a; Mongan 1992b; Oliver 2000; Pleym 2004; Reich 1991; Rocha 1994; Salmenpera 1991; Salzman 1986; Schott 1995).

### *Cardiac surgery*

Clinically important hypotension was more frequent for participants treated with DDAVP than for those given placebo (RR 2.88, 95% CI 1.32 to 6.30;  $I^2 = 0\%$ ; 13 trials, 762 participants; Analysis 1.17).

When we restricted the analysis to trials at low risk of bias, the effect estimate was similar (RR 2.98, 95% CI 0.64 to 13.90;  $I^2 = 0\%$ ; 3 trials, 245 participants; analysis not shown) (Bignami 2016; Frankville 1991; Salzman 1986).

### *Orthopaedic surgery*

Clinically important hypotension was more frequent for participants treated with DDAVP than for those given placebo (RR 2.05, 95% CI 0.99 to 4.24;  $I^2 = 0\%$ ; 2 trials, 109 participants; Analysis 1.17).

### *Paediatric cardiac surgery*

Owing to the small number of participants, we are uncertain whether results showed a difference between participants treated with DDAVP versus placebo (RR 0.94, 95% CI 0.06 to 14.27; 1 trial, 60 participants; Analysis 1.17).

### ***Sinus surgery***

One trial in this subgroup reported clinically important hypotension as an outcome ([Shao 2015](#)), however, no clinically important episodes of hypotension occurred in either arm of this trial.

### ***Kidney biopsy***

One trial in this subgroup reported clinically important hypotension as an outcome ([Manno 2011](#)), however, no clinically important episodes of hypotension occurred in either arm of this trial.

### **Quality of life**

No trials reported quality of life as an outcome.

## **DDAVP versus placebo: platelet dysfunction subgroup**

In 11 of the trials (606 participants) that compared DDAVP versus placebo, at least 75% of participants had platelet dysfunction.

### **Primary outcomes**

#### **Volume of blood transfused intraoperatively**

None of the trials that reported this outcome included participants with platelet dysfunction.

#### **Total volume of blood transfused**

The total volume of red cells transfused was less for those treated with DDAVP than for controls (MD -0.65 units, 95% CI -1.16 to -0.13 units;  $I^2 = 36\%$ ; 6 trials, 388 participants; [Analysis 2.1](#)).

#### **Number of participants transfused with blood intraoperatively**

Owing to the small number of participants, we are uncertain whether results showed a difference in the number of participants transfused with blood intraoperatively between participants treated with DDAVP and those given placebo (RR 0.55, 95% CI 0.22 to 1.38 units; 1 trial, 29 participants; [Analysis 2.2](#)).

#### **Total number of participants transfused with blood**

We found no difference in the number of participants transfused with blood when treated with DDAVP versus placebo (RR 0.83, 95% CI 0.66 to 1.04;  $I^2 = 14\%$ ; 5 trials, 258 participants; [Analysis 2.3](#)).

### **Intraoperative blood loss**

No trials reported intraoperative blood loss for this subgroup.

### **Total blood loss**

Ten trials (547 participants) in the platelet dysfunction subgroup reported total blood loss. Four trials reported this outcome in a way that did not allow inclusion in meta-analysis, and so we reported this information narratively in [Table 6](#) ([de Prost 1992](#); [Dilthey 1993](#); [Hemş inli 2012a](#); [Hemş inli 2012b](#)). We are very uncertain whether total blood loss is less for participants treated with DDAVP versus placebo owing to high levels of heterogeneity (MD -253.93 mL, 95% CI -408.01 to -99.85 mL;  $I^2 = 75\%$ ; 6 trials, 422 participants; [Analysis 2.4](#)).

### **Secondary outcomes**

#### **Reoperation due to bleeding**

The number of participants returning to theatre with bleeding was lower for participants treated with DDAVP than for those given placebo (pOR 0.39, 95% CI 0.18 to 0.84;  $I^2 = 0\%$ ; 6 trials, 413 participants; [Analysis 2.5](#)).

#### **All-cause mortality**

Owing to the small number of events, we are uncertain whether results showed a difference in all-cause mortality between participants treated with DDAVP versus placebo (pOR 0.72, 95% CI 0.12 to 4.22;  $I^2 = 24\%$ ; 6 trials, 422 participants; [Analysis 2.6](#)).

#### **All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)**

Owing to the small number of events, we are uncertain whether results showed a difference in thrombotic events between participants treated with DDAVP versus placebo (pOR 1.58, 95% CI 0.60 to 4.17;  $I^2 = 0\%$ ; 7 trials, 422 participants; [Analysis 2.7](#)).

#### **Myocardial infarction**

Owing to the small number of events, we are uncertain whether results showed a difference in myocardial infarction between participants treated with DDAVP versus placebo (pOR 2.72, 95% CI 0.60 to 12.37;  $I^2 = 0\%$ ; 4 trials, 277 participants; [Analysis 2.8](#)).

## Stroke

Owing to the small number of events, we are uncertain whether results showed a difference in stroke between participants treated with DDAVP versus placebo (pOR 1.21, 95% CI 0.07 to 20.17;  $I^2 = 0\%$ ; 3 trials, 157 participants; [Analysis 2.9](#)).

## Venous thromboembolism

Owing to the small number of events, we are uncertain whether results showed a difference in venous thromboembolism between participants treated with DDAVP versus placebo (pOR 0.56, 95% CI 0.06 to 5.50;  $I^2 = 60\%$ ; 3 trials, 157 participants; [Analysis 2.10](#)).

## Clinically important hypotension

Clinically important hypotension was more frequent among participants treated with DDAVP than in those given placebo (RR 6.58, 95% CI 1.18 to 36.76;  $I^2 = 0\%$ ; 5 trials, 315 participants; [Analysis 2.11](#)).

## DDAVP versus tranexamic acid

Three trials compared DDAVP versus tranexamic acid ([Ellis 2001](#); [Horrow 1991c](#); [Zohar 2001](#)).

## Primary outcomes

### Volume of blood transfused intraoperatively

No trial reported volume of blood transfused intraoperatively as an outcome.

### Total volume of blood transfused

Two orthopaedic surgery trials (60 participants) reported total volume of blood transfused ([Ellis 2001](#); [Zohar 2001](#)). One trial (20 participants) reported this outcome in a way that did not allow inclusion in meta-analysis; we reported this information in [Table 7](#). Investigators transfused more red cells for participants treated with DDAVP than for those given tranexamic acid (MD 0.60 units, 95% CI 0.09 to 1.11 units; 1 trial, 40 participants; [Analysis 3.1](#)).

### Number of participants transfused with blood intraoperatively

No trial reported the number of participants transfused with blood intraoperatively.

## Total number of participants transfused with blood

Three trials (135 participants) reported the total number of participants transfused with blood ([Ellis 2001](#); [Horrow 1991c](#); [Zohar 2001](#)). More participants were transfused with blood when given DDAVP than tranexamic acid (RR 2.42, 95% CI 1.04 to 5.64;  $I^2 = 0\%$ ; 3 trials, 135 participants; [Analysis 3.2](#)).

### Cardiac surgery

One trial (75 participants) reported the total number of participants transfused with blood ([Horrow 1991c](#)). Owing to the small number of participants, we are uncertain whether results showed a difference in the number transfused with blood when treated with DDAVP versus tranexamic acid (RR 1.46, 95% CI 0.82 to 2.59; 1 trial, 75 participants).

### Orthopaedic surgery

Two trials (105 participants) reported the total number of participants transfused with blood ([Ellis 2001](#); [Zohar 2001](#)). More participants were transfused with blood when given DDAVP than tranexamic acid (RR 4.15, 95% CI 1.58 to 10.90;  $I^2 = 0\%$ ; 2 trials, 60 participants).

## Intraoperative blood loss

No trial reported intraoperative blood loss.

## Total blood loss

Three trials (133 participants) reported total blood loss ([Hemš inli 2012c](#); [Horrow 1991c](#); [Zohar 2001](#)). One trial (28 participants) reported this outcome in a way that did not allow inclusion in meta-analysis, and so we reported this information in [Table 8](#). We pooled the results of the remaining trials for meta-analysis because baseline blood loss was similar between trials. Results showed a greater volume of blood loss among participants treated with DDAVP than tranexamic acid (MD 142.81 mL, 95% CI 79.78 to 205.84 mL;  $I^2 = 0\%$ ; 2 trials, 115 participants; [Analysis 3.3](#)).

### Cardiac surgery

One trial (75 participants) reported total blood loss ([Horrow 1991c](#)). Results showed a greater volume of blood loss among participants treated with DDAVP than tranexamic acid (MD 115.00 mL, 95% CI 35.38 to 194.62 mL; 1 trial, 75 participants).

### ***Orthopaedic surgery***

One trial (75 participants) reported total blood loss ([Zohar 2001](#)). Results showed a greater volume of blood loss among participants treated with DDAVP than tranexamic acid (MD 180.00 mL, 95% CI 86.82 to 273.18 mL; 1 trial, 40 participants).

## **Secondary outcomes**

### **Reoperation due to bleeding**

One cardiac surgery trial reported reoperation due to bleeding, but only a single event occurred ([Analysis 3.4](#)).

### **Number of participants with any bleeding (interventional procedures only, e.g. kidney biopsy)**

No trial reported the number of participants with any bleeding.

### **All-cause mortality**

No trial reported all-cause mortality.

### **All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)**

Two trials (115 participants) reported thrombotic events, and both contributed to the final pooled estimate ([Horrow 1991c](#); [Zohar 2001](#)). Owing to the small number of events, we are uncertain whether results showed a difference in the number of participants treated with DDAVP with thrombotic events versus those treated with tranexamic acid (RR 2.92, 95% CI 0.32 to 26.83;  $I^2 = 0\%$ ; 2 trials, 115 participants; [Analysis 3.5](#)).

### ***Cardiac surgery***

Owing to the small number of participants, we are uncertain whether results showed a difference between the number of participants who had thrombotic events treated with DDAVP versus tranexamic acid (RR 2.92, 95% CI 0.32 to 26.83; 1 trial, 75 participants) ([Horrow 1991c](#)).

### ***Orthopaedic surgery***

One trial reported thrombotic events, but no events occurred in either arm of the trial ([Zohar 2001](#)).

### **Myocardial infarction**

Two trials (115 participants) reported myocardial infarction, but no events occurred in either trial ([Analysis 3.6](#)).

### **Stroke**

Two trials (115 participants) reported stroke, and both contributed to the final pooled estimate ([Horrow 1991c](#); [Zohar 2001](#)). Owing to the small number of events, we are uncertain whether results showed a difference between the number of participants who had a stroke treated with DDAVP versus tranexamic acid (RR 2.92, 95% CI 0.32 to 26.83;  $I^2 = 0\%$ ; 2 trials, 115 participants; [Analysis 3.7](#)).

### ***Cardiac surgery***

Owing to the small number of events, we are uncertain whether results showed a difference in the number of participants who had a stroke treated with DDAVP versus tranexamic acid (RR 2.92, 95% CI 0.32 to 26.83; 1 trial, 75 participants; [Analysis 3.7](#)).

### ***Orthopaedic surgery***

One trial reported stroke, but no events occurred in either arm of the trial ([Analysis 3.7](#)).

### **Venous thromboembolism**

Two trials (115 participants) reported venous thromboembolism, but no events occurred in either trial ([Analysis 3.8](#)).

### **Clinically important hypotension**

No trial reported clinically important hypotension as an outcome.

### **Quality of life**

No trial reported quality of life as an outcome.

### **DDAVP versus aprotinin**

Two trials compared DDAVP versus aprotinin ([Casas 1995](#); [Rocha 1994](#)).

## **Primary outcomes**

### **Volume of blood transfused intraoperatively**

No trial reported volume of blood transfused intraoperatively as an outcome.

### **Total volume of blood transfused**

One cardiac surgery trial (53 participants) reported total volume of blood transfused. Results of this trial are reported in [Table 9](#).

### **Number of participants transfused with blood intraoperatively**

No trial reported the number of participants transfused with blood intraoperatively.

### **Total number of participants transfused with blood**

One trial (99 participants) reported the total number of participants transfused with blood ([Casas 1995](#)). More participants treated with DDAVP were transfused with blood than those treated with aprotinin (RR 2.41, 95% CI 1.45 to 4.02; 1 trial, 99 participants; [Analysis 4.1](#)).

### **Intraoperative blood loss**

No trial reported intraoperative blood loss.

### **Total blood loss**

Two cardiac surgery trials (152 participants) reported total volume of blood transfused but in a format that was not suitable for meta-analysis ([Casas 1995](#); [Rocha 1994](#)). Results of these trials are reported in [Table 10](#).

### **Secondary outcomes**

#### **Reoperation due to bleeding**

Two cardiac surgery trials reported reoperation due to bleeding ([Casas 1995](#); [Rocha 1994](#)). Owing to the small number of events, we are uncertain whether results showed a difference in the numbers of participants who required reoperation owing to bleeding (pOR 1.93, 95% CI 0.20 to 19.04;  $I^2 = 0\%$ ; 2 trials, 152 participants; [Analysis 4.2](#)).

#### **Number of participants with any bleeding (interventional procedures only)**

No trial reported the number of participants with any bleeding.

### **All-cause mortality**

One trial reported all-cause mortality, but no deaths occurred in either arm of the trial ([Analysis 4.3](#)).

### **All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)**

Two cardiac surgery trials (152 participants) reported thrombotic events, and both contributed to the final pooled estimate ([Casas 1995](#); [Rocha 1994](#)). Owing to the small number of events, we are uncertain whether results showed a difference in thrombotic events between those treated with DDAVP and those given aprotinin (pOR 0.98, 95% CI 0.06 to 15.89;  $I^2 = 0\%$ ; 2 trials, 152 participants; [Analysis 4.4](#)).

### **Myocardial infarction**

Two cardiac surgery trials (152 participants) reported myocardial infarction, but no events occurred in either trial ([Casas 1995](#); [Rocha 1994](#); [Analysis 4.5](#)).

### **Stroke**

Two cardiac surgery trials (152 participants) reported stroke, but only a single event occurred ([Casas 1995](#); [Rocha 1994](#); [Analysis 4.6](#)).

### **Venous thromboembolism**

Two trials (152 participants) reported venous thromboembolism, but no events occurred in either trial ([Casas 1995](#); [Rocha 1994](#); [Analysis 4.7](#)).

### **Clinically important hypotension**

One trial (53 participants) reported clinically important hypotension, but no events occurred in either arm of the trial ([Rocha 1994](#); [Analysis 4.8](#)).

### **Quality of life**

No trial reported quality of life as an outcome.

## ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

| Participant or population: participants with platelet dysfunction undergoing surgery   |   |   |                         |                          |                                 |                                 |          |
|--|---|---|-------------------------|--------------------------|---------------------------------|---------------------------------|----------|
| Intervention: desmopressin   |   |   |                         |                          |                                 |                                 |          |
| Comparison: placebo or standard care   |   |   |                         |                          |                                 |                                 |          |
| Outcomes   | Anticipated absolute effects* (95% CI)    |   |                         | Relative effect (95% CI) | No. of participants (studies)   | Quality of the evidence (GRADE) | Comments |
|  | Risk with placebo                         | Risk with desmo-pressin   |                         |                          |                                 |                                 |          |
| Red cell volume trans-fused (total)  | Red cell volume trans-fused was 2.6 units | Red cell volume trans-fused in the desmo-pressin group was 0.65 units less (1.16 less to 0.13 less) | -                       | 388 (6 RCTs)             | ⊕⊕○○<br>LOW <sup>a,b</sup>      |                                 |          |
| Number of participants receiving a red cell transfusion (total)  | 541 per 1000                              | 449 per 1000 (357 to 1000)  | RR 0.83 (0.66 to 1.04)  | 258 (5 RCTs)             | ⊕⊕○○<br>LOW <sup>a,b</sup>      |                                 |          |
| Blood loss (total)   | Mean total blood loss was 1098 mL         | Total blood loss in the desmopressin group was 253.93 mL less (408.01 mL less to 99.85 mL less)     | -                       | 422 (7 RCTs)             | ⊕⊕○○<br>LOW <sup>a,b</sup>      |                                 |          |
| All-cause mortality  | 14 per 1000                               | 10 per 1000 (2 to 59)   | pOR 0.72 (0.12 to 4.22) | 422 (7 RCTs)             | ⊕○○○<br>VERY LOW <sup>a,c</sup> |                                 |          |
| All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous throm-boembolism) | 32 per 1000                               | 51 per 1000 (19 to 133)   | pOR 1.58 (0.60 to 4.17) | 422 (7 RCTs)             | ⊕○○○<br>VERY LOW <sup>a,d</sup> |                                 |          |

|                 |              |   |              |   |
|-----------------|--------------|---|--------------|---|
| Quality of life | Not reported | - | (No studies) | - |
|-----------------|--------------|---|--------------|---|

\***The risk in the intervention group** (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; pOR: Peto odds ratio; RCT: randomised controlled trial; RR: risk ratio

#### GRADE Working Group grades of evidence

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>a</sup>Downgraded one level for risk of bias

<sup>b</sup>Downgraded one level for inconsistency due to variation in baseline level of transfusion and blood loss

<sup>c</sup>Downgraded two levels for imprecision, as confidence intervals include clinically important benefit and clinically important harm with low background event rate

<sup>d</sup>Downgraded one level for imprecision

| Participant or population: participants undergoing surgery<br>Intervention: desmopressin<br>Comparison: tranexamic acid               |   |   |                          |                               |                                   |          |
|---|---|---|--------------------------|-------------------------------|-----------------------------------|----------|
| Outcomes  | Anticipated absolute effects* (95% CI)        |   | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE)   | Comments |
|   | Risk with tranexamic acid                     | Risk with desmo-pressin   |                          |                               |                                   |          |
| Red cell volume transfused (total)  | Mean red cell volume transfused was 0.2 units | Red cell volume transfused in the desmo-pressin group was 0.6 units more (0.09 more to 1.11 more) | -                        | 40 (1 RCT)                    | ⊕⊕○○<br>LOW <sup>a,b</sup>        |          |
| Number of participants receiving a red cell transfusion (total)   | 239 per 1000                                  | 578 per 1000 (248 to 1000)  | RR 2.42 (1.04 to 5.64)   | 135 (3 RCTs)                  | ⊕○○○<br>VERY LOW <sup>a,b,c</sup> |          |
| Blood loss (total)  | Mean blood loss was 270 mL                    | Total blood loss in the desmopressin group was 142.81 mL more (79.78 mL more to 205.84 mL more)   | -                        | 115 (2 RCTs)                  | ⊕⊕○○<br>LOW <sup>a,b</sup>        |          |
| All-cause mortality   | Not reported                                  |   | -                        | (No studies)                  | -                                 |          |
| All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism) | 18 per 1000                                   | 51 per 1000 (6 to 471)  | RR 2.92 (0.32 to 26.83)  | 115 (2 RCTs)                  | ⊕○○○<br>VERY LOW <sup>a,d,e</sup> |          |

|  |              |   |              |   |
|--|--------------|---|--------------|---|
| Quality of life  | Not reported | - | (No studies) | - |
| <p><b>*The risk in the intervention group</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI)</p> <p>CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio</p>  |              |   |              |   |
| <p><b>GRADE Working Group grades of evidence</b></p> <p><b>High quality:</b> We are very confident that the true effect lies close to that of the estimate of the effect</p> <p><b>Moderate quality:</b> We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p><b>Low quality:</b> Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p> <p><b>Very low quality:</b> We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p> |              |   |              |   |

<sup>a</sup>Downgraded one level for risk of bias

<sup>b</sup>Downgraded one level for indirectness because most types of surgery or procedures were not represented by the included trials

<sup>c</sup>Downgraded one level for imprecision owing to wide confidence intervals

<sup>d</sup>Downgraded two levels for imprecision owing to very wide confidence intervals

<sup>e</sup>Outcome not downgraded for indirectness because already downgraded three levels for other reasons

| Participant or population: participants undergoing surgery<br>Intervention: desmopressin<br>Comparison: aprotinin  |  |                            |  |                          |                               |                                   |          |
|--|--|----------------------------|--|--------------------------|-------------------------------|-----------------------------------|----------|
| Outcomes   | Anticipated absolute effects* (95% CI) |                            |  | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE)   | Comments |
|  | Risk with aprotinin                    | Risk with desmo-pressin    |  |                          |                               |                                   |          |
| Red cell volume trans-fused (total)  | Not reported                           |                            |  | -                        | (No studies)                  | -                                 |          |
| Number of participants receiving a red cell transfusion (total)  | 265 per 1000                           | 639 per 1000 (385 to 1000) |  | RR 2.41 (1.45 to 4.02)   | 99 (1 RCT)                    | ⊕⊕○○<br>LOW <sup>a,b</sup>        |          |
| Blood loss (total)   | Not reported                           |                            |  | -                        | (No studies)                  | -                                 |          |
| All-cause mortality  | No deaths in either arm of the trial   |                            |  | Not estimable            | 53 (1 RCT)                    | ⊕○○○<br>VERY LOW <sup>a,c,d</sup> |          |
| All thrombotic events (including myocardial infarction, ischaemic stroke, other arte-rial thromboembolism, and venous throm-boembolism)  | 14 per 1000                            | 13 per 1000 (1 to 206)     |  | pOR 0.98 (0.06 to 15.89) | 152 (2 RCTs)                  | ⊕○○○<br>VERY LOW <sup>a,d,e</sup> |          |
| Quality of life  | Not reported                           |                            |  | -                        | (No studies)                  | -                                 |          |
| *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI) |  |                            |  |                          |                               |                                   |          |
| CI: confidence interval; pOR: Peto odds ratio; RCT: randomised controlled trial; RR: risk ratio  |  |                            |  |                          |                               |                                   |          |

#### GRADE Working Group grades of evidence

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>a</sup>Downgraded one level for risk of bias

<sup>b</sup>Downgraded one level for indirectness because most types of surgery or procedures were not represented by the included trials

<sup>c</sup>Downgraded two levels for imprecision (no deaths in either arm)

<sup>d</sup>Not downgraded for indirectness because already downgraded three levels for other reasons

<sup>e</sup>Downgraded two levels for imprecision (very wide confidence intervals)

## DISCUSSION

### Summary of main results

#### DDAVP versus placebo or standard care

Sixty-two trials compared DDAVP (1-deamino-8-D-arginine-vasopressin; desmopressin) versus placebo or standard care. Compared with placebo, DDAVP may lead to little or no difference in the total volume of red cells transfused for orthopaedic surgery, vascular surgery, or hepatic surgery ([Analysis 1.2](#)). DDAVP may slightly reduce the total volume of red cells transfused in adult cardiac surgery ([Analysis 1.2](#)). However, this difference is small and is unlikely to be of clinical benefit. DDAVP probably leads to little or no difference in the total number of people receiving a red cell transfusion ([Analysis 1.5](#)). It is uncertain whether DDAVP improves or worsens total blood loss because the quality of evidence is very low ([Analysis 1.7](#)). DDAVP may lead to little or no difference in the risk of mortality ([Analysis 1.12](#)) or thrombotic events ([Analysis 1.13](#)).

#### DDAVP versus placebo or standard care: platelet dysfunction subgroup

Ten trials compared DDAVP versus placebo or standard care in people with platelet dysfunction. Compared with placebo, DDAVP may lead to a reduction in the total volume of red cells transfused ([Analysis 2.1](#)) and in total blood loss ([Analysis 2.4](#)). DDAVP probably leads to little or no difference in the total number of people receiving a red cell transfusion ([Analysis 2.3](#)). It is uncertain whether DDAVP improves or worsens all-cause mortality ([Analysis 2.6](#)) or risk of thrombotic events ([Analysis 2.7](#)) compared with placebo because the quality of evidence is very low.

#### DDAVP versus tranexamic acid

Four trials compared DDAVP versus tranexamic acid. DDAVP may increase the total volume of red cells transfused ([Analysis 3.1](#)) and total blood loss ([Analysis 1.7](#)) compared with tranexamic acid. It is uncertain whether DDAVP improves or worsens the total number of people receiving a red cell transfusion ([Analysis 3.2](#)) or risk of thrombotic events ([Analysis 3.5](#)) compared with tranexamic acid because the quality of evidence is very low.

#### DDAVP versus aprotinin

Two trials compared DDAVP versus aprotinin. DDAVP may increase the total number of people who receive a red cell transfusion compared with aprotinin ([Analysis 4.1](#)). It is uncertain whether DDAVP improves or worsens risk of all-cause mortality ([Analysis 4.3](#)) or thrombotic events ([Analysis 4.4](#)) compared with aprotinin because the quality of evidence is very low.

### Overall completeness and applicability of evidence

This review provides the most up-to-date evidence for administration of DDAVP to minimise blood transfusion. The review identified 65 trials with 3874 participants and four ongoing trials with 147 participants. Most of these trials (46/65; 71%) were performed over 20 years ago, and changes in surgical and transfusion practice since that time may alter the relevance of these findings. The most common trial settings were adult cardiac surgery (39/65 trials; 60%) and orthopaedic surgery (12/65 trials; 18%); relatively few trials have examined the use of DDAVP in other types of surgery. Only 20 of the 65 (31%) trials administered DDAVP preoperatively, three trials (5%) administered DDAVP in combination with an antifibrinolytic agent, 12 trials (18%) included more than 75% of participants with platelet dysfunction, and no trials included people with thrombocytopenia or coagulopathy. These key groups are relatively under-represented in the review dataset. Across all outcomes, available data on overall mortality and adverse events due to thrombotic events are insufficient to show clearly whether an increase, or a decrease, in events is associated with DDAVP administration. No trials reported quality of life.

### Quality of the evidence

We have summarised the GRADE quality of evidence in [Summary of findings for the main comparison](#), [Summary of findings 2](#), [Summary of findings 3](#), and [Summary of findings 4](#). The overall quality of the evidence ranged from very low to moderate. We downgraded all outcomes one point for risk of bias. Most trials did not report sufficient detail to allow assessment of bias. We considered only one trial to be at low risk of bias in all domains. Domains with high risk of bias included blinding of outcome assessors, incomplete outcome data, and selective reporting. Heterogeneity was a problem for continuous outcomes, total volume of blood loss, and total number of red cells transfused owing to large differences in baseline blood loss between procedures. Mortality and thrombotic events were rare and, consequently, introduced risk of imprecision. Lastly, the trials in this review did not represent many types of surgery, and this introduced inconsistency. This was particularly the case for comparisons of DDAVP versus tranexamic acid or aprotinin.

### Potential biases in the review process

We noted no obvious biases within the review process. We conducted a wide search - that was not restricted by language or by full-text publication - to optimise the chances of identifying all relevant trials. Two review authors who were blinded to the other's results performed screening and data extraction in duplicate to

minimise bias. A limitation of this review is that for many outcomes, the original authors published results in a format that did not allow inclusion in meta-analysis (e.g. reported medians and ranges instead of means and standard deviations). This meant that many published trials did not contribute data to the outcomes, particularly for total volume of blood transfused and total blood loss.

## Agreements and disagreements with other studies or reviews

This review is an update of a Cochrane Review published in 2004 (Carless 2004). The original review identified 29 eligible trials. In 2008, another published meta-analysis included 38 eligible trials (Crescenzi 2008). Compared with the most recent systematic review of DDAVP for prevention of perioperative transfusion (Crescenzi 2008), this review identified 26 more trials with an additional 1386 participants. For the present update, we included interventional procedures and children, neither of which were eligible for inclusion in the original Cochrane Review. The overall findings of this update are similar to those of the original review, which also found small decreases in the total volume of red cells transfused and in total blood loss, but no difference in the number of participants receiving a red cell transfusion nor in overall mortality or thrombotic events. The original review examined heterogeneity through sensitivity analysis by subgroups (cardiac surgery and other): participants taking antiplatelet agents, use of cell salvage, use of a transfusion protocol, and duration of cardiopulmonary bypass. Data on the subgroup of participants with platelet dysfunction or taking antiplatelet agents have been co-published separately (Desborough 2017).

## AUTHORS' CONCLUSIONS

### Implications for practice

Findings from 65 trials conducted worldwide show no benefit

of DDAVP (1-deamino-8-D-arginine-vasopressin) for unselected patients. Small reductions in blood loss and in total volume of red cells transfused were noted in cardiac surgery, but these are unlikely to be clinically important. No difference was found in mortality or adverse events (such as thrombotic events) with the use of DDAVP, as there were so few events.

### Implications for research

The quality of the evidence available for assessment of the value of DDAVP in surgery was low. Benefits in unselected patients appear to be small, and it is unlikely that additional trials will change this finding. Subgroups of people with platelet dysfunction or taking antiplatelet agents may gain greater benefit from DDAVP, and this may be a topic for future research. Incorporation of point-of-care platelet function tests or viscoelastic tests in future trials may allow greater precision in the selection of patients who may derive the greatest benefit from DDAVP; this is another potential topic for research.

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## REFERENCES

### References to studies included in this review

#### Aida 1991a {published data only}

Aida H, Kuribayashi R, Sakurada T, Sekine S, Gotoh H, Seki K, et al. A study of desmopressin to reduce blood loss after surgery in patients on cardiopulmonary bypass [membrane oxygenator]. *Japanese Journal of Artificial Organs* 1991;20(2):2516–20.

#### Aida 1991b {published data only}

Aida H, Kuribayashi R, Sakurada T, Sekine S, Gotoh H,

Seki K, et al. A study of desmopressin to reduce blood loss after surgery in patients on cardiopulmonary bypass. *Japanese Journal of Artificial Organs* 1991;20(2):2516–20.

#### Alanay 1999 {published data only}

Acaroglu E, Alanay A, Surat A. Desmopressin (DDAVP) in scoliosis surgery. *Journal of Bone and Joint Surgery - British Volume*. 1997; Vol. 79:Abstract O343.

\* Alanay A, Acaroglu E, Ozdemir O, Erçelen O, Bulutçu E, Surat A. Effects of deamino-8-D-arginin vasopressin on

- blood loss and coagulation factors in scoliosis surgery. A double-blind randomized clinical trial. *Spine* 1999;**24**(9): 877–82.
- Andersson 1990 {published data only}**  
Andersson TL, Solem JO, Tengborn L, Vinge E. Effects of desmopressin acetate on platelet aggregation, von Willebrand factor, and blood loss after cardiac surgery with extracorporeal circulation. *Circulation* 1990;**81**(3):872–8.
- Ansell 1992 {published data only}**  
Ansell J, Klassen V, Lew R, Ball S, Weinstein M, VanderSalm T, et al. Does desmopressin acetate prophylaxis reduce blood loss after valvular heart operations? A randomized, double-blind study. *Journal of Thoracic and Cardiovascular Surgery* 1992;**104**(1):117–23.
- Bignami 2016 {published data only}**  
Desmopressin in Cardiac Surgery. Clinicaltrials.gov number: NCT00337766 (accessed 23 May 2017).  
Efficacy of desmopressin in patient with active bleeding after heart surgery. EudraCT Number: 2005-005199-33 (accessed 23 May 2017).  
\* Bignami E, Cattaneo M, Crescenzi G, Ranucci M, Guarracino F, Cariello C, et al. Desmopressin after cardiac surgery in bleeding patients. A multicenter randomized trial. *Acta Anesthesiologica Scandinavica* 2016;**60**(7): 892–900.
- Brown 1989 {published data only}**  
Brown MR, Swygert TH, Whitten CW, Hebel R. Desmopressin acetate following cardiopulmonary bypass: evaluation of coagulation parameters. *Journal of Cardiothoracic Anesthesia* 1989;**3**(6):726–9.
- Casas 1995 {published data only}**  
\* Casas JI, Zuazu-Jausoro I, Mateo J, Oliver A, Litvan H, Muniz-Diaz E, et al. Aprotinin versus desmopressin for patients undergoing operations with cardiopulmonary bypass. A double-blind placebo-controlled study. *Journal of Thoracic and Cardiovascular Surgery* 1995;**110**(4 Pt 1): 1107–17.  
Zuazu-Jausoro I, Oliver A, Casas I, Rodriguez A, Caralps JM, Aris A, et al. Aprotinin or desmopressin, which is the best one to control bleeding associated to cardiopulmonary bypass (CPB): A prospective randomized double blind trial. *Thrombosis and Haemostasis*. 1993; Vol. 69:Abstract 2671.
- Chuang 1993 {published data only}**  
Chuang HI, Horng YJ, Li Y, Chern FC, Shieh DY, Chiou IS, et al. [Clinical assessment of desmopressin to reduce blood loss in patients after cardiopulmonary bypass]. *Ma Zui Xue Za Zhi* 1993;**31**(1):35–42.
- Clagett 1995 {published data only}**  
Clagett GP, Valentine RJ, Myers SI, Chervu A, Heller J. Does desmopressin improve hemostasis and reduce blood loss from aortic surgery? A randomized, double-blind study. *Journal of Vascular Surgery* 1995;**22**(3):223–9.
- de Prost 1992 {published data only}**  
Prost D, Barbier-Boehm G, Hazebroucq J, Bielsky MC, Hvass U. Effect of desmopressin on excessive postoperative bleeding and blood product requirements associated with cardiopulmonary bypass. *Thrombosis Research*. 1992; Vol. 65:Abstract C132.  
\* de Prost D, Barbier-Boehm G, Hazebroucq J, Ibrahim H, Bielsky MC, Hvass U, et al. Desmopressin has no beneficial effect on excessive postoperative bleeding or blood product requirements associated with cardiopulmonary bypass. *Thrombosis and Haemostasis* 1992;**68**(2):106–10.
- Despotis 1999 {published data only}**  
Despotis GJ, Levine V, Saleem R, Spitznagel E, Joist JH. DDAVP reduces blood loss and blood component transfusion in cardiac surgery patients with impaired platelet function identified with a new point-of-care test. *Blood*. 1998; Vol. 92:Abstract 189.  
Despotis GJ, Levine V, Saleem R, Spitznagel E, Joist JH. DDAVP reduces blood loss and blood component transfusion in cardiac surgery patients with impaired platelet function identified with a new-point-of-care test. *Annals of Hematology*. 1999; Vol. 78:Abstract P054.  
\* Despotis GJ, Levine V, Saleem R, Spitznagel E, Joist JH. Use of point-of-care test in identification of patients who can benefit from desmopressin during cardiac surgery: a randomised controlled trial. *Lancet* 1999;**354**(9173): 106–10.
- Diltthey 1993 {published data only}**  
Diltthey G, Dietrich W, Spannagl M, Richter JA. Influence of desmopressin acetate on homologous blood requirements in cardiac surgical patients pretreated with aspirin. *Journal of Cardiothoracic and Vascular Anesthesia* 1993;**7**(4):425–30.
- Ellis 2001 {published data only}**  
Ellis MH, Fredman B, Zohar E, Ifrach N, Jedeikin R. The effect of tourniquet application, tranexamic acid, and desmopressin on the procoagulant and fibrinolytic systems during total knee replacement. *Journal of Clinical Anesthesia* 2001;**13**(7):509–13.
- Flordal 1991 {published data only}**  
Flordal PA, Ljungstrom KG, Svensson J, Ekman B, Neander G. Effects on coagulation and fibrinolysis of desmopressin in patients undergoing total hip replacement. *Thrombosis and Haemostasis* 1991;**66**(6):652–6.
- Flordal 1992 {published data only}**  
Flordal PA, Ljungstrom KG, Ekman B, Neander G. Effects of desmopressin on blood loss in hip arthroplasty. Controlled study in 50 patients. *Acta Orthopaedica Scandinavica* 1992;**63**(4):381–5.
- Frankville 1991 {published data only}**  
Frankville DD, Harper GB, Lake CL, Johns RA. Hemodynamic consequences of desmopressin administration after cardiopulmonary bypass. *Anesthesiology* 1991;**74**(6):988–96.
- Gratz 1992 {published data only}**  
\* Gratz I, Koehler J, Olsen D, Afshar M, DeCastro N, Spagna PM, et al. The effect of desmopressin acetate on postoperative hemorrhage in patients receiving aspirin

- therapy before coronary artery bypass operations. *Journal of Thoracic and Cardiovascular Surgery* 1992;**104**(5):1417–22.
- Koehler J, Gratz I, Larijani GE, Spagna P, Gomez F, Karayannis B, et al. The use of desmopressin to decrease bleeding in patients on aspirin therapy undergoing uncomplicated coronary artery bypass surgery (CABG). *Clinical Pharmacology and Therapeutics*. 1990; Vol. 47: Abstract PIII-107.
- Guay 1992 {published data only}**
- \* Guay J, Reinberg C, Poitras B, David M, Mathews S, Lortie L, et al. A trial of desmopressin to reduce blood loss in patients undergoing spinal fusion for idiopathic scoliosis. *Anesthesia and Analgesia* 1992;**75**(3):405–10.
- Guay J, Reinberg C, Rivard GE, Poitras B, Mathews S, David M. DDAVP does not reduce bleeding during spinal fusion for idiopathic scoliosis. *Canadian Journal of Anaesthesia*. 1990; Vol. 37:Abstract S14.
- Guyuron 1996 {published data only}**
- Guyuron B, Vaughan C, Schlechter B. The role of DDAVP (desmopressin) in orthognathic surgery. *Annals of Plastic Surgery* 1996;**37**(5):516–9.
- Hackmann 1989 {published data only}**
- Hackman T, Growe GH, Naiman SC, Townsend G, Gascoyne RD, Jamieson WR, et al. 1-Desamino-8-D-Arginine-Vasopressin (DDAVP) does not reduce blood loss in open-heart surgery. *Canadian Journal of Surgery*. 1988; Vol. 31:Abstract R63.
- Hackman T, Growe GH, Naiman SC, Townsend RD, Gascoyne WR, Jamieson S, et al. Lack of effect of DDAVP in open heart surgery. *Circulation*. 1988; Vol. 78:Abstract 2102.
- \* Hackmann T, Gascoyne RD, Naiman SC, Growe GH, Burchill LD, Jamieson WR, et al. A trial of desmopressin (1-desamino-8-D-arginine vasopressin) to reduce blood loss in uncomplicated cardiac surgery. *New England Journal of Medicine* 1989;**321**(21):1437–43.
- Hajjar 2007 {published data only}**
- Hajjar LA, Galas F, Fortim M, Melo, R, Ferreira R, Auler JO. Desmopressin acetate reduces blood loss after cardiac surgery: a double-blind randomized controlled trial. *Circulation*. 2007; Vol. 116, issue 16:396.
- Hedderich 1990 {published data only}**
- Hedderich GS, Petsikas DJ, Cooper BA, Leznoff M, Guerraty AJ, Poirier NL, et al. Desmopressin acetate in uncomplicated coronary artery bypass surgery: a prospective randomized clinical trial. *Canadian Journal of Surgery* 1990; **33**(1):33–6.
- Hemş inli 2012a {published data only}**
- Heminli D, Pulathan Z, Altun G, Gven KY, Civelek A. The effect of tranexamic acid and desmopressin acetate infusion on coagulation parameters in patients operated under dual antiplatelet therapy. *Heart Surgery Forum*. 2012; Vol. 15 Suppl 1:Abstract OP-088.
- Hemş inli 2012b {published data only}**
- Heminli D, Pulathan Z, Altun G, Gven KY, Civelek A. The effect of tranexamic acid and desmopressin acetate infusion on coagulation parameters in patients operated under dual antiplatelet therapy. *Heart Surgery Forum*. 2012; Vol. 15 Suppl 1:Abstract OP-088.
- Hemş inli 2012c {published data only}**
- Heminli D, Pulathan Z, Altun G, Gven KY, Civelek A. The effect of tranexamic acid and desmopressin acetate infusion on coagulation parameters in patients operated under dual antiplatelet therapy. *Heart Surgery Forum*. 2012; Vol. 15 Suppl 1:Abstract OP-088.
- Horror 1991a {published data only}**
- Horror JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. *Circulation* 1991;**84**(5):2063–70.
- Horror 1991b {published data only}**
- Horror JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. *Circulation* 1991;**84**(5):2063–70.
- Horror 1991c {published data only}**
- Horror JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. *Circulation* 1991;**84**(5):2063–70.
- Jin 2015 {published data only}**
- Ji H, Jin L. Effect of desmopressin on platelet aggregation and blood loss in patients undergoing valvular heart surgery. *Cardiology*. 2013; Vol. 126:Abstract.
- \* Jin L, Ji HW. Effect of desmopressin on platelet aggregation and blood loss in patients undergoing valvular heart surgery. *Chinese Medical Journal* 2015;**128**(5):644–7.
- Karnezis 1994a {published data only}**
- Karnezis TA, Stulberg SD, Wixson RL, Reilly P. The hemostatic effects of desmopressin on patients who had total joint arthroplasty. A double-blind randomized trial. *Journal of Bone and Joint Surgery. American Volume* 1994;**76**(10):1545–50.
- Karnezis 1994b {published data only}**
- Karnezis TA, Stulberg SD, Wixson RL, Reilly P. The hemostatic effects of desmopressin on patients who had total joint arthroplasty. A double-blind randomized trial. *Journal of Bone and Joint Surgery. American Volume* 1994;**76**(10):1545–50.
- Kobrinsky 1987 {published data only}**
- Kobrinsky NL, Israelis ED, Letts M, Patel L, Schwartz N, Cheang MS, et al. DDAVP shortens the bleeding time and decreases operative blood loss in hemostatically normal subjects undergoing spinal fusion surgery. *Blood*. 1985; Vol. 5:Abstract 1176.
- \* Kobrinsky NL, Letts RM, Patel LR, Israelis ED, Monson RC, Schwetz N, et al. 1-Desamino-8-D-arginine vasopressin (desmopressin) decreases operative blood loss in patients having Harrington rod spinal fusion surgery. A randomized, double-blinded, controlled trial.. *Annals of Internal Medicine* 1987;**107**:446–50.

**Kuitunen 1992 {published data only}**

Kuitunen AH. Haemostatic responses to desmopressin acetate after primary coronary artery bypass surgery. *Annals Chirurgiae et Gynaecologiae* 1992;**81**(1):11–8.

**Lazarchick 1995 {published data only}**

Lazarchick J, Conroy JM. The effect of 6% hydroxyethyl starch and desmopressin infusion on von Willebrand factor: ristocetin cofactor activity. *Annals of Clinical and Laboratory Science* 1995;**25**(4):306–9.

**Lee 2010 {published data only}**

Lee HK, Kim YJ, Jeong JU, Park JS, Chi HS, Kim SB. Desmopressin improves platelet dysfunction measured by in vitro closure time in uremic patients. *Nephron Clinical Practice* 2010;**114**(4):c248–52.

**Leino 2010 {published data only}**

Leino KA, Palve HK, Tiisanen HT, Tuppurainen TT. The effect of desmopressin on blood loss in patients with rheumatoid arthritis undergoing hip arthroplasty. *Acta Anaesthesiologica Scandinavica* 2010;**54**(7):863–70.

**Lethagen 1991 {published data only}**

Lethagen S, Rugarn P, Bergqvist D. Blood loss and safety with desmopressin or placebo during aorto-iliac graft surgery. *European Journal of Vascular Surgery* 1991;**5**(2):173–8.

**Letts 1998 {published data only}**

Letts M, Pang E, D'Astous J, Jarvis J, Lawton L, Luke B, et al. The influence of desmopressin on blood loss during spinal fusion surgery in neuromuscular patients. *Spine* 1998;**23**(4):475–8.

**Manno 2011 {published data only}**

Manno C, Bonifati C, Torres DD, Campobasso N, Schena FP. Desmopressin acetate in percutaneous ultrasound-guided kidney biopsy: a randomized controlled trial. *American Journal of Kidney Diseases* 2011;**57**(6):850–5.

**Marczinski 2007 {published data only}**

Use of preoperative desmopressin in preventing bleeding in patients treated with SSRIs. International Standard Randomised Controlled Trial Number: ISRCTN10353850.  
\* Marczinski SC, Van der Meer YG, Van der Beek en M, Egberts AC. Use of preoperative desmopressin in preventing bleeding in patients treated with SSRIs [Desmopressine preoperatief vermindert bloedverlies bij SSRI-gebruikers: gerandomiseerd placebogecontroleerd, dubbelblind onderzoek]. *Wetenschappelijk Platform* 2007;**1**(3):60–3.

**Marquez 1992 {published data only}**

Marquez J, Koehler S, Strelec SR, Benckart DH, Spero JA, Cottrington EM, et al. Repeated dose administration of desmopressin acetate in uncomplicated cardiac surgery: a prospective, blinded, randomized study. *Journal of Cardiothoracic and Vascular Anesthesia* 1992;**6**(6):674–6.

**Mongan 1992a {published data only}**

Mongan PD, Hosking MP. The role of desmopressin acetate in patients undergoing coronary artery bypass surgery. A controlled clinical trial with thromboelastographic risk stratification. *Anesthesiology* 1992b;**77**(1):38–46.

**Mongan 1992b {published data only}**

Mongan PD, Hosking MP. The role of desmopressin acetate in patients undergoing coronary artery bypass surgery. A controlled clinical trial with thromboelastographic risk stratification. *Anesthesiology* 1992;**77**(1):38–46.

**Oliver 2000 {published data only}**

Oliver WC Jr, Santrach PJ, Danielson GK, Nuttall GA, Schroeder DR, Ereth MH. Desmopressin does not reduce bleeding and transfusion requirements in congenital heart operations. *Annals of Thoracic Surgery* 2000;**70**(6):1923–30.

**Ozkisacik 2001 {published data only}**

Ozkisacik E, Islamoglu F, Posacioglu H, Yagdi T, Basarir S, Omay SB, et al. Desmopressin usage in elective cardiac surgery. *Journal of Cardiovascular Surgery (Torino)* 2001;**42**(6):741–7.

**Pleym 2004 {published data only}**

Pleym H, Stenseth R, Wahba A, Bjella L, Tromsdal A, Karevold A, et al. Prophylactic treatment with desmopressin does not reduce postoperative bleeding after coronary surgery in patients treated with aspirin before surgery. *Anesthesia and Analgesia* 2004;**98**(3):578–84.

**Reich 1991 {published data only}**

Reich DL, Hammerschlag BC, Rand JH, Weiss-Bloom L, Perucho H, Galla J, et al. Desmopressin acetate is a mild vasodilator that does not reduce blood loss in uncomplicated cardiac surgical procedures. *Journal of Cardiothoracic and Vascular Anesthesia* 1991;**5**(2):142–5.

**Reynolds 1993 {published data only}**

Reynolds LM, Nicolson SC, Jobs DR, Steven JM, Norwood WI, McGonigle ME, et al. Desmopressin does not decrease bleeding after cardiac operation in young children. *Journal of Thoracic and Cardiovascular Surgery* 1993;**106**(6):954–8.

**Rocha 1988 {published data only}**

Rocha E, Cuesta B, Paramo JA, Fernandez J, Hernandez M, Paloma MJ, et al. Can desmopressin acetate reduce bleeding in cardiac surgery with extracorporeal circulation?.. Sangre. 1987; Vol. 32:Abstract 74.  
\* Rocha E, Llorens R, Paramo JA, Arcas R, Cuesta B, Trenor AM. Does desmopressin acetate reduce blood loss after surgery in patients on cardiopulmonary bypass?. *Circulation* 1988;**77**(6):1319–23.

**Rocha 1994 {published data only}**

Hidalgo F, Llorens R, Melero JM, Arroyo JL, Rocha E. Influence of the administration of DDAVP versus aprotinin in the prevention of bleeding after cardiac surgery. *Thrombosis Research*. 1993; Vol. 70:Abstract C120.  
\* Rocha E, Hidalgo F, Llorens R, Melero JM, Arroyo JL, Paramo JA. Randomized study of aprotinin and DDAVP to reduce postoperative bleeding after cardiopulmonary bypass surgery. *Circulation* 1994;**90**(2):921–7.

**Salmenpera 1991 {published data only}**

Salmenpera M, Kuitunen A, Hynynen M, Heinonen J. Hemodynamic responses to desmopressin acetate after CABG: a double-blind trial. *Journal of Cardiothoracic and Vascular Anesthesia* 1991;**5**(2):146–9.

**Salzman 1986 {published data only}**

Millard F, Allen G, Salzman EW. Desmopressin acetate to reduce blood loss after cardiac surgery. *New England Journal of Medicine* 1986;**315**(13):834–5.

\* Salzman EW, Weinstein MJ, Weintraub RM, Ware JA, Thurer RL, Robertson L, et al. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. A double-blind randomized trial. *New England Journal of Medicine* 1986;**314**(22):1402–6.

Weinstein M, Ware JA, Troll J, Salzman E. Changes in von Willebrand factor during cardiac surgery: effect of desmopressin acetate. *Blood* 1988;**71**(6):1648–55.

**Schott 1995 {published data only}**

Schott U, Sollen C, Axelsson K, Rugarn P, Allvin I. Desmopressin acetate does not reduce blood loss during total hip replacement in patients receiving dextran. *Acta Anaesthesiologica Scandinavica* 1995;**39**(5):592–8.

**Seear 1989 {published data only}**

Seear M, Wadsworth L, Sheps S, Montgomery C, Ashmore P. The effect of desmopressin acetate (DDAVP) on post-operative blood loss after open heart surgery in children. *Blood*. 1987; Vol. 5:Abstract 380a.

\* Seear MD, Wadsworth LD, Rogers PC, Sheps S, Ashmore PG. The effect of desmopressin acetate (DDAVP) on postoperative blood loss after cardiac operations in children. *Journal of Thoracic and Cardiovascular Surgery* 1989;**98**(2): 217–9.

**Shao 2015 {published data only}**

Effects of desmopressin on blood loss and the quality of the surgical field during endoscopic sinus surgery. ClinicalTrials.gov number: NCT02125188 (accessed 23 May 2017).

\* Shao H, Kuang LT, Hou WJ, Zhang T. Effect of desmopressin administration on intraoperative blood loss and quality of the surgical field during functional endoscopic sinus surgery: a randomized, clinical trial. *BMC Anesthesiology* 2015;**15**:53.

**Sheridan 1994 {published data only}**

Sheridan DP, Card RT, Pinilla JC, Harding SM, Thomson DJ, Gauthier L, et al. Use of desmopressin acetate to reduce blood transfusion requirements during cardiac surgery in patients with acetylsalicylic-acid-induced platelet dysfunction. *Canadian Journal of Surgery* 1994;**37**(1):33–6.

**Spyt 1990 {published data only}**

\* Spyt TJ, Weerasena NA, Bain WH, Lowe GD, Rumley A. The effects of desmopressin acetate (DDAVP) on haemostasis and blood loss in routine coronary artery bypass surgery: a randomized, double-blind trial. *Perfusion* 1990;**5** (Suppl):57–61.

Weerasena NA, Spyt TJ, Rumley A, Bain WH, Lowe GD. Randomised, double-blind, placebo-controlled trial of desmopressin in routine coronary artery bypass surgery. *British Journal of Haematology*. 1990; Vol. 76:Abstract 38.

**Steinlechner 2011 {published data only}**

Steinlechner B, Spannagl M, Quehenberger P, Zeidler P, Jilma B. Patients with severe aortic valve stenosis and

impaired platelet function benefit from pre-operative desmopressin infusion. *Journal of Thrombosis and Haemostasis*. 2011; Vol. 9:Abstract P-MO-530.

\* Steinlechner B, Zeidler P, Base E, Birkenberg B, Ankersmit HJ, Spannagl M, et al. Patients with severe aortic valve stenosis and impaired platelet function benefit from preoperative desmopressin infusion. *Annals of Thoracic Surgery* 2011;**91**(5):1420–6.

**Temeck 1994 {published data only}**

Temeck BK, Bachenheimer LC, Katz NM, Coughlin SS, Wallace RB. Desmopressin acetate in cardiac surgery: a double-blind, randomized study. *Southern Medical Journal* 1994;**87**(6):611–5.

**Theroux 1997 {published data only}**

Theroux MC, Corrdry DH, Tietz AE, Miller F, Peoples JD, Kettrick RG. A study of desmopressin and blood loss during spinal fusion for neuromuscular scoliosis: a randomized, controlled, double-blinded study. *Anesthesiology* 1997;**87** (2):260–7.

**Wingate 1992a {published data only}**

Wingate GF, Lewis VL Jr, Green D, Wiedrich TA, Koenig WJ. Desmopressin decreases operative blood loss in spinal cord injury patients having flap reconstruction of pelvic pressure sores. *Plastic and Reconstructive Surgery* 1992;**89** (2):279–82.

**Wingate 1992b {published data only}**

Wingate GF, Lewis VL Jr, Green D, Wiedrich TA, Koenig WJ. Desmopressin decreases operative blood loss in spinal cord injury patients having flap reconstruction of pelvic pressure sores (low risk procedures only). *Plastic and Reconstructive Surgery* 1992;**89**(2):279–82.

**Wong 2003 {published data only}**

Wong AY, Irwin MG, Hui TW, Fung SK, Fan ST, Ma ES. Desmopressin does not decrease blood loss and transfusion requirements in patients undergoing hepatectomy. *Canadian Journal of Anaesthesia* 2003;**50**(1):14–20.

**Zohar 2001 {published data only}**

Zohar E, Fredman B, Ellis MH, Ifrach N, Stern A, Jedeikin R. A comparative study of the postoperative allogeneic blood-sparing effects of tranexamic acid and of desmopressin after total knee replacement. *Transfusion* 2001;**41**(10):1285–9.

**References to studies excluded from this review****EudraCT Number: 2009-017265-33 {published data only}**

Invloed van voeding op farmacokinetiek en -dynamiek van desmopressine tablet in vergelijking met desmopressine MELT-vorm. EudraCT Number: 2009-017265-33 (accessed 23 May 2017).

**Flordal 1993 {published data only}**

Flordal PA, Sahlin S. Use of desmopressin to prevent bleeding complications in patients treated with aspirin. *The British Journal of Surgery* 1993;**80**(6):723–4.

**Forero 2003 {published data only}**

Forero CF, Ramirez JH, Rojas G, Sierra JC. Effects of desmopressin on bleeding in patients undergoing surgery

- to correct scoliosis [Efectos de la desmopresina sobre el sangrado en pacientes sometidos a cirugía para corregir escoliosis]. *Revista Colombiana de Ortopedia y Traumatología* 2003;17(4):22–7.
- Gandhi 2014** *{published data only}*  
Gandhi CD, Bulsara KR, Fifi J, Kass-Hout T, Grant RA, Delgado Almandoz JE, et al. Platelet function inhibitors and platelet function testing in neurointerventional procedures. *Journal of Neurointerventional Surgery* 2014;6(8):567–77.
- Haith 1993** *{published data only}*  
Haith LR Jr, Patton ML, Goldman WT, McCutchan KM. Diminishing blood loss during operation for burns. *Surgery, Gynecology & Obstetrics* 1993;176(2):119–23.
- Hansen 1980** *{published data only}*  
Hansen PE, Hansen JH. Desmopressin (DDAVP) in lumbar puncture. *British Medical Journal* 1980; Vol. 280, issue 6223:1146.
- Hooghiemstra 2012** *{published data only}*  
Hooghiemstra E, Rademaker E, Stooker W, Lauwers H, Wester J, Rademaker B. Desmopressin haemostatic therapy during aortic valve replacement for severe aortic valve stenosis: effects on blood-loss, use of blood products and postoperative recovery. *Applied Cardiopulmonary Physiology*. 2012:Abstract P-26.
- IRCT2013092114728N1** *{published data only}*  
The effect of desmopressin in reducing bleeding after cardiac surgery in patients receiving antiplatelet drugs in comparison with placebo. Iranian Registry of Clinical Trials number: IRCT2013092114728N1 (accessed 23 May 2017).
- IRCT201409304345N3** *{published data only}*  
Effect of desmopressin on bleeding in coronary artery bypass graft surgery patients undergoing cardiopulmonary bypass pump with antiplatelet drugs. Iranian Registry of Clinical Trials number: IRCT201409304345N3 (accessed 23 May 2017).
- Johnson 1990** *{published data only}*  
Johnson RG, Murphy JM. The role of desmopressin in reducing blood loss during lumbar fusions. *Surgery, Gynecology & Obstetrics* 1990;171(3):223–6.
- Karger 2012** *{published data only}*  
\* Karger R, Reuter K, Rohlf J, Nimsky C, Sure U, Kretschmer V. The Platelet Function Analyzer (PFA-100) as a screening tool in neurosurgery. *ISRN Hematology* 2012; 2012:839242.  
Karger R, Reuter K, Rohlf J, Sure U, Kretschmer V. The platelet function analyzer (PFA-100) as a screening tool in neurosurgery. Symposium of the Nederlandse Vereniging voor Thrombose en Hemostase (NVTH). 2010:Abstract P10-09.
- Keyl 2011** *{published data only}*  
Keyl C, Kmita E, Kueri S, Zietak T, Trenk D. Effects of aspirin and desmopressin on platelet reactivity in patients undergoing cardiac surgery with extracorporeal circulation. *Thrombosis and Haemostasis* 2011;105(1):113–21.
- Kim 2015** *{published data only}*  
Kim JH, Baek CH, Min JY, Kim JS, Kim SB, Kim H. Desmopressin improves platelet function in uremic patients taking antiplatelet agents who require emergent invasive procedures. *Annals of Hematology* 2015;94(9):1457–61.
- Lozano 1999** *{published data only}*  
Lozano M, Escolar G, Bellucci S, Monteagudo J, Pico M, Ordinas A, et al. L-Deamino (8-D-arginine) vasopressin infusion partially corrects platelet deposition on subendothelium in Bernard-Soulier syndrome: the role of factor VIII. *Platelets* 1999;10(1):41–5.
- Mannucci 1994** *{published data only}*  
Mannucci PM, Carlsson S, Harris AS. Desmopressin, surgery and thrombosis. *Thrombosis and Haemostasis* 1994; Vol. 71, issue 1:154–5.
- Mirmansoori 2016** *{published data only}*  
Mirmansoori A, Farzi F, Sedighinejad A, Imantalab V, Mohammadzadeh A, Atrkar Roushan Z, et al. The effect of desmopressin on the amount of bleeding in patients undergoing coronary artery bypass graft surgery with a cardiopulmonary bypass pump after taking anti-platelet medicine. *Anesthesiology and Pain Medicine* 2016;6(5): e39226.
- Myrvang 2011** *{published data only}*  
Myrvang H. Biopsy: desmopressin reduces risk of bleeding after percutaneous kidney biopsy. *Nature Reviews. Nephrology* 2011;7(6):304.
- NCT00835211** *{published data only}*  
Desmopressin acetate 0.2 mg tablets, fasting. ClinicalTrials.gov number: NCT00835211 (accessed 23 May 2017).
- NCT01218074** *{published data only}*  
Platelets Antiaggregation Control Enhancement (PACE) study. ClinicalTrials.gov number: NCT01218074 (accessed 23 May 2017).
- NCT01382134** *{published data only}*  
Effect of aspirin, hemodilution and desmopressin on platelet dysfunction. ClinicalTrials.gov number: NCT01382134 (accessed 23 May 2017).
- NCT01606072** *{published data only}*  
Perioperative use of desmopressin (DDAVP) in breast cancer. ClinicalTrials.gov number: NCT01606072 (accessed 23 May 2017).
- NCT01623206** *{published data only}*  
Desmopressin (DDAVP) in patients with colorectal cancer and rectal bleeding. ClinicalTrials.gov number: NCT01623206 (accessed 23 May 2017).
- Nilsen 1984** *{published data only}*  
Nilsen DW, Haerem J, Westheim A, Skjennald A, Grendahl H, Godal HC. Venous thrombosis following diagnostic transvenous catheterization by percutaneous catheter insertion: an evaluation of desmopressin as a thromboprophylactic agent. *Thrombosis and Haemostasis* 1984;52(2):121–3.

**Ozal 2002 {published data only}**

Ozal E, Kuralay E, Bingol H, Cingoz F, Ceylan S, Tatar H. Does tranexamic acid reduce desmopressin-induced hyperfibrinolysis?. *The Journal of Thoracic and Cardiovascular Surgery* 2002;**123**(3):539–43.

**Palaia 2001 {published data only}**

Palaia DA, Rosenberg MH, Bonanno PC. The use of DDAVP desmopressin reduces the incidence of microhematomas after faciaplasty. *Annals of Plastic Surgery* 2001;**46**(5):463–6.

**Spiro 1982 {published data only}**

Spiro F, Polakow E. The effect of desmopressin on post-lumbar puncture/myelography morbidity. *South African Medical Journal* 1982; Vol. 62, issue 13:428.

**Stanca 2010 {published data only}**

Prevention of bleeding in patients with cirrhosis undergoing dental extraction. ClinicalTrials.gov number: NCT00816127 (accessed 23 May 2017).

\* Stanca CM, Montazem AH, Lawal A, Zhang JX, Schiano TD. Intranasal desmopressin versus blood transfusion in cirrhotic patients with coagulopathy undergoing dental extraction: a randomized controlled trial. *Journal of Oral and Maxillofacial Surgery* 2010;**68**(1):138–43.  
Stanca CM, Montazem AH, Zhang JH, Lawal A, Schiano TD. Intranasal desmopressin is effective in preventing bleeding after dental extraction in cirrhotic patients having moderate degrees of coagulopathy. *Hepatology*. 2007; Vol. 46:Abstract 568A.

**Weinberg 2015 {published data only}**

Weinberg RS, Grecco MO, Ferro GS, Seigelshifer DJ, Perroni NV, Terrier FJ, et al. A phase II dose-escalation trial of perioperative desmopressin (1-desamino-8-d-arginine vasopressin) in breast cancer patients. *SpringerPlus* 2015;**4**: 428.

**Zielske 2003 {published data only}**

Zielske D, Seyfert UT, Heim MU, Mrowietz C, Jung F. Effects of desmopressin on the primary haemostasis impaired by clopidogrel. *Annals of Hematology*. 2003; Vol. 82:Abstract 338.

**Zotz 2009 {published data only}**

Zotz RB. A stratified metaanalysis of desmopressin (DDAVP) for minimising perioperative allogeneic blood transfusion. *Blood*. 2009; Vol. 114:Abstract 1306.

**References to studies awaiting assessment****Jahangirifard 2017 {published data only}**

Comparison of desmopressin with placebo, in hemostasis after heart transplant surgery. Iranian Registry of Clinical Trials number: IRCT2015010512642N8 (accessed 23 May 2017).

\* Jahangirifard A, Razavi MR, Ahmadi ZH, Forozeshfard M. The effect of desmopressin on the amount of bleeding and transfusion requirements in patients undergoing heart transplant surgery. *Basic & Clinical Pharmacology & Toxicology* 2017; epub ahead of print. [DOI: 10.1111/bcpt.12780]

**References to ongoing studies****ISRCTN12845429 {published data only}**

DRIVE - Desmopressin for procedures or radiological interventions. ISRCTN number: ISRCTN12845429 (accessed 23 May 2017).

**NCT00885924 {published data only}**

Desmopressin as treatment for postoperative bleeding after cardiac surgery. ClinicalTrials.gov number: NCT00885924 (accessed 23 May 2017).

**NCT01982760 {published data only}**

DDAVP in the reduction of post-operative ecchymosis in rhinoplasty. ClinicalTrials.gov number: NCT01982760 (accessed 23 May 2017).

**NCT02084342 {published data only}**

Study of DDAVP combined with TXA on the blood loss and transfusion need during and after scoliosis correction surgery. ClinicalTrials.gov number: NCT02084342 (accessed 23 May 2017).

**Additional references****American Society of Anesthesiologists 2015**

American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology* 2015;**122** (2):241–75.

**Carson 2002**

Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 2002;**42**(7): 812–8.

**Cattaneo 1995**

Cattaneo M, Harris AS, Stromberg U, Mannucci PM. The effect of desmopressin on reducing blood loss in cardiac surgery - a meta-analysis of double-blind, placebo-controlled trials. *Thrombosis and Haemostasis* 1995;**74**(4): 1064–70.

**Crescenzi 2008**

Crescenzi G, Landoni G, Biondi-Zoccai G, Pappalardo F, Nuzzi M, Bignami E, et al. Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. *Anesthesiology* 2008;**109**(6): 1063–76.

**Deeks 2011**

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

**Delaney 2016**

Delaney M, Wendel S, Bercovitz RS, Cid J, Cohn C, Dunbar NM, et al. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* 2016;**388**:2825–36.

**Desborough 2016a**

Desborough MJ, Smethurst PA, Estcourt LJ, Stanworth SJ. Alternatives to allogeneic platelet transfusion. *British Journal of Haematology* 2016;**175**(3):381–92.

**Egger 1997**

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

**Estcourt 2017**

Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. Guidelines for the use of platelet transfusions. A British Society for Haematology Guideline. *British Journal of Haematology* 2017;**176**:365–94. [DOI: 10.1111/bjh.14423]

**Franchini 2007**

Franchini M. The use of desmopressin as a hemostatic agent: a concise review. *American Journal of Hematology* 2007;**82**(8):731–5.

**Fremes 1994**

Fremes SE, Wong BI, Lee E, Mai R, Christakis GT, McLean RF, et al. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. *Annals of Thoracic Surgery* 1994;**58**(6):1580–8.

**Harbord 2006**

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20):3443–57.

**Henry 2011**

Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD001886.pub4]

**Higgins 2011a**

Higgins JP, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

**Higgins 2011b**

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

**Higgins 2011c**

Higgins JP, Deeks JJ, Altman DG, editor(s). Chapter 16: Special topics in Statistics. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

**Higgins 2016**

Higgins JPT, Lasserson T, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews. *Methodological Expectations of Cochrane Intervention Reviews*. London: Cochrane, 2016.

**Holst 2015**

Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *BMJ* 2015;**350**:h1354.

**Kalambokis 2007**

Kalambokis G, Manousou P, Vibhakorn S, Marelli L, Cholongitas E, Senzolo M, et al. Transjugular liver biopsy - indications, adequacy, quality of specimens, and complications - a systematic review. *Journal of Hepatology* 2007;**47**(2):284–94.

**Kaufmann 2003**

Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *Journal of Thrombosis and Haemostasis* 2003;**1**(4):682–9.

**Keeling 2008**

Keeling D, Tait C, Makris M. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology. *Haemophilia* 2008;**14**(4):671–84.

**Ker 2012**

Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;**344**:e3054.

**Kozek-Langenecker 2013**

Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *European Journal of Anaesthesia* 2013;**30**(6):270–382.

**Köhler 1988**

Köhler M, Harris A. Pharmacokinetics and haematological effects of desmopressin. *European Journal of Clinical Pharmacology* 1988;**35**(3):281–5.

**Laffan 2014**

Laffan MA, Lester W, O'Donnell JS, Will A, Tait RC, Goodeve A, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *British Journal of Haematology* 2014;**167**(4):453–65.

**Laupacis 1997**

Laupacis A, Fergusson D. Drugs to minimise perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. *Anaesthesia and Analgesia* 1997;**85**(6):1258–67.

**Lefebvre 2011**

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [handbook.cochrane.org](http://handbook.cochrane.org).

**Levi 1999**

Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJM, Briet E, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999;**354**(9194): 1940–7.

**Mannucci 2004**

Mannucci PM. Treatment of von Willebrand's disease. *New England Journal of Medicine* 2004;**351**(7):683–94.

**Mehta 2009**

Mehta RH, Sheng S, O'Brien SM, Grover FL, Gammie JS, Ferguson TB, et al. Reoperation for bleeding in patients undergoing coronary artery bypass surgery: incidence, risk factors, time trends, and outcomes. *Circulation. Cardiovascular Quality and Outcomes* 2009;**2**(6):583–90.

**NICE 2014**

National Institute for Health and Care Excellence. Detecting, managing and monitoring haemostasis: viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems). NICE diagnostics guidance 13, available from: [www.nice.org.uk/dg13](http://www.nice.org.uk/dg13) 2014 (accessed 23 May 2017).

**Padhi 2015**

Padhi S, Kemmis-Betty S, Rajesh S, Hill J, Murphy MF, Guideline Development Group. Blood transfusion: summary of NICE guidance. *BMJ* 2015;**351**:h5832.

**RevMan 2014 [Computer program]**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Rossaint 2016**

Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Critical Care* 2016;**20**(1):100.

**Schünemann 2011a**

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [handbook.cochrane.org](http://handbook.cochrane.org).

**Schünemann 2011b**

Schünemann HJ, Oxman AD, Vist GE, Higgins JP, Deeks JJ, Glasziou P, et al. Cochrane Applicability and Recommendations Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic*

*Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [handbook.cochrane.org](http://handbook.cochrane.org).

**Smith 1989**

Smith TJ, Gill JC, Ambruso DR, Hathaway WE. Hyponatraemia and seizures in young children given DDAVP. *American Journal of Hematology* 1989;**31**(3): 199–202.

**Society of Thoracic Surgeons 2011**

Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Annals of Thoracic Surgery* 2011;**91**(3):944–82.

**Sterne 2011**

Sterne JA, Egger M, Moher D, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [handbook.cochrane.org](http://handbook.cochrane.org).

**Svensson 2014**

Svensson P, Bergqvist PB, Juul KV, Berntorp E. Desmopressin in the treatment of haematological disorders and in the prevention of surgical bleeding. *Blood Reviews* 2014;**28**(3):95–102.

**Tinegate 2016**

Tinegate H, Pendry K, Murphy M, Babra P, Grant-Casey J, Hopkinson C, et al. Where do all the red blood cells (RBCs) go? Results of a survey of RBC use in England and North Wales in 2014. *Transfusion* 2016;**56**(1):139–45.

**TSA 2011 [Computer program]**

Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark. TSA v0.9. Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, 2012.

**Walters 2016**

Walters G. NHSBT Portfolio of Blood Components and Guidance for their Clinical Use. SPECIFICATION SPN223/6.2. <http://hospital.blood.co.uk/media/28748/spn223.pdf> 2016 (accessed 23 May 2017).

**World Health Organization 2015**

World Health Organization. Blood safety and availability. Fact sheet No 279. Available from: [www.who.int/mediacentre/factsheets/fs279/en](http://www.who.int/mediacentre/factsheets/fs279/en) (accessed 17 May 2016).

**References to other published versions of this review****Carless 2004**

Carless PA, Henry DA, Moxey AJ, O'Connell D, McClelland B, Henderson KM, et al. Desmopressin use for minimising allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD001884.pub2]

**Desborough 2016**

Desborough M, Estcourt LJ, Doree C, Trivella M, Stanworth SJ. Desmopressin use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2016, Issue 2. [DOI: 10.1002/14651858.CD001884.pub2]

**Desborough 2017**

Desborough MJ, Oakland KA, Landoni G, Crivellari M, Doree C, Estcourt LJ, et al. Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents:

a systematic review and meta-analysis of randomized controlled trials. *Journal of Thrombosis and Haemostasis* 2017;**15**:263–72.

**Henry 1998**

Henry DA, Moxey AJ, Carless PA, O'Connell D, McClelland B, Henderson KM, et al. Desmopressin for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 1998, Issue 12. [DOI: 10.1002/14651858.CD001884]

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Aida 1991a

|               |   |
|---------------|---|
| Methods       | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Japan</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants  | <p><b>Inclusion criteria:</b> adults undergoing cardiac surgery with cardiopulmonary bypass with a membrane oxygenator</p> <p><b>Exclusion criteria:</b> not reported</p> <p><b>Number of participants randomised:</b> 9</p> <p><b>Number of participants analysed:</b> 9</p> <p><b>Age:</b> desmopressin arm: <math>52 \pm 5</math> years; placebo arm: <math>57 \pm 5</math> years</p> <p><b>Gender:</b> desmopressin arm: male 2, female 3; placebo arm: male 3, female 1</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: combined aortic valve replacement (AVR) and mitral valve replacement (MVR) 1, combined AVR and MVR and transoesophageal atrial pacing 2, MVR and transoesophageal atrial pacing 1, AVR and open mitral commissurotomy (OMC) 1</li> <li>Placebo arm: coronary artery bypass graft (CABG) 3, MVR 1</li> </ul> <p><b>Duration of surgery:</b> desmopressin arm: <math>378 \pm 54</math> minutes; placebo arm: <math>444 \pm 59</math> minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: <math>173 \pm 42</math> minutes; placebo arm: <math>167 \pm 27</math> minutes</p> <p><b>Emergency cases:</b> not reported</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (<math>0.3 \mu\text{g/kg}</math> intravenously in 50 mL 0.9% saline) 15 minutes after heparin reversal over 20 minutes (n = 5)</p> <p><b>Comparator arm:</b> placebo details not reported (n = 4)</p>   |
| Outcomes      | <p><b>Primary outcome:</b> blood loss 24 hours postoperatively (method for measurement not reported)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>Red cell transfusion 24 hours postoperatively</li> <li>Changes in laboratory measures of haemostasis</li> </ul>  |
| Notes         | <p>Translated from Japanese to English by Junko Kiriya. A single study was split into 4 groups, with randomisation to DDAVP or placebo, and randomisation to membrane oxygenation or bubble oxygenation. Results have been presented separately for the 2 types</p>   |

**Aida 1991a** (Continued)

|  |   |  |
|--|---|--|
|  | of oxygenators (see <a href="#">Aida 1991b</a> below). Blood loss and red cell transfusion requirements were reported as mL/kg, and no weights were reported. Consequently, results from this trial have been reported qualitatively and were not included in meta-analysis |  |
| <i><b>Risk of bias</b></i>                             |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>                                     |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement                           |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement                           |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Insufficient information for judgement                           |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | Insufficient information for judgement                           |
| Incomplete outcome data<br>All outcomes                | Low risk  | All participants accounted for in the final analysis             |
| Selective outcome reporting                            | Unclear risk  | Protocol not available   |
| Other sources of bias                                  | High risk   | More pre-randomisation bleeding in placebo arm than in DDAVP arm |

**Aida 1991b**

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Japan<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> adults undergoing cardiac surgery with cardiopulmonary bypass with a bubble oxygenator<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> 11<br><b>Number of participants analysed:</b> 11<br><b>Age:</b> desmopressin arm: 60 ± 8 years; placebo arm: 57 ± 17 years<br><b>Gender:</b> desmopressin arm: male 4, female 1; placebo arm: male 2, female 4<br><b>Type of surgery</b> <ul style="list-style-type: none"> <li>Desmopressin arm: MVR 2, OMC 1, maze procedure 1, combined AVR and MVR 1</li> <li>Placebo arm: CABG 3, MVR 2, combined MVR and AVR 1</li> </ul> <b>Duration of surgery:</b> desmopressin arm: 309 ± 96 minutes; placebo arm: 369 ± 87 minutes<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 137 ± 80 minutes; placebo arm: 148 ± 25 minutes |

|  |   |   |
|--|---|---|
|  | <b>Emergency cases:</b> not reported<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported   |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 μg/kg intravenously in 50 mL 0.9% saline) 15 minutes after heparin reversal over 20 minutes (n = 5)<br><b>Comparator arm:</b> placebo details not reported (n = 6)  |   |
| Outcomes   | <b>Primary outcome:</b> blood loss 24 hours postoperatively (method for measurement not reported)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Red cell transfusion 24 hours postoperatively</li><li>• Changes in laboratory measures of haemostasis</li></ul>  |   |
| Notes  | Translated from Japanese to English by Junko Kiriya. A single study was split into 4 groups with randomisation to DDAVP or placebo, and randomisation to membrane oxygenation or bubble oxygenation. Results have been presented separately for the 2 types of oxygenators (see <a href="#">Aida 1991a</a> above). Blood loss and red cell transfusion requirements were reported as mL/kg, and no weights were reported. Consequently, results from this trial have been reported qualitatively and were not included in meta-analysis |   |
| <b>Risk of bias</b>                                    |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Insufficient information for judgement  |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | Insufficient information for judgement  |
| Incomplete outcome data<br>All outcomes                | Low risk  | All participants accounted for in the final analysis                                  |
| Selective outcome reporting                            | Unclear risk  | Protocol not available  |
| Other sources of bias                                  | High risk   | More pre-randomisation in placebo arm than in DDAVP arm. Very small number randomised |

|                     |   |                       |
|---------------------|---|-----------------------|
| Methods             | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> orthopaedic surgery: scoliosis<br><b>Country:</b> Turkey<br><b>Registration:</b> not prospectively registered   |                       |
| Participants        | <b>Inclusion criteria:</b> idiopathic or congenital scoliosis requiring surgical intervention (anterior, posterior, or sequential surgery)<br><b>Exclusion criteria:</b> people with malformations, especially of the urinary system<br><b>Number of participants randomised:</b> 40<br><b>Number of participants analysed:</b> 40<br><b>Age:</b> desmopressin arm: 14.8 ± 4 years; placebo arm: 14.5 ± 3 years<br><b>Gender:</b> desmopressin arm: male 5, female 13; placebo arm: male 6, female 16<br><b>Type of surgery</b> <ul style="list-style-type: none"><li>Desmopressin arm: all undergoing scoliosis surgery: anterior 5, posterior 7, and sequential 6</li><li>Placebo arm: all undergoing scoliosis surgery: anterior 7, posterior 9, and sequential 6</li></ul> <b>Duration of surgery:</b> desmopressin arm: 241.7 ± 82.2 minutes; placebo arm: 202 ± 60.3 minutes<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> not reported |                       |
| Interventions       | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 100 mL 0.9% saline) at induction of anaesthesia over 20 minutes (n = 18)<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline) at induction of anaesthesia over 20 minutes (n = 22)   |                       |
| Outcomes            | <b>Primary outcomes</b> <ul style="list-style-type: none"><li>Blood loss perioperatively and up to 24 hours (measured by counting surgical sponges, measuring volume in cell saver and drain output)</li><li>Urine output 24 hours postoperatively</li></ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"><li>Red cell transfusion 24 hours postoperatively</li><li>Changes in laboratory measures of haemostasis</li></ul>  |                       |
| Notes               | Blood loss and red cell transfusion requirements reported as median and interquartile range, so not included in meta-analysis. Red cell transfusion reported in mL and converted to units with assumption that 300 mL is equivalent to 1 unit   |                       |
| <i>Risk of bias</i> |   |                       |
| Bias                | Authors' judgement  | Support for judgement |

**Alanay 1999** (Continued)

|  |              |  |
|--|--------------|--|
| Sequence Generation                                    | Unclear risk | Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk | Allocation determined by one of the investigators who was not involved in outcome assessment. No information on how allocation was concealed   |
| Blinding of participants and personnel<br>All outcomes | Low risk     | Quote: "The solutions were prepared by one of the current authors (AA) who was not involved in the evaluation of the study parameters. The patient, surgeon and anaesthesiologist remained blind to the type of treatment" |
| Blinding of outcome assessors<br>All outcomes          | Low risk     | Quote: "The solutions were prepared by one of the current authors (AA) who was not involved in the evaluation of the study parameters. The patient, surgeon and anaesthesiologist remained blind to the type of treatment" |
| Incomplete outcome data<br>All outcomes                | Low risk     | Reported all outcomes on all participants  |
| Selective outcome reporting                            | Unclear risk | Presented numerical data only for total blood loss (up to 24 hours) but also collected data on 0, 30, 60, 90, 120, and 150 minutes. These are displayed graphically only with a single P value                             |
| Other sources of bias                                  | High risk    | Five participants were re-randomised   |

**Andersson 1990**

|              |  |
|--------------|--|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Sweden<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> CABG with 3 (or more) veins or internal mammary arterial bypass grafts<br><b>Exclusion criteria:</b> previous cardiac surgery; previous coagulation disorders; coumarin anticoagulants, heparin, or acetylsalicylic acid within 7 days before surgery<br><b>Number of participants randomised:</b> 100<br><b>Number of participants analysed:</b> 19<br><b>Age:</b> desmopressin arm: 57 ± 12 years; placebo arm: 61 ± 5 years<br><b>Gender:</b> desmopressin arm: male 8, female 2; placebo arm: male 8, female 1<br><b>Type of surgery:</b> all undergoing CABG |

|  |   |  |
|--|---|--|
|  | <b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 70 ± 23 minutes; placebo arm: 69 ± 12 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |  |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) 15 minutes after heparin reversal over 15 minutes (n = 10)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) 15 minutes after heparin reversal over 15 minutes (n = 9)  |  |
| Outcomes   | <b>Primary outcome:</b> changes in laboratory measures of haemostasis<br><b>Secondary outcome:</b> total blood loss (measured by drain output)  |  |
| Notes  |   |  |
| <i>Risk of bias</i>                                    |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk  | Quote: “The treatment code was not broken until all five blocks were completed”. However method of concealment was not reported  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Described as a double-blind study, but method of blinding was not reported. Participants were given DDAVP or placebo; however, facial flushing may have been observed or experienced |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | Double-blind, placebo-controlled trial; method of blinding not reported but placebo available. However, facial flushing may have been observed                                       |
| Incomplete outcome data<br>All outcomes                | High risk   | Additional unpublished data for the whole study. Paper reports only 19 of the 100 participants   |

Andersson 1990 (Continued)

|                             |              |   |
|-----------------------------|--------------|---|
| Selective outcome reporting | Unclear risk | Protocol not available  |
| Other sources of bias       | High risk    | Funded in part by Ferring AB, Malmo, Sweden (a manufacturer of DDAVP) |

Ansell 1992

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> multi-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants  | <p><b>Inclusion criteria:</b> age 18 to 75 years; elective cardiac valve operations with, or without, coronary artery bypass</p> <p><b>Exclusion criteria:</b> recent myocardial infarction (timing not specified); unstable angina; deep vein thrombosis or pulmonary embolism; history of bleeding diathesis or platelet defect; unstable haemodynamic status; pertinent drug allergy; pregnancy</p> <p><b>Number of participants randomised:</b> 92</p> <p><b>Number of participants analysed:</b> 83</p> <p><b>Age:</b> desmopressin arm: 61.9 ± 10.7 years; placebo arm: 60.1 ± 9.2 years</p> <p><b>Gender:</b> desmopressin arm: male 24, female 17; placebo arm: male 21, female 21</p> <p><b>Type of surgery:</b> all valve replacements, but not possible to determine how many in each category</p> <p><b>Duration of surgery:</b> desmopressin arm: 261 ± 70 minutes; placebo arm: 242.5 ± 61.4 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 118.6 ± 39 minutes; placebo arm: 111.8 ± 41.5 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> desmopressin arm: epsilon-aminocaproic acid (dose not specified) 1; placebo arm: none</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 41)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 42)</p>   |
| Outcomes      | <p><b>Primary outcome:</b> total blood loss (measured by drain output)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Volume of red cell transfusions</li> <li>• Number of participants receiving any red cell transfusion</li> <li>• Reoperation due to bleeding</li> <li>• All-cause mortality</li> </ul>   |

|  |                         |  |
|--|-------------------------|--|
|  | ● Thromboembolic events |  |
| Notes  |                         |  |
| <i>Risk of bias</i>                                    |                         |  |
| Bias   | Authors' judgement      | Support for judgement  |
| Sequence Generation                                    | Low risk                | Quote: "Randomisation was provided by a series of computer-generated random numbers"   |
| Allocation concealment                                 | Unclear risk            | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Unclear risk            | Quote: "All study medication was dispensed in a blinded fashion by the investigator or hospital pharmacy and was administered in a blinded fashion". Medication dispensing was performed by the investigator, so unclear if blinding could be maintained |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk            | Quote: "All study medication was dispensed in a blinded fashion by the investigator or hospital pharmacy and was administered in a blinded fashion". Medication dispensing was performed by the investigator, so unclear if blinding could be maintained |
| Incomplete outcome data<br>All outcomes                | High risk               | 92 participants enrolled and 9 excluded from analysis: 7 did not receive study drug, 1 inadvertently received drug preoperatively, and 1 had no blood loss data collected (5 in DDAVP arm, 4 in placebo)   |
| Selective outcome reporting                            | Unclear risk            | Protocol not available   |
| Other sources of bias                                  | High risk               | One participant in the DDAVP arm received epsilon-aminocaproic acid. Three participants in the DDAVP arm and 1 participant on the placebo arm received another dose of DDAVP. Funded in part by Rorer Central Research (a manufacturer of DDAVP)         |

|                     |  |
|---------------------|--|
| Methods             | <p><b>Type of study:</b> multi-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Italy</p> <p><b>Registration:</b> prospectively registered: NCT00337766</p>   |
| Participants        | <p><b>Inclusion criteria:</b> age <math>\geq 18</math> years; elective cardiac surgery; diffuse intraoperative bleeding without a surgical source <i>or</i> excessive postoperative bleeding from chest tubes defined as 100 mL over 30 minutes, or 2 mL/kg/h for at least 2 hours</p> <p><b>Exclusion criteria:</b> lack of informed consent; myocardial infarction within previous 7 days</p> <p><b>Number of participants randomised:</b> 135</p> <p><b>Number of participants analysed:</b> 135</p> <p><b>Age:</b> desmopressin arm: <math>64 \pm 13.3</math> years; placebo arm: <math>62 \pm 13.2</math> years</p> <p><b>Gender:</b> desmopressin arm: male 50, female 18; placebo arm: male 50, female 17</p> <p><b>Type of surgery:</b> all cardiac surgery</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> not reported</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> desmopressin arm: 25; placebo arm: 29</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> desmopressin arm: 1; placebo arm: 1</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> a slow intravenous bolus of 1 g tranexamic acid was administered before surgery to all participants. At 1 participating centre, this was followed by a continuous infusion of 400 mg/h during the surgical intervention. At the other 2 participating centres, a further dose of 500 mg was administered following cardiopulmonary bypass</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> 1 unit of red cells transfused if haemoglobin <math>&lt; 80</math> g/L</p> |
| Interventions       | <p><b>Intervention arm:</b> DDAVP (<math>0.3 \mu\text{g/kg}</math> intravenously in 50 mL 0.9% saline) administered over 20 minutes in the event of excessive bleeding (<math>n = 68</math>)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) administered over 20 minutes in the event of excessive bleeding (<math>n = 67</math>)</p>   |
| Outcomes            | <p><b>Primary outcome:</b> total number of participants receiving a red cell transfusion</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Total volume of red cells transfused</li> <li>• Total blood loss (measured by drain output)</li> <li>• All-cause mortality</li> <li>• Thrombotic events</li> <li>• Clinically significant hypotension</li> </ul>  |
| Notes               | <p>Trial was stopped after 135/200 participants recruited owing to futility. Total volume of red cells transfused and total blood loss were reported as median and interquartile range, which could not be incorporated into meta-analysis so this trial has been reported narratively</p>   |
| <i>Risk of bias</i> |  |

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Low risk           | Quote: "A computer-generated randomization sequence stratified by center with blocks of 20 was used"  |
| Allocation concealment                                 | Low risk           | Opaque, sealed envelopes that were sequentially numbered  |
| Blinding of participants and personnel<br>All outcomes | Low risk           | Quote: "Patients, managing physicians, and nurses were blinded to treatment assignment for the whole duration of the study. Desmopressin and placebo were prepared in a separate room, as colourless fluids in unlabelled bottles, by personnel who was not involved in patients' management and data collection" |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Quote: "Patients, managing physicians, and nurses were blinded to treatment assignment for the whole duration of the study. Desmopressin and placebo were prepared in a separate room, as colourless fluids in unlabelled bottles, by personnel who was not involved in patients' management and data collection" |
| Incomplete outcome data<br>All outcomes                | Low risk           | All participants included in final analysis   |
| Selective outcome reporting                            | Low risk           | All prespecified outcomes reported  |
| Other sources of bias                                  | Low risk           | No other clear sources of bias. Supported by departmental funds only  |

## Brown 1989

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> elective CABG surgery<br><b>Exclusion criteria:</b> none reported<br><b>Number of participants randomised:</b> 20<br><b>Number of participants analysed:</b> 19<br><b>Age:</b> desmopressin arm: 61.7 ± 8.1 years; placebo arm: 62.5 ± 6.9 years<br><b>Gender:</b> desmopressin arm: male 8, female 2; placebo arm: male 6, female 3 |

|  |   |  |
|--|---|--|
|  | <b>Type of surgery:</b> all CABG surgery<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 109 ± 33 minutes; placebo arm: 89 ± 38 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> desmopressin arm: 6; placebo arm: 5<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> not reported   |  |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 0.9% saline (volume not reported)) immediately after heparin reversal over 10 minutes (n = 10)<br><b>Comparator arm:</b> placebo (0.9% saline (volume not reported)) immediately after heparin reversal over 10 minutes (n = 9)  |  |
| Outcomes   | <b>Primary outcome:</b> changes in laboratory measures of haemostasis<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Volume of red cells transfused intraoperatively and in total</li><li>• Intraoperative blood loss and total blood loss (measured by volume in suction reservoir, weighing surgical sponges, estimated blood loss on surgical drapes, drain output, and estimated bleeding into bandages)</li><li>• Reoperation due to bleeding</li><li>• Thromboembolic events</li><li>• Clinically significant hypotension (not formally an outcome but data included in final report)</li></ul> |  |
| Notes  | Volume of red cells reported as mL rather than in units. Converted into units assuming 1 unit is equivalent to 300 mL   |  |
| <b><i>Risk of bias</i></b>                             |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | High risk   | Infusion given over 10 minutes, resulting in notable hypotension and compromising blinding |
| Blinding of outcome assessors<br>All outcomes          | High risk   | Infusion given over 10 minutes, resulting in notable hypotension and compromising blinding |

**Brown 1989** (Continued)

|   |              |   |
|---|--------------|---|
| Incomplete outcome data<br>All outcomes | Low risk     | 20 randomised, 1 excluded owing to 'TEG technical error'; however, this is unlikely to bias results |
| Selective outcome reporting             | Unclear risk | Protocol not available  |
| Other sources of bias                   | Unclear risk | Insufficient information for judgement  |

**Casas 1995**

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single-centre, 3-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Spain</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> age <math>\geq 18</math> years; CABG, valve replacement, annuloplasty, combined valve replacement and CABG, or closure of atrial septal defect</p> <p><b>Exclusion criteria:</b> emergency operations; history of a bleeding disorder; allergy or previous exposure to aprotinin</p> <p><b>Number of participants randomised:</b> 149</p> <p><b>Number of participants analysed:</b> 140</p> <p><b>Age:</b> desmopressin arm: <math>58 \pm 12</math> years; placebo arm: <math>54 \pm 12</math> years; aprotinin arm: <math>57 \pm 10</math> years</p> <p><b>Gender:</b> desmopressin arm: male 33, female 17; placebo arm: male 31, female 20; aprotinin arm: male 31, female 17</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>• Desmopressin arm: CABG 19, valve replacement 24, reoperation 4, mitral annuloplasty 3</li> <li>• Placebo arm: CABG 21, valve replacement 19, combined CABG and valve replacement 3, reoperation 3, mitral annuloplasty 3, other 2</li> <li>• Aprotinin arm: CABG 19, valve replacement 22, combined CABG and valve replacement 1, reoperation 4, mitral annuloplasty 2</li> </ul> <p><b>Duration of surgery:</b> desmopressin arm: <math>188 \pm 41</math> minutes; placebo arm: <math>184 \pm 55</math> minutes; aprotinin arm: <math>178 \pm 77</math> minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: <math>89 \pm 40</math> minutes; placebo arm: <math>99 \pm 36</math> minutes; aprotinin arm: <math>87 \pm 25</math> minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> desmopressin arm: 7; placebo arm: 5; aprotinin arm: 7</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> none</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> desmopressin arm: 0; placebo arm: 0; aprotinin arm: all received aprotinin</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> red cells transfused if haemoglobin <math>&lt; 80</math> g/L, or if participant was in shock because of haemorrhage</p> |

|  |   |   |
|--|---|---|
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 μg/kg intravenously in 50 mL 0.9% saline) immediately after heparin reversal over 20 to 30 minutes; placebo (200 mL 0.9% saline preoperatively, 200 mL in fluid prime, and 50 mL/h from skin incision to skin closure) (n = 50)<br><b>Comparator arm:</b> placebo (200 mL 0.9% saline preoperatively, 200 mL in fluid prime, 50 mL/h from skin incision to skin closure, and 50 mL immediately after heparin reversal over 20 to 30 minutes) (n = 51)<br><b>Aprotinin arm:</b> aprotinin (2 million KIU in 200 mL preoperatively, 2 million KIU in 200 mL in fluid prime, 500,000 KIU in 50 mL/h from skin incision to skin closure). placebo (50 mL 0.9% saline) immediately after heparin reversal over 20 to 30 minutes (n = 48) |   |
| Outcomes   | <b>Primary outcomes</b> <ul style="list-style-type: none"><li>• Blood loss up to 24 hours postoperatively (measured by weighing surgical sponges and volume in suction reservoir and drain output)</li><li>• Total volume of red cells transfused (not reported in a way that allowed inclusion in this review)</li></ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Number of participants receiving any red cell transfusion</li><li>• Reoperation due to bleeding</li><li>• Thromboembolic events</li></ul>   |   |
| Notes  | Blood loss was reported as mL/m <sup>2</sup> body surface area. No body surface area data were reported and consequently results from this trial for blood loss have been reported qualitatively rather than included in meta-analysis  |   |
| <b>Risk of bias</b>                                    |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement  |
| Allocation concealment                                 | Low risk  | Quote: “Sealed envelopes ensured only the pharmacist who prepared the encoded infusions knew whether a patient received desmopressin, aprotinin or placebo”   |
| Blinding of participants and personnel<br>All outcomes | Low risk  | Only pharmacist preparing the investigational medicinal product (IMP) was aware of allocation   |
| Blinding of outcome assessors<br>All outcomes          | Low risk  | Only pharmacist preparing the IMP was aware of allocation   |
| Incomplete outcome data<br>All outcomes                | High risk   | 140/149 (94%) participants included in the final analysis with clear reasons for exclusions. Participants who returned to theatre with bleeding were excluded from analysis (1 in DDAVP group and 2 in aprotinin group) |

Casas 1995 (Continued)

|                             |              |  |
|-----------------------------|--------------|--|
| Selective outcome reporting | Unclear risk | Protocol not available   |
| Other sources of bias       | High risk    | Supported in part by QF Bayer, Spain (a manufacturer of aprotinin) |

Chuang 1993

|                     |   |                       |
|---------------------|---|-----------------------|
| Methods             | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Taiwan<br><b>Registration:</b> not prospectively registered  |                       |
| Participants        | <b>Inclusion criteria:</b> adults undergoing cardiac surgery with cardiopulmonary bypass<br><b>Exclusion criteria:</b> none reported<br><b>Number of participants randomised:</b> 48<br><b>Number of participants analysed:</b> 48<br><b>Age:</b> not reported<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> all cardiac surgery with cardiopulmonary bypass (types of surgery not specified)<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> not reported<br><b>Emergency cases:</b> not reported<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |                       |
| Interventions       | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously (volume and type of diluent not reported)) 1 hour after heparin reversal (speed of infusion not specified) (n = 48)<br><b>Comparator arm:</b> placebo (no details reported) (n = 48)  |                       |
| Outcomes            | <b>Primary outcome:</b> changes in laboratory measures of haemostasis<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Blood loss up to 24 hours postoperatively (measurement method not reported)</li><li>• Volume of red cells transfused</li></ul>   |                       |
| Notes               | Despite a worldwide search, we were unable to obtain the full text for this paper. Consequently, we extracted data from the abstract only   |                       |
| <i>Risk of bias</i> |   |                       |
| Bias                | Authors' judgement  | Support for judgement |

**Chuang 1993** (Continued)

|  |              |   |
|--|--------------|---|
| Sequence Generation                                    | Unclear risk | Abstract only: insufficient information for judgement |
| Allocation concealment                                 | Unclear risk | Abstract only: insufficient information for judgement |
| Blinding of participants and personnel<br>All outcomes | Unclear risk | Abstract only: insufficient information for judgement |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk | Abstract only: insufficient information for judgement |
| Incomplete outcome data<br>All outcomes                | Unclear risk | Abstract only: insufficient information for judgement |
| Selective outcome reporting                            | Unclear risk | Abstract only: no protocol available                  |
| Other sources of bias                                  | Unclear risk | Abstract only: insufficient information for judgement |

**Clagett 1995**

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> vascular surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants | <p><b>Inclusion criteria:</b> elective infrarenal aortic aneurysm repair or aortofemoral bypass for occlusive disease</p> <p><b>Exclusion criteria:</b> aspirin within 7 days of operation; acquired or congenital haemorrhagic diathesis; emergency operation; creatinine <math>\geq 3</math> mg/dL; thoracoabdominal reconstruction; aortorenal or visceral bypass</p> <p><b>Number of participants randomised:</b> 91</p> <p><b>Number of participants analysed:</b> 91</p> <p><b>Age:</b> desmopressin arm: <math>62 \pm 9</math> years; placebo arm: <math>64 \pm 8</math> years</p> <p><b>Gender:</b> desmopressin arm: male 43, female 0; placebo arm: male 48, female 0</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: aortic aneurysm repair 25; aortofemoral bypass for occlusive disease 18</li> <li>Placebo arm: aortic aneurysm repair 27; aortofemoral bypass for occlusive disease 21</li> </ul> <p><b>Duration of surgery:</b> desmopressin arm: <math>273 \pm 73</math> minutes; placebo arm: <math>252 \pm 76</math> minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> not reported</p> |

|  |  |  |
|--|--|--|
|  | <b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> not reported   |  |
| Interventions  | <b>Intervention arm:</b> DDAVP (20 µg intravenously in 50 mL 0.9% saline) immediately after intravenous heparinisation and just before aortic cross-clamp application over 15 minutes (n = 43)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) immediately after intravenous heparinisation and just before aortic cross-clamp application over 15 minutes (n = 48)  |  |
| Outcomes   | <b>Primary outcomes</b> <ul style="list-style-type: none"><li>• Total blood loss (reported but unclear if this included time before DDAVP was administered, so not included in review) (measured by weighing surgical sponges, volume in suction reservoir, and estimates from surgical nurses and anaesthetists)</li><li>• Total volume of red cells transfused</li></ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Number of participants receiving any transfusion</li><li>• All-cause mortality</li><li>• Thromboembolic events</li><li>• Laboratory measures of haemostasis</li></ul> |  |
| Notes  | Paper reports intraoperative blood loss at 3 points: pre-clamp (DDAVP given at end of this), during clamp, and after clamp. No combined figure is provided for intraoperative blood loss for period after DDAVP given. Total intraoperative blood loss includes intraoperative blood loss before DDAVP given; consequently, this has not been included in meta-analysis. Transfusion during the operation could not be calculated, as this was reported as 2 separate groups: clamp and post clamp   |  |
| <b>Risk of bias</b>                                    |  |  |
| <b>Bias</b>  | <b>Authors' judgement</b>  | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk   | Insufficient information for judgement   |
| Allocation concealment                                 | Low risk   | Participants were randomised by drawing a sealed envelope  |
| Blinding of participants and personnel<br>All outcomes | Low risk   | Quote: “The only person to have knowledge of treatment assignment was the pharmacist who kept records and prepared DDAVP or placebo in identical-appearing plastic bags of 50 mL normal saline solution” |
| Blinding of outcome assessors<br>All outcomes          | Low risk   | The only person to have knowledge of treatment assignment was the pharmacist who kept records  |

Clagett 1995 (Continued)

|   |              |   |
|---|--------------|---|
| Incomplete outcome data<br>All outcomes | Low risk     | All participants included in final analysis |
| Selective outcome reporting             | Unclear risk | Protocol not available                      |
| Other sources of bias                   | Unclear risk | Insufficient information for judgement      |

de Prost 1992

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> France</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants  | <p><b>Inclusion criteria:</b> open heart surgery; significant postoperative blood loss (<math>&gt; 75 \text{ mL/m}^2/\text{h}</math>) at any time during the first 6 hours post surgery; prolonged bleeding time (<math>&gt; 10</math> minutes)</p> <p><b>Exclusion criteria:</b> <math>&lt; 15</math> years of age; massive mediastinal haemorrhage requiring reoperation</p> <p><b>Number of participants randomised:</b> 92</p> <p><b>Number of participants analysed:</b> 92 (81 for bleeding outcomes)</p> <p><b>Age:</b> desmopressin arm: <math>60 \pm 13</math> years; placebo arm: <math>55 \pm 16</math> years</p> <p><b>Gender:</b> desmopressin arm: male 37, female 10; placebo arm: male 32, female 13</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: CABG 29, one-valve 9, two-valves 4, valve + CABG 1, valve + Bentall 1, other 3</li> <li>Placebo arm: CABG 18, one-valve 18, two-valves 2, valve + CABG 3, valve + Bentall 1, other 3</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: <math>83 \pm 31</math> minutes; placebo arm: <math>82 \pm 30</math> minutes</p> <p><b>Emergency cases:</b> not reported</p> <p><b>Antiplatelet agents:</b> not clear: "participants usually stopped antiplatelet drugs preoperatively"</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> prolonged bleeding time for all participants</p> <p><b>Thrombocytopenia:</b> none</p> <p><b>Antifibrinolytics:</b> desmopressin arm: aprotinin 2; placebo arm: aprotinin 6</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> red cell transfusion if haematocrit <math>&lt; 30\%</math></p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (<math>0.3 \mu\text{g/kg}</math> intravenously in 50 mL 0.9% saline) at any time from the end of the operation to 6 hours postoperatively over 30 minutes (<math>n = 47</math>)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) at any time from the end of the operation to 6 hours postoperatively over 30 minutes (<math>n = 45</math>)</p>   |

de Prost 1992 (Continued)

|  |   |   |
|--|---|---|
| Outcomes   | <b>Primary outcome:</b> blood loss after 24 hours (measured by volume of suction drainage)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>● Volume of red cells transfused after 24 hours</li><li>● Reoperation due to bleeding</li><li>● Changes in laboratory measures of haemostasis</li></ul> |   |
| Notes  | Blood loss reported in mL/m <sup>2</sup> , so not included in meta-analysis and reported narratively  |   |
| <i><b>Risk of bias</b></i>                             |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Insufficient information for judgement: reported as “double-blind” but no details given   |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | Insufficient information for judgement: reported as “double-blind” but no details given   |
| Incomplete outcome data<br>All outcomes                | High risk   | Blood loss reported only for participants who did not undergo reoperation: 3/47 in DDAVP arm and 8/45 in placebo arm required reoperation |
| Selective outcome reporting                            | Unclear risk  | Protocol not available  |
| Other sources of bias                                  | High risk   | Supported by grants from Ferring (a manufacturer of DDAVP)  |

Despotis 1999

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> elective cardiac surgery involving cardiopulmonary bypass; abnormal platelet function after cardiopulmonary bypass (defined as hemoSTATUS < 60% in channel 5)<br><b>Exclusion criteria:</b> urgent procedures; pre-existing disorders of haemostasis; treatment with antifibrinolytic or antiplatelet agents within 2 days of surgery; intraoperative microvascular bleeding requiring blood component transfusion |

|                     |  |                       |
|---------------------|--|-----------------------|
|                     | <p><b>Number of participants randomised:</b> 101</p> <p><b>Number of participants analysed:</b> 101</p> <p><b>Age:</b> desmopressin arm: 64 ± 10 years; placebo arm: 66 ± 10 years</p> <p><b>Gender:</b> desmopressin arm: male 30, female 20; placebo arm: male 34, female 17</p> <p><b>Type of surgery</b></p> <p>Number of procedures reported rather than procedures undergone by each participant; therefore numbers higher than numbers of participants</p> <ul style="list-style-type: none"><li>Desmopressin arm: CABG 37, valve replacement 14, combined CABG and valve replacement 6, reoperation 8</li><li>Placebo arm: CABG 46, valve replacement 10, combined CABG and valve replacement 6, reoperation 6</li></ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 147 ± 49 minutes; placebo arm: 146 ± 38 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> desmopressin arm: 26; placebo arm: 33</p> <p><b>Anticoagulants:</b> desmopressin arm: warfarin 3; placebo arm: 0</p> <p><b>Coagulopathy:</b> all had hemoSTATUS &lt; 60% in channel 5</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics</b></p> <ul style="list-style-type: none"><li>Desmopressin arm: epsilon-aminocaproic acid (5 g loading dose, 5 g in the cardiopulmonary bypass circuit, and 1 g/h infusion) 25</li><li>Placebo arm: epsilon-aminocaproic acid (5 g loading dose, 5 g in the cardiopulmonary bypass circuit, and 1 g/h infusion) 31</li></ul> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> no protocol, transfusion given at discretion of treating physicians</p> |                       |
| Interventions       | <p><b>Intervention arm:</b> DDAVP (0.4 µg/kg intravenously in 50 mL 0.9% saline) over 30 minutes (timing of administration unclear) (n = 50)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) over 30 minutes (timing of administration unclear) (n = 51)</p>   |                       |
| Outcomes            | <p><b>Primary outcomes</b></p> <ul style="list-style-type: none"><li>Total blood loss (measured by drain output)</li><li>Volume of red cells transfused</li></ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"><li>Reoperation due to bleeding</li><li>All-cause mortality</li><li>Thromboembolic events</li><li>Clinically important hypotension</li></ul>  |                       |
| Notes               |  |                       |
| <i>Risk of bias</i> |  |                       |
| Bias                | Authors' judgement   | Support for judgement |

**Despotis 1999** (Continued)

|  |              |  |
|--|--------------|--|
| Sequence Generation                                    | Low risk     | Quote: "Randomisation was based on a computer-generated random-number table and done according to a sequential allocation schedule"  |
| Allocation concealment                                 | Unclear risk | Quote: "Randomisation was based on a computer-generated random-number table and done according to a sequential allocation schedule that was generated by an investigator not involved in treatment assignment." Insufficient details for judgement about allocation concealment  |
| Blinding of participants and personnel<br>All outcomes | Low risk     | Quote: "Desmopressin and placebo were administered intravenously as colourless fluids from unlabelled syringes, aspirated in a separate room and transported to the operating room by one of the investigators (not masked to treatment status but not involved in the management of the patients). Desmopressin was given as 0.4 g/kg over 30 min, and placebo patients received a corresponding volume of normal saline. Managing physicians, nurses, and patients were masked to treatment status perioperatively, and no protocol violations were noted" |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk | Not clear who assessed outcomes and whether blinded  |
| Incomplete outcome data<br>All outcomes                | Low risk     | All participants included in final analysis  |
| Selective outcome reporting                            | Unclear risk | Protocol not available   |
| Other sources of bias                                  | High risk    | Material support provided by Rhône-Poulenc Rone Pharmaceuticals Inc (a manufacturer of DDAVP)  |

**Dilthey 1993**

|         |   |
|---------|---|
| Methods | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Germany<br><b>Registration:</b> not prospectively registered |
|---------|---|

|                        |  |  |
|------------------------|--|--|
| Participants           | <p><b>Inclusion criteria:</b> elective first-time myocardial revascularisation; aspirin within previous 5 days; male</p> <p><b>Exclusion criteria:</b> preoperative haemoglobin &lt; 135 g/L; preoperative prolongation of PT or aPTT; any anticoagulant treatment other than aspirin; intraoperative use of aprotinin</p> <p><b>Number of participants randomised:</b> 40</p> <p><b>Number of participants analysed:</b> 39</p> <p><b>Age:</b> desmopressin arm: 56 ± 9 years; placebo arm: 58 ± 8 years</p> <p><b>Gender:</b> desmopressin arm: male 19, female 0; placebo arm: male 20, female 0</p> <p><b>Type of surgery:</b> all undergoing elective CABG</p> <p><b>Duration of surgery:</b> desmopressin arm: 240 ± 37 minutes; placebo arm: 248 ± 48 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 88 ± 25 minutes; placebo arm: 81 ± 22 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> desmopressin arm: aspirin 19; placebo arm: aspirin 20</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> none</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> none</p> <p><b>Cell salvage:</b> all participants</p> <p><b>Transfusion protocol:</b> red cells transfused if haematocrit &lt; 30%</p> |  |
| Interventions          | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 0.9% saline (volume not reported)) 5 minutes after heparin reversal over 15 minutes (n = 19)</p> <p><b>Comparator arm:</b> placebo (0.9% saline (volume not reported)) 5 minutes after heparin reversal over 15 minutes (n = 20)</p>   |  |
| Outcomes               | <p><b>Primary outcome:</b> total volume of red cells transfused</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"><li>• Number of participants receiving a red cell transfusion</li><li>• Total blood loss (measured by drain output)</li><li>• Clinically significant hypotension</li></ul>  |  |
| Notes                  | Blood loss and volume of red cells transfused up to 24 hours postoperatively reported as median and range. Consequently, these results have been reported narratively and were not included in meta-analysis   |  |
| <i>Risk of bias</i>    |  |  |
| <b>Bias</b>            | <b>Authors' judgement</b>  | <b>Support for judgement</b>           |
| Sequence Generation    | Unclear risk   | Insufficient information for judgement |
| Allocation concealment | Unclear risk   | Insufficient information for judgement |

**Dilthey 1993** (Continued)

|  |              |   |
|--|--------------|---|
| Blinding of participants and personnel<br>All outcomes | Low risk     | Quote: “the anaesthesiologist and surgeon responsible for postoperative treatment were blinded to the substance given”                    |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk | Quote: “surgeon responsible for postoperative treatment was blinded”, but does not say whether this surgeon was the outcome assessor      |
| Incomplete outcome data<br>All outcomes                | High risk    | One participant randomised to DDAVP was “excluded from analysis because, in the early postoperative course, he showed excessive bleeding” |
| Selective outcome reporting                            | Unclear risk | Protocol not available  |
| Other sources of bias                                  | Low risk     | Insufficient information for judgement  |

**Ellis 2001**

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single-centre, open-label, 3-arm, parallel-group RCT</p> <p><b>Setting:</b> orthopaedic surgery</p> <p><b>Country:</b> Israel</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants | <p><b>Inclusion criteria:</b> ASA scale 1-3; undergoing elective total knee replacement</p> <p><b>Exclusion criteria:</b> New York Heart Association (NYHA) 3 or 4 classified heart failure; chronic renal failure; liver cirrhosis; bleeding disorders; current anticoagulant therapy</p> <p><b>Number of participants randomised:</b> 30</p> <p><b>Number of participants analysed:</b> 30</p> <p><b>Age:</b> desmopressin arm: 72 ± 6 years; placebo arm: 72 ± 8 years; tranexamic acid: 71 ± 5 years</p> <p><b>Gender:</b> desmopressin arm: male 2, female 8; placebo arm: male 3, female 7; tranexamic acid arm: male 4, female 6</p> <p><b>Type of surgery:</b> all undergoing elective total knee replacement</p> <p><b>Duration of surgery:</b> desmopressin arm: 133 ± 16 minutes; placebo arm: 134 ± 14 minutes; tranexamic acid arm: 135 ± 11 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> desmopressin arm: 0; placebo arm: 0; tranexamic acid arm: all receiving tranexamic acid</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> red cells transfused if haematocrit &lt; 27%</p> |

|               |   |
|---------------|---|
| Interventions | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 0.9% saline (volume not reported)) 30 minutes before tourniquet removed over 30 minutes. Followed by infusion of placebo (10 mL/kg) until 12 hours after tourniquet deflated (n = 10)</p> <p><b>Comparator arm:</b> standard care (n = 10)</p> <p><b>Tranexamic acid arm:</b> tranexamic acid: 15 mg/kg 30 minutes before tourniquet removed over 30 minutes, then 10 mg/kg/h until 12 hours after tourniquet deflated (n = 10)</p> |
| Outcomes      | <p><b>Primary outcome:</b> change in laboratory measures of haemostasis</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Total volume of red cells transfused</li> <li>• Number of participants receiving a red cell transfusion</li> </ul>  |
| Notes         | Volume of red cells transfused reported as mean only. Consequently, results for this outcome are reported narratively and were not included in meta-analysis. Red cell transfusion reported in mL and converted to units with assumption that 300 mL is equivalent to 1 unit  |

### *Risk of bias*

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Low risk           | Quote: "computer generated randomisation table"   |
| Allocation concealment                                 | Unclear risk       | Insufficient information to make judgement  |
| Blinding of participants and personnel<br>All outcomes | High risk          | Control group received standard of care with no intervention or placebo. Participants and personnel were adequately blinded to whether they were in the tranexamic acid or DDAVP arms (but not control) |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Quote: "the decision to transfuse ... was taken by an independent observer who was blinded to treatment modality"   |
| Incomplete outcome data<br>All outcomes                | Low risk           | Complete outcome data reported for all groups   |
| Selective outcome reporting                            | Unclear risk       | Protocol not available  |
| Other sources of bias                                  | Unclear risk       | Insufficient information for judgement  |

## Flordal 1991

|               |   |
|---------------|---|
| Methods       | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> orthopaedic surgery<br><b>Country:</b> Sweden<br><b>Registration:</b> not prospectively registered  |
| Participants  | <b>Inclusion criteria:</b> undergoing total hip replacement<br><b>Exclusion criteria:</b> prostaglandin synthesis inhibitors<br><b>Number of participants randomised:</b> 12<br><b>Number of participants analysed:</b> 12<br><b>Age:</b> not reported<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> all undergoing elective total hip replacement<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) at start of surgery and again 6 hours postoperatively over 20 to 30 minutes (n = 6)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) at start of surgery and again 6 hours postoperatively over 20 to 30 minutes (n = 6)   |
| Outcomes      | <b>Primary outcome:</b> change in laboratory measures of haemostasis<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Total blood loss (measurement method not reported)</li> <li>• Thromboembolic events</li> </ul>   |
| Notes         | Blood loss reported as mean only. Consequently, this outcome has been reported narratively and was not included in meta-analysis  |

### *Risk of bias*

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Unclear risk       | Insufficient information for judgement                            |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement                            |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | Reported as double-blind but with insufficient details of methods |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk       | Reported as double-blind but with insufficient details of methods |

**Flordal 1991** (Continued)

|   |              |   |
|---|--------------|---|
| Incomplete outcome data<br>All outcomes | Low risk     | All participants included in final analysis   |
| Selective outcome reporting             | Unclear risk | Protocol not available  |
| Other sources of bias                   | High risk    | Study was supported in part by Ferring AB (a manufacturer of DDAVP). Methods for reporting main outcome (total blood loss) were not clear |

**Flordal 1992**

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> orthopaedic surgery</p> <p><b>Country:</b> Sweden</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants  | <p><b>Inclusion criteria:</b> elective total hip replacement</p> <p><b>Exclusion criteria:</b> &gt; 80 years old; severe vascular, hepatic, or renal disease; prostaglandin synthesis inhibitors</p> <p><b>Number of participants randomised:</b> 50</p> <p><b>Number of participants analysed:</b> 50</p> <p><b>Age:</b> desmopressin arm: 64 ± 9 years; placebo arm: 68 ± 9 years</p> <p><b>Gender:</b> desmopressin arm: male 12, female 13; placebo arm: male 12, female 13</p> <p><b>Type of surgery:</b> all undergoing elective total hip replacement</p> <p><b>Duration of surgery:</b> desmopressin arm: 106 ± 23 minutes; placebo arm: 104 ± 20 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) at start of surgery and again 6 hours postoperatively over 20 to 30 minutes (n = 25)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) at start of surgery and again 6 hours postoperatively over 20 to 30 minutes (n = 25)</p>   |
| Outcomes      | <p><b>Primary outcome:</b> blood loss: intraoperative and total (measured by estimating blood in surgical swabs, paper drapes, and folds; volume in suction reservoir; and change in haemoglobin preoperatively and postoperatively compared with estimated total blood volume)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Volume of red cells transfused</li> </ul>  |

**Flordal 1992** (Continued)

|  |                           |   |
|--|---------------------------|---|
|  | ● Thromboembolic events   |   |
| Notes  |                           |   |
| <i>Risk of bias</i>                                    |                           |   |
| <b>Bias</b>  | <b>Authors' judgement</b> | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk              | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk              | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk              | Reported as performed in a double-blind fashion but no details of methods   |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk              | Reported as performed in a double-blind fashion but no details of methods   |
| Incomplete outcome data<br>All outcomes                | Low risk                  | All participants included in final analysis   |
| Selective outcome reporting                            | Unclear risk              | Protocol not available  |
| Other sources of bias                                  | Unclear risk              | DDAVP supplied free of charge by Ferring AB (a manufacturer of DDAVP), but unclear if they had any role in the study design |

**Frankville 1991**

|              |  |
|--------------|--|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered  |
| Participants | <b>Inclusion criteria:</b> elective primary CABG<br><b>Exclusion criteria:</b> warfarin or heparin within 24 hours of surgery; documented coagulopathies or platelet disorders; allergy to DDAVP; renal failure; stroke or venous thromboembolism within 3 months<br><b>Number of participants randomised:</b> 40<br><b>Number of participants analysed:</b> 40<br><b>Age:</b> desmopressin arm: 59.9 ± 10.7 years; placebo arm: 59.6 ± 11.2 years<br><b>Gender:</b> desmopressin arm: male 17, female 3; placebo arm: male 17, female 3<br><b>Type of surgery:</b> all undergoing elective CABG<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 50.8 ± 14.4 minutes; placebo arm: 50.7 ± 10.7 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none |

|               |   |
|---------------|---|
|               | <b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> not reported   |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) 5 minutes after heparin reversal over 15 minutes (n = 20)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) 5 minutes after heparin reversal over 15 minutes (n = 20)   |
| Outcomes      | <b>Primary outcome:</b> clinically significant hypotension<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Total blood loss (measured by drain output)</li> <li>• Number of participants receiving a red cell transfusion</li> <li>• Volume of red cells transfused</li> <li>• Reoperation due to bleeding</li> </ul> |
| Notes         | Volume of red cells transfused reported as mean only (no standard deviation), so reported narratively and not included in meta-analysis   |

***Risk of bias***

| Bias   | Authors' judgement | Support for judgement  |
|--|--------------------|--|
| Sequence Generation                                    | Unclear risk       | Insufficient information to make judgement   |
| Allocation concealment                                 | Low risk           | Sealed envelopes used  |
| Blinding of participants and personnel<br>All outcomes | Low risk           | Desmopressin and placebo solutions were identical in appearance. Surgeon, anaesthesiologist, and investigator collecting experimental data were unaware of which solution was administered |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Desmopressin and placebo solutions were identical in appearance. Surgeon, anaesthesiologist, and investigator collecting experimental data were unaware of which solution was administered |
| Incomplete outcome data<br>All outcomes                | Low risk           | All participants included in final analysis  |
| Selective outcome reporting                            | Unclear risk       | Protocol not available   |

Frankville 1991 (Continued)

|                       |              |  |
|-----------------------|--------------|--|
| Other sources of bias | Unclear risk | Insufficient information for judgement |
|-----------------------|--------------|--|

Gratz 1992

|                     |   |                       |
|---------------------|---|-----------------------|
| Methods             | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered   |                       |
| Participants        | <b>Inclusion criteria:</b> elective CABG operations; aspirin within 7 days of surgery<br><b>Exclusion criteria:</b> valvular heart disease; need for intra-aortic balloon pump; re-doing CABG<br><b>Number of participants randomised:</b> 65<br><b>Number of participants analysed:</b> 59<br><b>Age:</b> desmopressin arm: 62.2 ± 10.4 years; placebo arm: 62.7 ± 12.3 years<br><b>Gender:</b> desmopressin arm: male 19, female 10; placebo arm: male 23, female 7<br><b>Type of surgery:</b> all undergoing elective CABG<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 80.4 ± 29 minutes; placebo arm: 95.4 ± 25.6 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> aspirin taken by all participants<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> not reported |                       |
| Interventions       | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) immediately after heparin reversal over 30 minutes (n = 29)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) immediately after heparin reversal over 30 minutes (n = 30)   |                       |
| Outcomes            | <b>Primary outcome:</b> total blood loss (measured by weighing surgical sponges, volume in cell saver, and suction drainage)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Volume of red cells transfused</li><li>• Number of participants receiving a red cell transfusion</li><li>• All-cause mortality</li><li>• Thromboembolic events</li><li>• Laboratory measures of haemostasis</li></ul>   |                       |
| Notes               |   |                       |
| <i>Risk of bias</i> |   |                       |
| Bias                | Authors' judgement  | Support for judgement |

Gratz 1992 (Continued)

|  |              |   |
|--|--------------|---|
| Sequence Generation                                    | Unclear risk | Insufficient detail for judgement. "Patients were assigned to the DDAVP or placebo groups according to a randomization schedule"  |
| Allocation concealment                                 | Unclear risk | Insufficient detail for judgement. "all study medication was dispensed in blinded fashion ...The solutions were prepared by research pharmacists"   |
| Blinding of participants and personnel<br>All outcomes | Low risk     | Quote: "The solutions were prepared by a research pharmacist". "Members of all the anaesthesia and surgical teams were blinded to the nature of the DDAVP or placebo infusion"  |
| Blinding of outcome assessors<br>All outcomes          | Low risk     | Quote: "The solutions were prepared by a research pharmacist". "Members of all the anaesthesia and surgical teams were blinded to the nature of the DDAVP or placebo infusion"  |
| Incomplete outcome data<br>All outcomes                | Low risk     | Six participants excluded from final analysis (3 in each group): 2 died intraoperatively, 1 inadvertently received DDAVP, 3 required insertion of an intra-aortic balloon pump. Incomplete outcome data balanced between groups |
| Selective outcome reporting                            | Unclear risk | Protocol not available  |
| Other sources of bias                                  | High risk    | Supported in part by a grant from Rhone-Poulenc Rorer (a manufacturer of DDAVP)   |

Guay 1992

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> orthopaedic surgery: spinal</p> <p><b>Country:</b> Canada</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> ASA 1-2; idiopathic scoliosis; undergoing scheduled spinal fusion surgery</p> <p><b>Exclusion criteria:</b> different surgical technique used; history of bleeding diathesis; ingestion of drugs known to interfere with haemostasis; abnormal bleeding time (&gt; 9 minutes) ; aPTT &gt; 36 seconds; PT &gt; 25 seconds; TT &gt; 16 seconds; platelet count &lt; 150 × 10<sup>9</sup>/L</p> <p><b>Number of participants randomised:</b> 31</p> <p><b>Number of participants analysed:</b> 30</p> |

|  |  |  |
|--|--|--|
|  | <b>Age:</b> desmopressin arm: 13.5 ± 1.9 years; placebo arm: 15.1 ± 1.9 years<br><b>Gender:</b> desmopressin arm: male 1, female 14; placebo arm: male 1, female 14<br><b>Type of surgery:</b> all undergoing elective spinal fusion scoliosis surgery<br><b>Duration of surgery:</b> desmopressin arm: 246 ± 72 minutes; placebo arm: 222 ± 42 minutes<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cell transfusion for bleeding causing 20% to 30% fall in calculated blood volume |  |
| Interventions  | <b>Intervention arm:</b> DDAVP (10 µg/m <sup>2</sup> body surface area intravenously in 100 mL 0.9% saline) at time of first skin incision over 20 minutes (n = 15)<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline) at time of first skin incision over 20 minutes (n = 15)   |  |
| Outcomes   | <b>Primary outcome:</b> blood loss: intraoperative and total (measurement method not reported)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Volume of red cells transfused intraoperatively and from end of operation to 24 hours postoperatively (no report of total volume transfused)</li><li>• Reoperation due to bleeding</li><li>• Laboratory measures of haemostasis</li></ul>  |  |
| Notes  | Volume of red cells transfused includes both autologous and allogeneic blood transfusion   |  |
| <i>Risk of bias</i>                                    |  |  |
| <b>Bias</b>  | <b>Authors' judgement</b>  | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk   | Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk   | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Low risk   | Quote: “The design was double blind, and the surgeon, the anesthesiologist, and the investigator collecting the experimental data were all unaware of which solution was administered” |
| Blinding of outcome assessors<br>All outcomes          | Low risk   | Quote: “the investigators collecting the experimental data were unaware of which solution was administered”  |

**Guay 1992** (Continued)

|   |              |   |
|---|--------------|---|
| Incomplete outcome data<br>All outcomes | Low risk     | All participants included in final analysis |
| Selective outcome reporting             | Unclear risk | Protocol not available                      |
| Other sources of bias                   | Unclear risk | Insufficient information for judgement      |

**Guyuron 1996**

|               |   |
|---------------|---|
| Methods       | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> maxillofacial surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered   |
| Participants  | <b>Inclusion criteria:</b> bimaxillary osteotomy; normal preoperative PT and aPTT; no history of bleeding disorder or easy bruising<br><b>Exclusion criteria:</b> none reported<br><b>Number of participants randomised:</b> 20<br><b>Number of participants analysed:</b> 20<br><b>Age:</b> not reported<br><b>Gender:</b> desmopressin arm: male 1, female 9; placebo arm: male 4, female 6<br><b>Type of surgery:</b> all undergoing bimaxillary osteotomy and osteoplastic genioplasty<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |
| Interventions | <b>Intervention arm:</b> DDAVP (20 µg intravenously in 50 mL 0.9% saline) 30 minutes preoperatively over 30 minutes (n = 10)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) 30 minutes preoperatively over 30 minutes (n = 10)   |
| Outcomes      | <b>Primary outcome:</b> blood loss: up to 24 hours postoperatively (measured by estimating blood loss in surgical sponges and suction drainage)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Total volume of red cells transfused</li> <li>• Number of participants receiving a red cell transfusion</li> </ul>  |
| Notes         | Total blood loss reported as mean and range, so outcome reported narratively and not included in meta-analysis. Volume of red cells transfused reported as mean only, so reported narratively and not included in meta-analysis   |

**Guyuron 1996** (Continued)

| <i>Risk of bias</i>                                    |                    |   |
|--|--------------------|---|
| Bias   | Authors' judgement | Support for judgement   |
| Sequence Generation                                    | Unclear risk       | Insufficient information for judgement                                |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement                                |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | Insufficient information for judgement                                |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Quote: "the evaluating team was not apprised of the DDAVP recipients" |
| Incomplete outcome data<br>All outcomes                | Low risk           | All participants included in final analysis                           |
| Selective outcome reporting                            | Unclear risk       | Protocol not available  |
| Other sources of bias                                  | Unclear risk       | Insufficient information for judgement                                |

**Hackmann 1989**

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Canada</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> &gt; 18 years old; elective cardiac surgery involving cardiopulmonary bypass</p> <p><b>Exclusion criteria:</b> pregnancy; known bleeding disorder such as haemophilia, von Willebrand disease, or immune thrombocytopenic purpura; abnormal coagulation (PT, aPTT or TT); platelet count &lt; <math>100 \times 10^9/L</math>; clotting parameters that had not returned to normal after cessation of anticoagulant drugs</p> <p><b>Number of participants randomised:</b> 164</p> <p><b>Number of participants analysed:</b> 150</p> <p><b>Age:</b> desmopressin arm: &lt; 45 years: 5, 46-60 years: 27, 61-75 years: 39, &gt; 75 years: 3; placebo arm: &lt; 45 years: 6, 46-60 years: 26, 61-75 years: 39, &gt; 75 years: 5</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: CABG 57, valve replacement 12, combined CABG and valve replacement 5</li> <li>Placebo arm: CABG 51, valve replacement 18, combined CABG and valve replacement 6, atrial septal defect repair 1</li> </ul> <p><b>Duration of surgery:</b> desmopressin arm: <math>306 \pm 89</math> minutes; placebo arm: <math>318 \pm 114</math> minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: <math>168 \pm 58</math> minutes; placebo</p> |

|  |   |   |
|--|---|---|
|  | arm: 161 ± 52 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> desmopressin arm: 16 aspirin, 10 dipyridamole; placebo arm: 11 aspirin, 4 dipyridamole<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> not reported  |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 μg/kg intravenously in 25 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 74)<br><b>Comparator arm:</b> placebo (25 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 76)   |   |
| Outcomes   | <b>Primary outcome:</b> blood loss: perioperative and total (measured by weighing surgical sponges, estimating blood on surgical drapes, measuring suction bottles and drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Volume of red cells transfused</li><li>• Laboratory measures of haemostasis</li><li>• Number of participants receiving a red cell transfusion</li><li>• Reoperation due to bleeding</li><li>• All-cause mortality</li></ul> |   |
| Notes  | Blood loss and volume of red cells transfused reported as median and range, so these outcomes were reported narratively and were not included in meta-analysis. Volume of red cells transfused was reported in mL, and this was converted to units, assuming that 1 unit is equivalent to 300 mL  |   |
| <i>Risk of bias</i>                                    |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Low risk  | Quote: “All patients, all treating physicians, and all investigators involved in collecting data, measuring blood loss, or performing and interpreting laboratory tests were blinded to the treatment assigned” |
| Blinding of outcome assessors<br>All outcomes          | Low risk  | Quote: “All patients, all treating physicians, and all investigators involved in collecting data, measuring blood loss, or performing and interpreting laboratory tests were blinded to the treatment assigned” |

|   |              |   |
|---|--------------|---|
| Incomplete outcome data<br>All outcomes | High risk    | 14 participants who were randomised were excluded from the outcome results, including 3 participants who died “during surgery or shortly afterward”. It is not clear which treatment these participants had been allocated to |
| Selective outcome reporting             | Unclear risk | Protocol not available  |
| Other sources of bias                   | Low risk     | No other clear source of bias. Supported by a grant from the British Columbia Heart Foundation  |

Hajjar 2007

|               |   |  |
|---------------|---|--|
| Methods       | <b>Type of study:</b> 2-arm parallel-group RCT (unclear if single-centre or multi-centre trial)<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Brazil<br><b>Registration:</b> not prospectively registered   |  |
| Participants  | <b>Inclusion criteria:</b> cardiac surgery requiring cardiopulmonary bypass<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> not reported<br><b>Number of participants analysed:</b> 150<br><b>Age:</b> not reported<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> all cardiac surgery requiring cardiopulmonary bypass. Information on individual types of surgery not reported<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> not reported<br><b>Emergency cases:</b> not reported<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |  |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) immediately after the end of surgery over 15 minutes (n = 75)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) immediately after the end of surgery over 15 minutes (n = 75)   |  |
| Outcomes      | <b>Primary outcome:</b> blood loss: up to 72 hours (method not reported)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Volume of red cells transfused</li> </ul>  |  |

## Hajjar 2007 (Continued)

|  |  |   |                              |
|--|--|---|------------------------------|
|  | <ul style="list-style-type: none"><li>• Laboratory measures of haemostasis</li><li>• Thromboembolic events (prespecified but not reported)</li></ul>   |   |                              |
| Notes  | Abstract only with full text not expected to be published. Blood loss reported as mL/m <sup>2</sup> , so reported narratively and not included in meta-analysis. Volume of red cells reported in mL and converted to units by assuming 1 unit to be equivalent to 300 mL. Original author contacted on 23 March 2016, 6 April 2016, and 6 July 2016, but did not respond |   |                              |
| <i>Risk of bias</i>                                    |  |   |                              |
| <b>Bias</b>  | <b>Authors' judgement</b>  |   | <b>Support for judgement</b> |
| Sequence Generation                                    | Unclear risk   | Abstract: insufficient information for judgement  |                              |
| Allocation concealment                                 | Unclear risk   | Abstract: insufficient information for judgement  |                              |
| Blinding of participants and personnel<br>All outcomes | Unclear risk   | Abstract: insufficient information for judgement. Reported as “double-blinded” but without explanation of methods |                              |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk   | Abstract: insufficient information for judgement. Reported as “double-blinded” but without explanation of methods |                              |
| Incomplete outcome data<br>All outcomes                | Unclear risk   | Abstract: insufficient information for judgement  |                              |
| Selective outcome reporting                            | Unclear risk   | Abstract: protocol not available  |                              |
| Other sources of bias                                  | Unclear risk   | Abstract: insufficient information for judgement  |                              |

## Hedderich 1990

|              |  |
|--------------|--|
| Methods      | <b>Type of study:</b> 2-arm, parallel-group RCT (unclear if single-centre or multi-centre trial)<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Canada<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> uncomplicated CABG<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> 62<br><b>Number of participants analysed:</b> 59 to 62<br><b>Age:</b> desmopressin arm: 61 ± 10 years; placebo arm: 59 ± 9 years<br><b>Gender:</b> groups reported together: 47 male, 15 female<br><b>Type of surgery:</b> all CABG requiring cardiopulmonary bypass |

|  |   |   |
|--|---|---|
|  | <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 92 ± 21 minutes; placebo arm: 89 ± 24 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> desmopressin arm: 12; placebo arm: 13</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |   |
| Interventions  | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 100 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 31)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 31)</p>   |   |
| Outcomes   | <p><b>Primary outcomes</b></p> <ul style="list-style-type: none"><li>● Blood loss total (measured by weighing surgical sponges, suction drainage, and drain output)</li><li>● Volume of red cells transfused total</li></ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"><li>● Reoperation due to bleeding</li><li>● All-cause mortality</li><li>● Thromboembolic events</li></ul>   |   |
| Notes  | DDAVP was given towards the end of the procedure; therefore, intraoperative outcome was not used  |   |
| <i><b>Risk of bias</b></i>                             |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Low risk  | Computer-generated random number table  |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | High risk   | Not blinded; important as outcome includes transfusion  |
| Blinding of outcome assessors<br>All outcomes          | High risk   | Not blinded; important for measurement of blood loss  |
| Incomplete outcome data<br>All outcomes                | High risk   | Excluded participants who required re-exploration for bleeding from further analysis: 2 in DDAVP group and 1 in placebo group |

**Hedderich 1990** (Continued)

|                             |              |  |
|-----------------------------|--------------|--|
| Selective outcome reporting | Unclear risk | Protocol not available                 |
| Other sources of bias       | Unclear risk | Insufficient information for judgement |

**Hemş inli 2012a**

|                     |  |                       |
|---------------------|--|-----------------------|
| Methods             | <b>Type of study:</b> single-centre, 4-arm, parallel-group, open-label RCT. <a href="#">Hemş inli 2012a</a> reported DDAVP vs placebo. <a href="#">Hemş inli 2012b</a> reported DDAVP and tranexamic acid vs tranexamic acid. <a href="#">Hemş inli 2012c</a> reported DDAVP vs tranexamic acid<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Turkey<br><b>Registration:</b> not prospectively registered  |                       |
| Participants        | <b>Inclusion criteria:</b> emergency CABG; dual antiplatelet therapy<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> not reported<br><b>Number of participants analysed:</b> 20<br><b>Age:</b> not reported<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> all emergency CABG<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> not reported<br><b>Emergency cases:</b> desmopressin arm: 10; standard care arm: 10<br><b>Antiplatelet agents:</b> desmopressin arm: dual antiplatelet therapy 10; standard care arm: dual antiplatelet therapy 10<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |                       |
| Interventions       | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously (diluent and diluent volume not reported)) over 20 minutes (timing of infusion not reported) (n = 10)<br><b>Comparator arm:</b> standard care (n = 10)   |                       |
| Outcomes            | <b>Primary outcome:</b> total blood loss (method for measurement not reported)<br><b>Secondary outcomes:</b> volume of red cells transfused (data not reported in manuscript)  |                       |
| Notes               | Abstract only. Blood loss reported as mean (no standard deviation), so data for this outcome are reported narratively and were not included in meta-analysis. Study investigator, Dr Altun, contacted on 28 June 2016. This study is complete and is planned for publication   |                       |
| <i>Risk of bias</i> |  |                       |
| Bias                | Authors' judgement   | Support for judgement |

**Hem<sub>s</sub> inli 2012a** (Continued)

|  |              |   |
|--|--------------|---|
| Sequence Generation                                    | Unclear risk | Abstract: insufficient information for judgement            |
| Allocation concealment                                 | Unclear risk | Abstract: insufficient information for judgement            |
| Blinding of participants and personnel<br>All outcomes | High risk    | Not blinded. Control arm is standard care, not placebo      |
| Blinding of outcome assessors<br>All outcomes          | High risk    | Not blinded. Control arm is standard care, not placebo      |
| Incomplete outcome data<br>All outcomes                | Unclear risk | Abstract: insufficient information for judgement            |
| Selective outcome reporting                            | High risk    | Outcome data make reference to a table that is not provided |
| Other sources of bias                                  | Unclear risk | Abstract: insufficient information for judgement            |

**Hem<sub>s</sub> inli 2012b**

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single centre, 4-arm, parallel-group, open-label RCT. <a href="#">Hem<sub>s</sub> inli 2012a</a> reported DDAVP vs placebo. <a href="#">Hem<sub>s</sub> inli 2012b</a> reported DDAVP and tranexamic acid vs tranexamic acid. <a href="#">Hem<sub>s</sub> inli 2012c</a> reported DDAVP vs tranexamic acid</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Turkey</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants | <p><b>Inclusion criteria:</b> emergency CABG; dual antiplatelet therapy</p> <p><b>Exclusion criteria:</b> not reported</p> <p><b>Number of participants randomised:</b> not reported</p> <p><b>Number of participants analysed:</b> 20</p> <p><b>Age:</b> not reported</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery:</b> all emergency CABG</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> not reported</p> <p><b>Emergency cases:</b> desmopressin and tranexamic acid arm: 16; tranexamic acid arm: 18</p> <p><b>Antiplatelet agents:</b> desmopressin and tranexamic acid arm: 16; tranexamic acid arm: 18</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> desmopressin and tranexamic acid arm: 16; tranexamic acid arm: 18</p> <p><b>Cell salvage:</b> not reported</p> |

|  |  |   |                              |
|--|--|---|------------------------------|
|  | <b>Transfusion protocol:</b> not reported  |   |                              |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 $\mu$ g/kg intravenously (diluent and diluent volume not reported)) over 20 minutes (timing of infusion not reported). Tranexamic acid (10 mg/kg intravenously) over 30 minutes, then 1 mg/kg for 10 hours administered at time of first skin incision (n = 16)<br><b>Comparator arm:</b> tranexamic acid (10 mg/kg intravenously) over 30 minutes, then 1 mg/kg for 10 hours administered at time of first skin incision (n = 18) |   |                              |
| Outcomes   | <b>Primary outcome:</b> total blood loss (method for measurement not reported)<br><b>Secondary outcomes:</b> volume of red cells transfused (data not reported in manuscript)  |   |                              |
| Notes  | Abstract only. Blood loss reported as mean (no standard deviation), so data for this outcome are reported narratively and were not included in meta-analysis. Study investigator, Dr Altun, contacted on 28 June 2016. This study is complete and is planned for publication   |   |                              |
| <i>Risk of bias</i>                                    |  |   |                              |
| <b>Bias</b>  | <b>Authors' judgement</b>  |   | <b>Support for judgement</b> |
| Sequence Generation                                    | Unclear risk   | Abstract: insufficient information for judgement            |                              |
| Allocation concealment                                 | Unclear risk   | Abstract: insufficient information for judgement            |                              |
| Blinding of participants and personnel<br>All outcomes | Unclear risk   | Abstract: insufficient information for judgement            |                              |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk   | Abstract: insufficient information for judgement            |                              |
| Incomplete outcome data<br>All outcomes                | Unclear risk   | Abstract: insufficient information for judgement            |                              |
| Selective outcome reporting                            | High risk  | Outcome data make reference to a table that is not provided |                              |
| Other sources of bias                                  | Unclear risk   | Abstract: insufficient information for judgement            |                              |

## Hemş inli 2012c

|                        |   |  |  |
|------------------------|---|--|--|
| Methods                | <b>Type of study:</b> single-centre, 4-arm, parallel-group, open-label RCT. <a href="#">Hemş inli 2012a</a> reported DDAVP vs placebo. <a href="#">Hemş inli 2012b</a> reported DDAVP and tranexamic acid vs tranexamic acid. <a href="#">Hemş inli 2012c</a> reported DDAVP vs tranexamic acid<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Turkey<br><b>Registration:</b> not prospectively registered   |  |  |
| Participants           | <b>Inclusion criteria:</b> emergency CABG; dual antiplatelet therapy<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> not reported<br><b>Number of participants analysed:</b> 28<br><b>Age:</b> not reported<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> all emergency CABG<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> not reported<br><b>Emergency cases:</b> desmopressin arm: 10; tranexamic acid arm: 18<br><b>Antiplatelet agents:</b> desmopressin arm: 10; tranexamic acid arm: 18<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> desmopressin arm: 10; tranexamic acid arm: 18<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |  |  |
| Interventions          | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously (diluent and diluent volume not reported)) over 20 minutes (timing of infusion not reported) (n = 10)<br><b>Comparator arm:</b> tranexamic acid (10 mg/kg intravenously) over 30 minutes, then 1 mg/kg for 10 hours administered at time of first skin incision (n = 18)  |  |  |
| Outcomes               | <b>Primary outcome:</b> total blood loss (method for measurement not reported)<br><b>Secondary outcome:</b> volume of red cells transfused (data not reported in manuscript)  |  |  |
| Notes                  | Abstract only. Blood loss reported as mean (no standard deviation), so data for this outcome are reported narratively and were not included in meta-analysis. Study investigator, Dr Altun, contacted on 28 June 2016. This study is complete and is planned for publication  |  |  |
| <b>Risk of bias</b>    |   |  |  |
| <b>Bias</b>            | <b>Authors' judgement</b>   | <b>Support for judgement</b>                     |  |
| Sequence Generation    | Unclear risk  | Abstract: insufficient information for judgement |  |
| Allocation concealment | Unclear risk  | Abstract: insufficient information for judgement |  |

|  |              |  |
|--|--------------|--|
| Blinding of participants and personnel<br>All outcomes | Unclear risk | Abstract: insufficient information for judgement             |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk | Abstract: insufficient information for judgement             |
| Incomplete outcome data<br>All outcomes                | Unclear risk | Abstract: insufficient information for judgement             |
| Selective outcome reporting                            | High risk    | Outcome data makes reference to a table that is not provided |
| Other sources of bias                                  | Unclear risk | Abstract: insufficient information for judgement             |

## Horrow 1991a

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single-centre, 4-arm, parallel-group, RCT. Horrow 1991a reported DDAVP vs placebo. Horrow 1991b reported DDAVP and tranexamic acid vs tranexamic acid and placebo. Horrow 1991c reported DDAVP vs tranexamic acid</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants | <p><b>Inclusion criteria:</b> elective cardiac surgery</p> <p><b>Exclusion criteria:</b> warfarin or oestrogens within 7 days of surgery; active haematuria; serum creatinine <math>\geq 2</math> mg/dL; personal or family history of abnormal bleeding; intra-aortic balloon counterpulsation</p> <p><b>Number of participants randomised:</b> 84</p> <p><b>Number of participants analysed:</b> 82</p> <p><b>Age:</b> desmopressin arm: <math>63 \pm 11</math> years; placebo arm: <math>64 \pm 10</math> years</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: aortocoronary bypass grafting (ACBG) 32, valve replacement 3, combined ACBG and valve replacement 2, ASD repair 1</li> <li>Placebo arm: ACBG 36, valve replacement 6, combined ACBG and valve replacement 2</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: <math>92 \pm 34</math> minutes; placebo arm: <math>98 \pm 33</math> minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> all participants</p> |

|  |   |   |
|--|---|---|
|  | <b>Transfusion protocol:</b> red cells transfused if haematocrit < 21%, chest tube drainage ≥ 250 mL/h, or haematocrit < 24%, with haemodynamic evidence of hypovolaemia  |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 μg/kg intravenously (diluent and diluent volume not reported)) after heparin reversal over 20 minutes (n = 38)<br><b>Comparator arm:</b> placebo (0.9% saline (diluent volume not reported)) (timing and speed of infusion not reported) (n = 44) |   |
| Outcomes   | <b>Primary outcome:</b> blood loss (measured by drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Number of participants receiving a red cell transfusion</li><li>• Reoperation due to bleeding</li><li>• Thromboembolic events</li></ul>            |   |
| Notes  |   |   |
| <i>Risk of bias</i>                                    |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Low risk  | Quote: “A table of random numbers determined patient allocation to one of four groups”  |
| Allocation concealment                                 | Low risk  | Quote: “Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions”   |
| Blinding of participants and personnel<br>All outcomes | Low risk  | Quote: “Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions. Actual group assignments became known months after patient participation ended” |
| Blinding of outcome assessors<br>All outcomes          | Low risk  | Quote: “Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions. Actual group assignments became known months after patient participation ended” |
| Incomplete outcome data<br>All outcomes                | Unclear risk  | 4 randomised were then excluded postoperatively; 1 developed a rash but 1 in each of the placebo and tranexamic acid groups returned to theatre, and 1 in the combined group “could not be separated from ECC”          |

## Horrow 1991a (Continued)

|                             |              |  |
|-----------------------------|--------------|--|
| Selective outcome reporting | Unclear risk | Protocol not available   |
| Other sources of bias       | Low risk     | No other clear sources of bias. Supported by a grant from the Mary L Smith Charitable Lead Trust |

## Horrow 1991b

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> single-centre, 4-arm, parallel-group RCT. <a href="#">Horrow 1991a</a> reported DDAVP vs placebo. <a href="#">Horrow 1991b</a> reported DDAVP and tranexamic acid vs tranexamic acid and placebo. <a href="#">Horrow 1991c</a> reported DDAVP vs tranexamic acid</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants  | <p><b>Inclusion criteria:</b> elective cardiac surgery</p> <p><b>Exclusion criteria:</b> warfarin or oestrogens within 7 days of surgery; active haematuria; serum creatinine <math>\geq 2</math> mg/dL; personal or family history of abnormal bleeding; intra-aortic balloon counterpulsation</p> <p><b>Number of participants randomised:</b> 79</p> <p><b>Number of participants analysed:</b> 77</p> <p><b>Age:</b> desmopressin and tranexamic acid arm: <math>63 \pm 9</math> years; tranexamic acid and placebo arm: <math>65 \pm 11</math> years</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin and tranexamic acid arm: ACBG 34, valve replacement 6</li> <li>Tranexamic acid and placebo arm: ACBG 26, valve replacement 6, combined ACBG and valve replacement 2, ASD repair 3</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin and tranexamic acid arm: <math>92 \pm 31</math> minutes; tranexamic acid and placebo arm: <math>87 \pm 40</math> minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> all participants treated with tranexamic acid 10 mg/kg loading dose over 30 minutes, then 1 mg/kg/h for 10 hours</p> <p><b>Cell salvage:</b> all participants</p> <p><b>Transfusion protocol:</b> red cells transfused if haematocrit <math>&lt; 21\%</math>, chest tube drainage <math>\geq 250</math> mL/h, or haematocrit <math>&lt; 24\%</math> with haemodynamic evidence of hypovolaemia</p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (0.3 <math>\mu</math>g/kg intravenously (diluent and diluent volume not reported)) after heparin reversal over 20 minutes. Tranexamic acid 10 mg/kg loading dose after induction of anaesthesia and before first skin incision over 30 minutes, then 1 mg/kg/h for 10 hours (<math>n = 40</math>)</p> <p><b>Comparator arm:</b> placebo (0.9% saline (diluent volume not reported)) (timing and speed of infusion not reported). Tranexamic acid 10 mg/kg loading dose after induction</p>   |

|  |  |   |
|--|--|---|
|  | of anaesthesia and before first skin incision over 30 minutes, then 1 mg/kg/h for 10 hours (n = 37)  |   |
| Outcomes   | <b>Primary outcome:</b> blood loss (measured by drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Number of participants receiving a red cell transfusion</li><li>• Reoperation due to bleeding</li><li>• Thromboembolic events</li></ul> |   |
| Notes  |  |   |
| <i><b>Risk of bias</b></i>                             |  |   |
| <b>Bias</b>  | <b>Authors' judgement</b>  | <b>Support for judgement</b>  |
| Sequence Generation                                    | Low risk   | Quote: "A table of random numbers determined patient allocation to one of four groups"  |
| Allocation concealment                                 | Low risk   | Quote: "Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions"   |
| Blinding of participants and personnel<br>All outcomes | Low risk   | Quote: "Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions. Actual group assignments became known months after patient participation ended" |
| Blinding of outcome assessors<br>All outcomes          | Low risk   | Quote: "Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions. Actual group assignments became known months after patient participation ended" |
| Incomplete outcome data<br>All outcomes                | Unclear risk   | 4 randomised participants were excluded postoperatively; 1 developed a rash but 1 in each of placebo and tranexamic acid groups returned to theatre, and 1 in the combined group "could not be separated from ECC"      |
| Selective outcome reporting                            | Unclear risk   | Protocol not available  |
| Other sources of bias                                  | Low risk   | No other clear sources of bias. Supported by a grant from the Mary L Smith Charitable Lead Trust  |

## Horrow 1991c

|                     |   |
|---------------------|---|
| Methods             | <p><b>Type of study:</b> single-centre, 4-arm, parallel-group RCT. <a href="#">Horrow 1991a</a> reported DDAVP vs placebo. <a href="#">Horrow 1991b</a> reported DDAVP and tranexamic acid vs tranexamic acid and placebo. <a href="#">Horrow 1991c</a> reported DDAVP vs tranexamic acid</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants        | <p><b>Inclusion criteria:</b> elective cardiac surgery</p> <p><b>Exclusion criteria:</b> warfarin or oestrogens within 7 days of surgery; active haematuria; serum creatinine <math>\geq 2</math> mg/dL; personal or family history of abnormal bleeding; intra-aortic balloon counterpulsation</p> <p><b>Number of participants randomised:</b> 77</p> <p><b>Number of participants analysed:</b> 75</p> <p><b>Age:</b> desmopressin arm: <math>63 \pm 11</math> years; tranexamic acid arm: <math>65 \pm 11</math> years</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: ACBG 32, valve replacement 3, combined ACBG and valve replacement 2, ASD repair 1</li> <li>Tranexamic acid arm: ACBG 26, valve replacement 6, combined ACBG and valve replacement 2, ASD repair 3</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: <math>92 \pm 34</math> minutes; tranexamic acid arm: <math>87 \pm 40</math> minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> desmopressin arm: 0; tranexamic acid arm: all participants in tranexamic acid arm treated with tranexamic acid 10 mg/kg loading dose over 30 minutes, then 1 mg/kg/h for 10 hours</p> <p><b>Cell salvage:</b> all participants</p> <p><b>Transfusion protocol:</b> red cells transfused if haematocrit <math>&lt; 21\%</math>, chest tube drainage <math>\geq 250</math> mL/h, or haematocrit <math>&lt; 24\%</math> with haemodynamic evidence of hypovolaemia</p> |
| Interventions       | <p><b>Intervention arm:</b> DDAVP (<math>0.3 \mu\text{g/kg}</math> intravenously (diluent and diluent volume not reported)) after heparin reversal over 20 minutes (<math>n = 38</math>)</p> <p><b>Comparator arm:</b> tranexamic acid 10 mg/kg loading dose after induction of anaesthesia and before first skin incision over 30 minutes, then 1 mg/kg/h for 10 hours (<math>n = 37</math>)</p>   |
| Outcomes            | <p><b>Primary outcome:</b> blood loss (measured by drain output)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>Number of participants receiving a red cell transfusion</li> <li>Reoperation due to bleeding</li> <li>Thromboembolic events</li> </ul>   |
| Notes               |   |
| <i>Risk of bias</i> |   |

**Horrow 1991c** (Continued)

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Low risk           | Quote: "A table of random numbers determined patient allocation to one of four groups"  |
| Allocation concealment                                 | Low risk           | Quote: "Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions"   |
| Blinding of participants and personnel<br>All outcomes | Low risk           | Quote: "Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions. Actual group assignments became known months after patient participation ended" |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Quote: "Coded infusion bags and sealed envelopes prepared by a pharmacist not involved in the study provided double-blinded conditions"   |
| Incomplete outcome data<br>All outcomes                | Unclear risk       | 4 randomised participants were then excluded postoperatively; 1 developed a rash but 1 in each of placebo and tranexamic acid groups returned to theatre, and 1 in the combined group "could not be separated from ECC" |
| Selective outcome reporting                            | Unclear risk       | Protocol not available  |
| Other sources of bias                                  | Low risk           | No other clear sources of bias. Supported by a grant from the Mary L Smith Charitable Lead Trust  |

**Jin 2015**

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> China<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> undergoing elective valvular surgery; ASA classification 2-3; no coronary heart disease or decompensated heart failure; no blood disease (no further information given); normal preoperative coagulation tests and platelet count; no anticoagulant or haemostasis treatment for 1 week before surgery<br><b>Exclusion criteria:</b> emergency or repeat surgery |

|  |   |   |
|--|---|---|
|  | <p><b>Number of participants randomised:</b> 102</p> <p><b>Number of participants analysed:</b> 102</p> <p><b>Age:</b> desmopressin arm: 49 ± 10 years; placebo arm: 53 ± 9 years</p> <p><b>Gender:</b> desmopressin arm: 21 male, 31 female; placebo arm: 21 male, 29 female</p> <p><b>Type of surgery:</b> all undergoing elective valve replacement surgery</p> <p><b>Duration of surgery:</b> desmopressin arm: 215 ± 67 minutes; placebo arm: 205 ± 76 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 110 ± 49 minutes; placebo arm: 101 ± 50 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> none</p> <p><b>Thrombocytopenia:</b> none</p> <p><b>Antifibrinolytics:</b> all participants received tranexamic acid 30 mg/kg during surgery</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |   |
| Interventions  | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) 30 minutes before cardiac rewarming over 10 minutes (n = 52)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) 30 minutes before cardiac rewarming over 10 minutes (n = 50)</p>  |   |
| Outcomes   | <p><b>Primary outcomes</b></p> <ul style="list-style-type: none"><li>• Total blood loss (method for measurement not reported)</li><li>• Laboratory measures of haemostasis</li></ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"><li>• Number of participants receiving a red cell transfusion</li><li>• All-cause mortality</li><li>• Thromboembolic events</li></ul>   |   |
| Notes  |   |   |
| <i>Risk of bias</i>                                    |   |   |
| <b>Bias</b>  | <b>Authors’ judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Insufficient information to make judgement  |
| Allocation concealment                                 | Unclear risk  | Insufficient information to make judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Insufficient information for judgement: “a double-blind method was utilized”, but DDAVP was infused over 10 minutes, which may have broken blinding |

|   |              |   |
|---|--------------|---|
| Blinding of outcome assessors<br>All outcomes | Unclear risk | Insufficient information for judgement: “a double-blind method was utilized”, but DDAVP was infused over 10 minutes, which may have broken blinding |
| Incomplete outcome data<br>All outcomes       | Low risk     | All participants included in final analysis   |
| Selective outcome reporting                   | Unclear risk | Protocol not available  |
| Other sources of bias                         | Unclear risk | Insufficient information to make judgement  |

## Karnezis 1994a

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> 2 separate single-centre, 2-arm, parallel-group RCTs. <a href="#">Karnezis 1994a</a> reported DDAVP vs placebo for participants undergoing total knee replacement. <a href="#">Karnezis 1994b</a> reported DDAVP vs placebo for participants undergoing total hip replacement</p> <p><b>Setting:</b> orthopaedic surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants  | <p><b>Inclusion criteria:</b> primary total knee replacement</p> <p><b>Exclusion criteria:</b> history of operative intervention involving hip or knee; coagulation disorder; coronary artery disease; warfarin or heparin within 7 days of procedure; bilateral or revision procedures</p> <p><b>Number of participants randomised:</b> 36</p> <p><b>Number of participants analysed:</b> 36</p> <p><b>Age:</b> desmopressin arm: 65 ± 5.3 years; placebo arm: 66 ± 9.3 years</p> <p><b>Gender:</b> desmopressin arm: 7 male, 10 female; placebo arm: 9 male, 10 female</p> <p><b>Type of surgery:</b> all undergoing elective total knee replacement surgery</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not used</p> <p><b>Transfusion protocol:</b> red cells transfused if haematocrit &lt; 22% to 24%</p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) 30 minutes before complete closure of the wound over 20 minutes (n = 17)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) 30 minutes before complete closure of the wound over 20 minutes (n = 19)</p>   |

|  |   |  |
|--|---|--|
| Outcomes   | <b>Primary outcomes</b> <ul style="list-style-type: none"><li>Blood loss (reported graphically and not possible to extract these data accurately) (measured by drain output)</li><li>Volume of red cells transfused</li></ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"><li>All-cause mortality</li><li>Thromboembolic events</li><li>Reoperation (reported, but group that participants were in was unclear)</li></ul> |  |
| Notes  | Blood loss reported graphically but not numerically, so not possible to extract data for meta-analysis. Volume of red cells reported in mL rather than units. Converted to units with the assumption that 300 mL is equivalent to 1 unit red cells. Three participants returned to theatre for a lateral release, but it was unclear from which groups these participants came  |  |
| <i>Risk of bias</i>                                    |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>   |
| Sequence Generation                                    | Low risk  | Quote: "allocated ... with use of a randomization table"   |
| Allocation concealment                                 | Unclear risk  | Insufficient detail for judgement. Quote: "only pharmacists were aware of the treatment group"   |
| Blinding of participants and personnel<br>All outcomes | Low risk  | Quote: "All patients, treating physicians, and investigators collecting the data were blinded to the assigned treatment. Only the pharmacist was aware of the treatment group" |
| Blinding of outcome assessors<br>All outcomes          | Low risk  | Quote: "All patients, treating physicians, and investigators collecting the data were blinded to the assigned treatment. Only the pharmacist was aware of the treatment group" |
| Incomplete outcome data<br>All outcomes                | High risk   | Unclear which group participants who required reoperation were in. Full numerical data for blood loss not presented  |
| Selective outcome reporting                            | Unclear risk  | Protocol not available   |
| Other sources of bias                                  | Low risk  | No other clear source of bias. Quote: "No funds were received in support of study"   |

## Karnezis 1994b

|                     |  |                       |
|---------------------|--|-----------------------|
| Methods             | <b>Type of study:</b> 2 separate single-centre, 2-arm, parallel-group RCTs. <a href="#">Karnezis 1994a</a> reported DDAVP vs placebo for participants undergoing total knee replacement. <a href="#">Karnezis 1994b</a> reported DDAVP vs placebo for participants undergoing total hip replacement<br><b>Setting:</b> orthopaedic surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered   |                       |
| Participants        | <b>Inclusion criteria:</b> primary total hip replacement<br><b>Exclusion criteria:</b> history of operative intervention involving hip or knee; coagulation disorder; coronary artery disease; warfarin or heparin within 7 days of procedure; bilateral or revision procedures<br><b>Number of participants randomised:</b> 56<br><b>Number of participants analysed:</b> 56<br><b>Age:</b> desmopressin arm: 65 ± 7.8 years; placebo arm: 67 ± 6.7 years<br><b>Gender:</b> desmopressin arm: 12 male, 14 female; placebo arm: 14 male, 16 female<br><b>Type of surgery:</b> all undergoing elective total hip replacement surgery<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 22% to 24% |                       |
| Interventions       | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) 30 minutes before complete closure of the wound over 20 minutes (n = 26)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) 30 minutes before complete closure of the wound over 20 minutes (n = 30)  |                       |
| Outcomes            | <b>Primary outcomes</b> <ul style="list-style-type: none"><li>Blood loss (reported graphically and not possible to extract this data accurately) (measured by drain output)</li><li>Volume of red cells transfused</li></ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"><li>All-cause mortality</li><li>Thromboembolic events</li><li>Reoperation (reported but unclear which group participants were in)</li></ul>   |                       |
| Notes               | Blood loss reported graphically but not numerically, so not possible to extract data for meta-analysis. Volume of red cells reported in mL rather than units. Converted to units assuming that 300 mL is equivalent to 1 unit red cells. Three participants returned to theatre for a lateral release, but it is unclear which groups these participants were from   |                       |
| <b>Risk of bias</b> |  |                       |
| Bias                | Authors' judgement   | Support for judgement |

**Karnezis 1994b** (Continued)

|  |              |  |
|--|--------------|--|
| Sequence Generation                                    | Low risk     | Quote: “allocated ... with use of a randomization table”   |
| Allocation concealment                                 | Unclear risk | Insufficient detail for judgement. Quote: “only pharmacists were aware of the treatment group”   |
| Blinding of participants and personnel<br>All outcomes | Low risk     | Quote: “All patients, treating physicians, and investigators collecting the data were blinded to the assigned treatment. Only the pharmacist was aware of the treatment group” |
| Blinding of outcome assessors<br>All outcomes          | Low risk     | Quote: “All patients, treating physicians, and investigators collecting the data were blinded to the assigned treatment. Only the pharmacist was aware of the treatment group” |
| Incomplete outcome data<br>All outcomes                | High risk    | Unclear which group participants who required reoperation were in. Full numerical data for blood loss not presented  |
| Selective outcome reporting                            | Unclear risk | Protocol not available   |
| Other sources of bias                                  | Low risk     | No other clear source of bias. Quote: “No funds were received in support of study”   |

**Kobrinisky 1987**

|              |  |
|--------------|--|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> orthopaedic surgery<br><b>Country:</b> Canada<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> scheduled spinal fusion with Harrington rod instrumentation<br><b>Exclusion criteria:</b> bleeding diathesis; aspirin within 14 days; bleeding time > 9 minutes on preoperative screen<br><b>Number of participants randomised:</b> 35<br><b>Number of participants analysed:</b> 35<br><b>Age:</b> desmopressin arm: 14.8 ± 3.3 years; placebo arm: 15.3 ± 1.8 years<br><b>Gender:</b> desmopressin arm: 8 male, 9 female; placebo arm: 7 male, 11 female<br><b>Type of surgery:</b> all undergoing spinal fusion with Harrington rod instrumentation<br><b>Duration of surgery:</b> desmopressin arm: 178 minutes (mean); placebo arm: 177 minutes (mean)<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none |

|               |  |
|---------------|--|
|               | <b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported  |
| Interventions | <b>Intervention arm:</b> DDAVP (10 $\mu\text{g}/\text{m}^2$ body surface area intravenously in 0.5 $\mu\text{g}/\text{mL}$ (diluent not reported)) immediately after induction of anaesthesia over 20 minutes (n = 17)<br><b>Comparator arm:</b> placebo (type of placebo and volume not reported) immediately after induction of anaesthesia over 20 minutes (n = 18) |
| Outcomes      | <b>Primary outcome:</b> blood loss intraoperatively and total blood loss (measured by weighing surgical sponges and suction drainage)<br><b>Secondary outcome:</b> volume of red cells transfused intraoperatively   |
| Notes         | All participants given DDAVP 3 days before surgery to assess its effects in addition to DDAVP/placebo immediately before surgery. Blood loss perioperatively and volume of red cells transfused reported as mean and mean difference with 95% confidence intervals. Standard deviations for each outcome have been calculated from these data                          |

**Risk of bias**

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Unclear risk       | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | Quote: "The medication was sent to the operating room in a syringe labelled "spinal fusion study medication ...", "Neither the surgeon nor the anaesthetist was aware of the treatment groups to which patients were assigned"<br>Insufficient detail provided about volume and type of placebo for judgement |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk       | Quote: "The medication was sent to the operating room in a syringe labelled "spinal fusion study medication...", "Neither the surgeon nor the anaesthetist was aware of the treatment groups to which patients were assigned"<br>Insufficient detail provided about volume and type of placebo for judgement  |

**Kobrinisky 1987** (Continued)

|   |              |  |
|---|--------------|--|
| Incomplete outcome data<br>All outcomes | Low risk     | All participants included in final analysis (although no data for 5 in each group for duration of surgery). Data missing from 1 participant who received DDAVP and 1 who received placebo for red cell transfusions. No explanation given. However, this represented < 10% total |
| Selective outcome reporting             | Unclear risk | Protocol not available   |
| Other sources of bias                   | Unclear risk | Desmopressin was provided by Richmond Pharmaceuticals Inc, but unclear if company had a role in study design   |

**Kuitunen 1992**

|               |   |
|---------------|---|
| Methods       | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Finland<br><b>Registration:</b> not prospectively registered   |
| Participants  | <b>Inclusion criteria:</b> elective primary CABG<br><b>Exclusion criteria:</b> previous cardiac surgery; coagulation disorder; coumarin anticoagulant, heparin or acetylsalicylic acid within 5 days of surgery<br><b>Number of participants randomised:</b> 33<br><b>Number of participants analysed:</b> 30<br><b>Age:</b> desmopressin arm: 57 ± 9 years; placebo arm: 59 ± 5 years<br><b>Gender:</b> desmopressin arm: 14 male, 1 female; placebo arm: 14 male, 1 female<br><b>Type of surgery:</b> all undergoing primary CABG<br><b>Duration of surgery:</b> desmopressin arm: 247 ± 42 minutes; placebo arm: 244 ± 39 minutes<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 94 ± 19 minutes; placebo arm: 103 ± 23 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 20% during cardiopulmonary bypass, and if haematocrit < 30% postoperatively |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 100 mL 0.9% saline) immediately after sternal closure over 15 minutes (n = 15)<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline) immediately after sternal closure over 15 minutes (n = 15)   |

**Kuitunen 1992** (Continued)

|  |  |  |
|--|--|--|
| Outcomes   | <b>Primary outcome:</b> laboratory measures of haemostasis<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Total volume of red cells transfused</li><li>• Total blood loss (measured by drain output)</li><li>• All-cause mortality</li></ul> |  |
| Notes  | Volume of red cells transfused reported as mean and range, so reported narratively and not included in meta-analysis   |  |
| <i><b>Risk of bias</b></i>                             |  |  |
| <b>Bias</b>  | <b>Authors' judgement</b>  | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk   | Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk   | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Unclear risk   | Insufficient information for judgement. Study reported it was double-blind but without giving details  |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk   | Insufficient information for judgement. Study reported it was double-blind but without giving details  |
| Incomplete outcome data<br>All outcomes                | High risk  | Three participants excluded after randomisation without justification in the protocol: 1 in the placebo arm died, and 2 in the DDAVP arm had significant complications |
| Selective outcome reporting                            | Unclear risk   | No protocol available  |
| Other sources of bias                                  | Low risk   | No other clear sources of bias. The study was supported by grants from the Paulo Foundation and Helsinki University Central Hospital                                   |

**Lazarchick 1995**

|              |  |
|--------------|--|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> type of surgery not reported<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered         |
| Participants | <b>Inclusion criteria:</b> undergoing a surgical procedure with expected blood loss < 750 mL<br><b>Exclusion criteria:</b> none reported<br><b>Number of participants randomised:</b> not reported |

|  |   |  |
|--|---|--|
|  | <b>Number of participants analysed:</b> 23<br><b>Age:</b> not reported<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> not reported<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> not reported<br><b>Emergency cases:</b> not reported<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |  |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 $\mu$ g/kg intravenously in 10 mL 0.9% saline) after anaesthetic induction (duration of infusion not reported) (n = 12)<br><b>Comparator arm:</b> placebo (10 mL 0.9% saline) after anaesthetic induction (duration of infusion not reported) (n = 11)  |  |
| Outcomes   | <b>Primary outcome:</b> laboratory measures of haemostasis<br><b>Secondary outcomes:</b> none reported  |  |
| Notes  | No outcomes of interest to this review were reported in this trial  |  |
| <i>Risk of bias</i>                                    |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>           |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Insufficient information for judgement |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | Insufficient information for judgement |
| Incomplete outcome data<br>All outcomes                | Unclear risk  | Insufficient information for judgement |
| Selective outcome reporting                            | Unclear risk  | No protocol available                  |
| Other sources of bias                                  | Unclear risk  | Insufficient information for judgement |

|                        |   |  |
|------------------------|---|--|
| Methods                | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> dialysis catheter insertion<br><b>Country:</b> South Korea<br><b>Registration:</b> not prospectively registered   |  |
| Participants           | <b>Inclusion criteria:</b> uraemic patients who had not yet started dialysis; undergoing dialysis catheter insertion; prolonged closure time on platelet function analyser-100<br><b>Exclusion criteria:</b> chronic liver disease; infectious diseases (not specified); drugs that interfere with platelet function within 10 days of entering study<br><b>Number of participants randomised:</b> 48<br><b>Number of participants analysed:</b> 48<br><b>Age:</b> desmopressin arm: median 60 (range 28-93) years; placebo arm: median 57 (range 27-66) years<br><b>Gender:</b> desmopressin arm: 16 male, 8 female; placebo arm: 15 male, 9 female<br><b>Type of surgery:</b> all undergoing catheter insertion for dialysis<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> not reported<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |  |
| Interventions          | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) over 30 minutes (timing of infusion not clear) (n = 24)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) over 30 minutes (timing of infusion not clear) (n = 24)   |  |
| Outcomes               | <b>Primary outcome:</b> laboratory measures of haemostasis<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Reoperation due to bleeding</li><li>• Number of participants with any bleeding (measured by number of blood-soaked gauze pads)</li></ul>  |  |
| Notes                  |   |  |
| <b>Risk of bias</b>    |   |  |
| <b>Bias</b>            | <b>Authors' judgement</b>   | <b>Support for judgement</b>           |
| Sequence Generation    | Unclear risk  | Insufficient information for judgement |
| Allocation concealment | Unclear risk  | Insufficient information for judgement |

Lee 2010 (Continued)

|  |              |   |
|--|--------------|---|
| Blinding of participants and personnel<br>All outcomes | High risk    | No information on blinding; probably an open-label trial. Outcomes relatively subjective and could be biased by revealing treatment |
| Blinding of outcome assessors<br>All outcomes          | High risk    | No information on blinding; probably an open-label trial. Outcomes relatively subjective and could be biased by revealing treatment |
| Incomplete outcome data<br>All outcomes                | Low risk     | All participants included in final analysis   |
| Selective outcome reporting                            | Unclear risk | Protocol not available  |
| Other sources of bias                                  | Low risk     | No other clear source of bias. This study was supported by Baxter Korea (not a manufacturer of DDAVP)                               |

Leino 2010

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single-centre, 3-arm, parallel-group RCT</p> <p><b>Setting:</b> orthopaedic surgery</p> <p><b>Country:</b> Finland</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> seropositive rheumatoid arthritis; scheduled for total hip arthroplasty under spinal anaesthesia</p> <p><b>Exclusion criteria:</b> revision arthroplasty; contraindications for spinal anaesthesia; hepatic malfunction assessed by "thorough anamnesis"; renal malfunction assessed by serum creatinine; "anamnesic" or diagnosed coagulation disorder; warfarin treatment; any treatment other than acetylsalicylic acid or NSAIDs affecting thrombocyte function or other components of coagulation; later excluded 4 participants who experienced intra-operative surgical problems with ensuing blood loss over 400 mL</p> <p><b>Number of participants randomised:</b> 75</p> <p><b>Number of participants analysed:</b> 71</p> <p><b>Age:</b> desmopressin (0.2 µg/kg) arm: 62 ± 13 years; desmopressin (0.4 µg/kg) arm: 59 ± 13 years; placebo arm: 61 ± 13 years</p> <p><b>Gender:</b> desmopressin (0.2 µg/kg) arm: 14 male, 10 female; desmopressin (0.4 µg/kg) arm: 11 male, 12 female; placebo arm: 17 male, 7 female</p> <p><b>Type of surgery:</b> all undergoing total hip replacement</p> <p><b>Duration of surgery:</b> desmopressin (0.2 µg/kg) arm: 102 ± 27 minutes; desmopressin (0.4 µg/kg) arm: 104 ± 24 minutes; placebo arm: 107 ± 33 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> none</p> |

|  |   |  |
|--|---|--|
|  | <b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haemoglobin < 90 g/L   |  |
| Interventions  | <b>Intervention arm 1:</b> DDAVP (0.2 µg/kg intravenously in 50 mL 0.9% saline) at start of surgery over 30 minutes (n = 24)<br><b>Intervention arm 2:</b> DDAVP (0.4 µg/kg intravenously in 50 mL 0.9% saline) at start of surgery over 30 minutes (n = 23)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) at start of surgery over 30 minutes (n = 24)   |  |
| Outcomes   | <b>Primary outcome:</b> total blood loss (measured by estimating blood loss from surgical swabs and suction drainage)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Volume of red cells transfused intraoperatively and total volume of red cells transfused</li><li>• Intraoperative blood loss</li><li>• Thromboembolic events</li></ul> |  |
| Notes  | Intraoperative data for mean blood loss and volume of red cells transfused estimated from figure. Standard deviation not available, so results reported narratively. DDAVP (0.4 µg/kg) arm used for comparison versus placebo in analysis   |  |
| <i>Risk of bias</i>                                    |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>   |
| Sequence Generation                                    | Low risk  | Treatment assignment was determined using a randomisation list   |
| Allocation concealment                                 | Low risk  | Sealed envelopes   |
| Blinding of participants and personnel<br>All outcomes | Low risk  | Study drugs were randomised and prepared by an independent pharmacist, and the study code was stored at the pharmacy department. All participants, personnel, and investigators were blinded to treatment assignment for the duration of the study. Placebo was prepared in identical volume and syringe |
| Blinding of outcome assessors<br>All outcomes          | Low risk  | Study drugs were randomised and prepared by an independent pharmacist, and the study code was stored at the pharmacy department. All participants, personnel, and investigators were blinded to treatment assignment for the duration of the study   |

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|---|--------------|---|
| Incomplete outcome data<br>All outcomes | Unclear risk | Quote: "Four patients had to be excluded during the study due to intraoperative surgical problems with ensuing blood loss over 400 mL, including one from the D 0.2 group [DDAVP 0.2 µg/kg group] due to arterial damage, one from the placebo group due to femoral fracture and two from the D 0.4 group [DDAVP 0.4 µg/kg group] due to other complications with acetabular cup. Thus, all the statistical analyses were based on 71 patients"<br>Judgement comment: an intention-to-treat analysis was not used, but only 4 participants were excluded for surgical reasons |
| Selective outcome reporting             | Unclear risk | No protocol available to ensure all prespecified outcomes reported  |
| Other sources of bias                   | Unclear risk | Insufficient information for judgement  |

# Lethagen 1991

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> vascular surgery<br><b>Country:</b> Sweden<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> elective surgery aortoiliac graft surgery for aortoiliac occlusive disease or aneurysms<br><b>Exclusion criteria:</b> history of increased bleeding tendency; prolonged preoperative bleeding time; acetylsalicylic acid within 10 days before surgery<br><b>Number of participants randomised:</b> 50<br><b>Number of participants analysed:</b> 50<br><b>Age:</b> not reported<br><b>Gender:</b> desmopressin arm: 19 male, 6 female; placebo arm: 18 male, 7 female<br><b>Type of surgery</b> <ul style="list-style-type: none"> <li>Desmopressin arm: aortic aneurysm 13, vaso-occlusive disease 12</li> <li>Placebo arm: aortic aneurysm 13, vaso-occlusive disease 11, congenital coarctation of the aorta 1</li> </ul> <b>Duration of surgery:</b> desmopressin arm: 197 ± 62 minutes; placebo arm: 215 ± 93 minutes<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> not reported |

|  |   |   |
|--|---|---|
|  | <b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 30%   |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 μg/kg intravenously in 10 mL 0.9% saline) immediately before the start of the operation over 10 minutes (n = 25)<br><b>Comparator arm:</b> placebo (10 mL 0.9% saline) immediately before the start of the operation over 10 minutes (n = 25)   |   |
| Outcomes   | <b>Primary outcome:</b> blood loss: intraoperatively and in total (measured by estimating blood loss in surgical swabs, suction bottles, and drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Volume of red cells transfused intraoperatively and in total</li><li>• Thromboembolic events</li></ul>                |   |
| Notes  | Volume of red cells transfused reported as mL, so converted to units based on the assumption that 1 unit is equivalent to 300 mL<br>One death occurred, but the study arm in which it occurred was not reported. Death caused by rupture of part of the upper anastomosis of a repair of an abdominal aortic aneurysm, on the sixth postoperative day |   |
| <i>Risk of bias</i>                                    |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Method of sequence generation not reported  |
| Allocation concealment                                 | Unclear risk  | Method of allocation concealment not reported   |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | DDAVP given over 10 minutes and likely to cause facial flushing, resulting in loss of blinding. The abstract states that this was a double-blind placebo-controlled study and reported no further details   |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | DDAVP given over 10 minutes and likely to cause facial flushing, resulting in loss of blinding. The abstract states that this was a double-blind placebo-controlled study and reported no further details. Assessor for pre-operative bleeding was the anaesthetist who was “taking note of suction bottles and counting swabs”<br>No statement about how blinding occurred |

**Lethagen 1991** (Continued)

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|---|-----------|---|
| Incomplete outcome data<br>All outcomes | High risk | Quote: “six patients in whom surgical complications significantly contributed to blood loss and transfusion requirements were identified and excluded”<br>Judgement comment: Six participants (3 from each arm) were excluded from the analysis, but it was reported that exclusion of these data did not alter the findings. However, data for all participants were not reported, so this could not be confirmed  |
| Selective outcome reporting             | High risk | Quote: “The aim of our study was to investigate if desmopressin given to patients without a history of increased bleeding tendency undergoing aorto-iliac graft surgery could reduce blood loss and the transfusion requirement. We also aimed to analyse changes in factor VIII/von Willebrand factor (FVIII/vWF) levels and to monitor the safety profile of desmopressin in relation to blood loss”<br>The safety profile of desmopressin in relation to blood loss was not reported in full |
| Other sources of bias                   | Low risk  | No other clear sources of bias. Supported by grants from the Swedish Medical Research Council   |

**Letts 1998**

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> 2-arm, parallel-group RCT (unclear whether single-centre or multi-centre trial)<br><b>Setting:</b> orthopaedic surgery<br><b>Country:</b> Canada<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> paediatric patients undergoing spine fusion for neuromuscular scoliosis<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> 30<br><b>Number of participants analysed:</b> 30<br><b>Age:</b> desmopressin arm: 13.4 ± 2.1 years; placebo arm: 13.8 ± 2.8 years<br><b>Gender:</b> desmopressin arm: 9 male, 7 female; placebo arm: 9 male, 5 female<br><b>Type of surgery:</b> all undergoing spine fusion<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> not reported |

|               |   |
|---------------|---|
|               | <b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported   |
| Interventions | <b>Intervention arm:</b> DDAVP (10 $\mu\text{g}/\text{m}^2$ body surface area (route of administration, diluent, and volume of diluent not reported)) immediately after induction of anaesthesia (duration of infusion not reported) (n = 16)<br><b>Comparator arm:</b> placebo (0.9% saline (volume not reported)) immediately after induction of anaesthesia (duration of infusion not reported) (n = 14) |
| Outcomes      | <b>Primary outcome:</b> blood loss: intraoperatively (measured by estimating blood loss in surgical sponges and suction drainage)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Volume of red cells transfused</li> <li>• Clinically significant hypotension</li> </ul>   |
| Notes         | Perioperative blood loss and perioperative volume of red cells transfused did not distinguish between outcomes before and after administration of DDAVP/placebo. Consequently, these outcomes could not be included in meta-analysis  |

### *Risk of bias*

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Unclear risk       | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | Insufficient information for judgement. Surgical team reported to be blinded to treatment, but no details provided  |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk       | Insufficient information for judgement  |
| Incomplete outcome data<br>All outcomes                | Unclear risk       | Insufficient information for judgement  |
| Selective outcome reporting                            | Unclear risk       | No protocol available   |
| Other sources of bias                                  | Unclear risk       | Scoliosis on average 13 degrees more severe in DDAVP group. Desmopressin was supplied by UpJohn Co of Toronto, but unclear if they had a role in study design |

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> kidney biopsy</p> <p><b>Country:</b> Italy</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants  | <p><b>Inclusion criteria:</b> undergoing percutaneous ultrasound-guided biopsy of the native kidney in the Bari renal unit; aged 16 to 80 years; blood pressure 140/90 mmHg with or without antihypertensive therapy; serum creatinine level &lt; 1.5 mg/dL and/or estimated glomerular filtration rate (GFR) &lt; 60 mL/min/1.73 m<sup>2</sup> (calculated by the Modification of Diet in Renal Disease (MDRD) study equation); normal coagulation parameters (bleeding time evaluated by the Simplate method, with values for prothrombin time, partial thromboplastin time, platelets, and fibrinogen in the reference range)</p> <p><b>Exclusion criteria:</b> solitary kidney; kidney cancer; hydro-/pyonephrosis; significantly decreased kidney size on ultrasound image; severe obesity (body mass index 30 kg/m<sup>2</sup>); acute kidney injury</p> <p>Medications that could interfere with haemostasis were withdrawn before the procedure: antiplatelet agents at least 7 days before and heparins 1 to 2 days before the kidney biopsy</p> <p><b>Number of participants randomised:</b> 162</p> <p><b>Number of participants analysed:</b> 162</p> <p><b>Age:</b> desmopressin arm: 39.5 ± 14.2 years; placebo arm: 41.7 ± 15 years</p> <p><b>Gender:</b> desmopressin arm: 45 male, 35 female; placebo arm: 43 male, 39 female</p> <p><b>Type of surgery:</b> all undergoing percutaneous ultrasound-guided renal biopsy</p> <p><b>Duration of surgery:</b> desmopressin arm: median 2 passes (IQR 2 to 3); placebo arm: median 2 passes (IQR 2 to 3)</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg subcutaneously (volume and diluent not reported)) 1 hour before the biopsy (duration of infusion not reported) (n = 80)</p> <p><b>Comparator arm:</b> placebo (1 mL 0.9% saline subcutaneously) 1 hour before the biopsy (duration of infusion not reported) (n = 82)</p>   |
| Outcomes      | <p><b>Primary outcome:</b> number of participants with any bleeding (number of participants with a haematoma ≥ 20 mm diameter or haematuria)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Number of participants requiring a red cell transfusion intraoperatively and in total</li> <li>• Thromboembolic events</li> <li>• Clinically important hypotension</li> </ul>   |
| Notes         |  |

| <i>Risk of bias</i>                                    |                    |  |
|--|--------------------|--|
| Bias   | Authors' judgement | Support for judgement  |
| Sequence Generation                                    | Low risk           | Quote: "1:1 allocation assignment sequence was generated using random-number tables; a list divided into blocks of 10 was adequately concealed to prevent attempts to subvert randomisation. Block randomisation was by a computer-generated random number list prepared by an investigator with no clinical involvement in the trial"   |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement<br>Quote: "A 1:1 allocation assignment sequence was generated using random-number tables; a list divided into blocks of 10 was adequately concealed to prevent attempts to subvert randomization. Block randomization was by a computer-generated random number list prepared by an investigator with no clinical involvement in the trial" |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | A placebo was used and therapy was administered by a nurse not involved in the study, however, it was given subcutaneously leading to risk of facial flushing. It is unclear whether other members of the research team were present when the drug was administered. Facial flushing was not reported as an adverse event, so it is unclear whether it occurred                    |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Ultrasonographer blinded to randomisation  |
| Incomplete outcome data<br>All outcomes                | Low risk           | Quote: "All patients were analyzed for the primary and secondary outcomes"   |
| Selective outcome reporting                            | Unclear risk       | No protocol available to assess whether all outcomes reported  |
| Other sources of bias                                  | Low risk           | No other obvious sources of bias. No financial support for the study   |

|                     |  |
|---------------------|--|
| Methods             | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> abdominal, breast, and orthopaedic surgery</p> <p><b>Country:</b> Netherlands</p> <p><b>Registration:</b> prospectively registered (ISRCTN10353850)</p>   |
| Participants        | <p><b>Inclusion criteria:</b> &gt; 18 years old; taking a serotonergic antidepressant (fluvoxamine, fluoxetine, paroxetine, sertraline, venlafaxine, lomipramine, citalopram) for at least 2 weeks; undergoing orthopaedic, abdominal, or breast surgery</p> <p><b>Exclusion criteria:</b> no informed consent; primary haemostasis disorder; hyponatraemia (sodium (serum) &lt; 130 mmol/L); laparoscopic surgery; use of vitamin K antagonists, aspirin, iron supplements, methotrexate, or heparin; acute coronary syndrome (unstable angina or myocardial infarction); spinal anaesthesia during surgery</p> <p><b>Number of participants randomised:</b> 28</p> <p><b>Number of participants analysed:</b> 28</p> <p><b>Age:</b> desmopressin arm: 54.2 ± 14.9 years; placebo arm: 49.1 ± 12.1 years</p> <p><b>Gender:</b> desmopressin arm: 0 male, 14 female; placebo arm: 2 male, 12 female</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>• Desmopressin arm: abdominal surgery 8, breast surgery 2, orthopaedic surgery 4</li> <li>• Placebo arm: abdominal surgery 8, breast surgery 2, orthopaedic surgery 4</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> none</p> <p><b>Thrombocytopenia:</b> none</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |
| Interventions       | <p><b>Intervention arm:</b> DDAVP (15 µg if body weight &lt; 50 kg; 30 µg if body weight 50 kg to 100 kg; and 45 µg if body weight &gt; 100 kg (route of administration, diluent, and diluent volume not reported)) (timing and duration of infusion not reported) (n = 14)</p> <p><b>Comparator arm:</b> placebo (0.9% saline (volume and route of administration not reported) (timing and duration of infusion not reported) (n = 14)</p>   |
| Outcomes            | <p><b>Primary outcome:</b> intraoperative blood loss (measured by estimating blood loss in surgical gauze and drain output)</p> <p><b>Secondary outcomes:</b> number of participants receiving a red cell transfusion intraoperatively</p>   |
| Notes               | <p>Contacted original author, Dr Susanne Marczinski, on 25 February 2016 and 3 March 2016. She provided a published version of the trial in Dutch but was not able to supply any unpublished data. The paper was translated from Dutch into English by Michiel ten Hove. Perioperative blood loss was reported as mean and range. This outcome is reported narratively in this review and was not included in meta-analysis</p>  |
| <i>Risk of bias</i> |  |

**Marczinski 2007** (Continued)

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Unclear risk       | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Low risk           | Both the placebo and the desmopressin ampoule were produced by the production department of the hospital and provided the same label. Because of this, no one at the surgical department knew if participants were randomised to treatment with placebo or with desmopressin  |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Both the placebo and the desmopressin ampoule were produced by the production department of the hospital and provided the same label. Because of this, no one at the surgical department knew if participants were randomised to treatment with placebo or with desmopressin  |
| Incomplete outcome data<br>All outcomes                | Low risk           | All participants included in the final analysis, but this was an interim analysis and it is unclear why the trial was stopped before all participants were recruited  |
| Selective outcome reporting                            | Low risk           | All prespecified outcomes from protocol included in final manuscript  |
| Other sources of bias                                  | High risk          | Plan from protocol was to recruit 45 participants; final publication of results stopped at 28 participants (62% of planned recruitment number). Timing of DDAVP administration unclear. Speed of DDAVP administration (and whether this would have led to facial flushing) also unclear. Sponsored by Hospital Geldersei Vallei |

**Marquez 1992**

|         |   |
|---------|---|
| Methods | <b>Type of study:</b> single-centre, 3-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered |
|---------|---|

|               |   |                       |
|---------------|---|-----------------------|
| Participants  | <p><b>Inclusion criteria:</b> CABG without prior cardiac surgery; no aspirin, NSAIDs, coumarin, or heparin administration (10 days before surgery)</p> <p><b>Exclusion criteria:</b> mediastinal exploration for surgical bleeding or haemodynamic instability pre-CPB or post-CPB, but before DDAVP administration</p> <p><b>Number of participants randomised:</b> 70</p> <p><b>Number of participants analysed:</b> 65</p> <p><b>Age:</b> desmopressin (2 doses) arm: 63.6 ± 1.8 years; desmopressin (1 dose) arm: 59.8 ± 1.2 years; placebo arm: 61.7 ± 1.5 years</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery:</b> all undergoing elective CABG</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin (2 doses) arm: 85.1 ± 9.2 minutes; desmopressin (1 dose) arm: 88.6 ± 9.4 minutes; placebo arm: 91.3 ± 10.7 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> red cells transfused if haemoglobin &lt; 100 g/L</p> |                       |
| Interventions | <p><b>Intervention arm 1:</b> DDAVP (0.3 µg/kg intravenously (volume and diluent not reported)) immediately after heparin reversal and again 12 hours postoperatively (duration of infusion not reported) (n = 22)</p> <p><b>Intervention arm 2:</b> DDAVP (0.3 µg/kg intravenously (volume and diluent not reported)) immediately after heparin reversal (duration of infusion not reported). Placebo (0.9% saline (volume not reported) 12 hours postoperatively (duration of infusion not reported) (n = 21)</p> <p><b>Comparator arm:</b> placebo (0.9% saline (volume not reported)) immediately after heparin reversal and again 12 hours postoperatively (duration of infusion not reported) (n = 22)</p>  |                       |
| Outcomes      | <p><b>Primary outcome:</b> total blood loss (measured by estimating blood loss in surgical sponges and suction drainage)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"><li>• Total volume of red cells transfused</li><li>• Number of participants receiving a red cell transfusion</li><li>• Thromboembolic events</li><li>• Clinically important hypotension</li></ul>   |                       |
| Notes         | DDAVP (1 dose) group used for comparison vs placebo for main analysis. Blood loss and volume of red cells transfused reported as medians. These outcomes are reported narratively in this review and were not included in meta-analysis   |                       |
| Risk of bias  |   |                       |
| Bias          | Authors' judgement  | Support for judgement |

**Marquez 1992** (Continued)

|  |              |   |
|--|--------------|---|
| Sequence Generation                                    | Unclear risk | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk | Quote: “patients ... randomized into 3 blinded groups” but no further details given                             |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk | Quote: “patients ... randomized into 3 blinded groups” but no further details given                             |
| Incomplete outcome data<br>All outcomes                | High risk    | Quote: “three patients excluded after randomisation for mediastinal exploration secondary to surgical bleeding” |
| Selective outcome reporting                            | Unclear risk | No protocol available   |
| Other sources of bias                                  | High risk    | Study discontinued prematurely without appropriate rationale  |

**Mongan 1992a**

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> 2 separate single-centre, 2-arm, parallel-group RCTs. Separated according to post-cardiopulmonary bypass thromboelastography maximum amplitude (MA). <a href="#">Mongan 1992a</a> reported those with MA &gt; 50 mm and <a href="#">Mongan 1992b</a> reported those with MA ≤ 50 mm</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> elective primary CABG</p> <p><b>Exclusion criteria:</b> preoperative anticoagulation/aspirin within 1 week of surgery; re-exploration due to surgical bleeding; postoperative evidence of fibrinolysis</p> <p><b>Number of participants randomised:</b> 3 participants excluded between <a href="#">Mongan 1992a</a> and <a href="#">Mongan 1992b</a> before administration of DDAVP or placebo</p> <p><b>Number of participants analysed:</b> 86</p> <p><b>Age:</b> desmopressin arm: 61.5 ± 9.3 years; placebo arm: 60.9 ± 9.7 years</p> <p><b>Gender:</b> desmopressin arm: 40 male, 4 female; placebo arm: 36 male, 6 female</p> <p><b>Type of surgery:</b> all undergoing elective CABG</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 127.6 ± 36.9 minutes; placebo arm: 131.7 ± 31.9 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> all had thromboelastography MA &gt; 50 mm. No other information on coagulopathies</p> <p><b>Thrombocytopenia:</b> not reported</p> |

|               |   |
|---------------|---|
|               | <b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 24%   |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) after heparin reversal and before chest closure over 15 minutes (n = 44)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) after heparin reversal and before chest closure over 15 minutes (n = 42)   |
| Outcomes      | <b>Primary outcomes</b> <ul style="list-style-type: none"> <li>• Blood loss intraoperatively and in total (measured by drain output)</li> <li>• Volume of red cell transfusion intraoperatively and in total</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Number of participants receiving a red cell transfusion</li> <li>• All-cause mortality</li> <li>• Thromboembolic events</li> <li>• Clinically important hypotension</li> </ul> |
| Notes         | Volume of red cells transfused reported as absolute number of red cells. Mean volume of red cells transfused was calculated from this. This outcome is presented narratively and was not included in meta-analysis  |

***Risk of bias***

| Bias   | Authors' judgement | Support for judgement  |
|--|--------------------|--|
| Sequence Generation                                    | Low risk           | Computer-generated random number table   |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | Insufficient information for judgement   |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk       | Insufficient information for judgement   |
| Incomplete outcome data<br>All outcomes                | Low risk           | Three excluded - 1 for fibrinolysis, 2 for surgical bleeding before administration of DDAVP/placebo - prespecified in protocol |
| Selective outcome reporting                            | Unclear risk       | No protocol available  |
| Other sources of bias                                  | Unclear risk       | Insufficient information for judgement   |

## Mongan 1992b

|                     |  |
|---------------------|--|
| Methods             | <p><b>Type of study:</b> 2 separate single-centre, 2-arm, parallel-group RCTs. Separated according to post-CPB thromboelastography maximum amplitude (MA). <a href="#">Mongan 1992a</a> reported those with MA &gt; 50 mm and <a href="#">Mongan 1992b</a> reported those with MA ≤ 50 mm</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants        | <p><b>Inclusion criteria:</b> elective primary CABG</p> <p><b>Exclusion criteria:</b> preoperative anticoagulation/aspirin within 1 week of surgery; re-exploration due to surgical bleeding; postoperative evidence of fibrinolysis</p> <p><b>Number of participants randomised:</b> 3 participants excluded between <a href="#">Mongan 1992a</a> and <a href="#">Mongan 1992b</a> before administration of DDAVP or placebo</p> <p><b>Number of participants analysed:</b> 29</p> <p><b>Age:</b> desmopressin arm: 58.8 ± 10.7 years; placebo arm: 65.8 ± 10 years</p> <p><b>Gender:</b> desmopressin arm: 9 male, 4 female; placebo arm: 11 male, 5 female</p> <p><b>Type of surgery:</b> all undergoing elective CABG</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 131.3 ± 41.2 minutes; placebo arm: 136.1 ± 37.3 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> none</p> <p><b>Coagulopathy:</b> all had thromboelastography MA ≤ 50 mm. No other information on coagulopathies</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> red cells transfused if haematocrit &lt; 24%</p> |
| Interventions       | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) after heparin reversal and before chest closure over 15 minutes (n = 13)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) after heparin reversal and before chest closure over 15 minutes (n = 16)</p>   |
| Outcomes            | <p><b>Primary outcomes</b></p> <ul style="list-style-type: none"> <li>• Blood loss intraoperatively and in total (measured by drain output)</li> <li>• Volume of red cell transfusion intraoperatively and in total</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Number of participants receiving a red cell transfusion</li> <li>• All-cause mortality</li> <li>• Thromboembolic events</li> <li>• Clinically important hypotension</li> </ul>  |
| Notes               | <p>Volume of red cells transfused reported as absolute number of red cells. Mean volume of red cells transfused was calculated from this. This outcome is presented narratively and was not included in meta-analysis</p>  |
| <i>Risk of bias</i> |  |

**Mongan 1992b** (Continued)

| Bias   | Authors' judgement | Support for judgement  |
|--|--------------------|--|
| Sequence Generation                                    | Low risk           | Computer-generated random number table   |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | Insufficient information for judgement   |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk       | Insufficient information for judgement   |
| Incomplete outcome data<br>All outcomes                | Low risk           | Three excluded - 1 for fibrinolysis, 2 for surgical bleeding before administration of DDAVP/placebo - prespecified in protocol |
| Selective outcome reporting                            | Unclear risk       | No protocol available  |
| Other sources of bias                                  | Unclear risk       | Insufficient information for judgement   |

**Oliver 2000**

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> paediatric cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> &lt; 40 years old; undergoing complex congenital heart operation requiring cardiopulmonary bypass</p> <p><b>Exclusion criteria:</b> operation expected to have minimal blood loss; pre-existing bleeding disorder</p> <p><b>Number of participants randomised:</b> 60</p> <p><b>Number of participants analysed:</b> 60</p> <p><b>Age:</b> desmopressin arm: 13.9 ± 10 years; placebo arm: 18.1 ± 9.8 years</p> <p><b>Gender:</b> desmopressin arm: 15 male, 16 female; placebo arm: 11 male, 18 female</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: tricuspid valve repair or replacement 5, right ventricle to pulmonary artery conduit 7, mitral valve repair 3, modified Fontan 2, closure of VSD 4, AV valve repair or replacement 4, Konno procedure 2, BCPA 2, right ventricular outflow reconstruction 2, other 5 (some participants underwent more than one procedure)</li> <li>Placebo arm: tricuspid valve repair or replacement 12, right ventricle to pulmonary artery conduit 7, mitral valve repair 3, modified Fontan 5, closure of VSD 1, AVR 3, Pulmonary valve replacement 3, other 6 (some participants underwent more than one procedure).</li> </ul> <p><b>Duration of surgery:</b> desmopressin arm: 450 ± 145 minutes; placebo arm: 447.4 ± 95.6 minutes</p> |

|                        |  |  |
|------------------------|--|--|
|                        | <b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 141.2 ± 79.8 minutes; placebo arm: 144.2 ± 44.6 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> desmopressin arm: 3; placebo arm: 1<br><b>Anticoagulants:</b> desmopressin arm: 2; placebo arm: 2<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> no protocol. Decisions about transfusion made postoperatively by staff cardiothoracic surgeon   |  |
| Interventions          | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL (10 mL if weight < 10 kg) 0.9% saline) 10 minutes after heparin reversal and after aPTT returned to within 10% of normal over 20 to 30 minutes (n = 31)<br><b>Comparator arm:</b> placebo (50 mL (10 mL if weight < 10 kg) 0.9% saline) 10 minutes after heparin reversal and after aPTT returned to within 10% of normal over 20 to 30 minutes (n = 29)  |  |
| Outcomes               | <b>Primary outcomes</b> <ul style="list-style-type: none"><li>• Blood loss intraoperatively and from end of procedure to 24 hours postoperatively (no measure of total blood loss) (measured by volume of suction drainage)</li><li>• Volume of red cell transfusion intraoperatively and from end of procedure to 24 hours postoperatively (no measurement of total)</li></ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Number of participants receiving a red cell transfusion</li><li>• Reoperation due to bleeding</li><li>• All-cause mortality</li><li>• Clinically significant hypotension</li></ul> |  |
| Notes                  | Blood loss measured in mL/m <sup>2</sup> , so this outcome is reported narratively and was not included in meta-analysis. Transfusion requirements reported in units, so not possible to combine with other paediatric cases; results are reported narratively and were not included in meta-analysis. Blood loss and transfusion requirements extracted from figures in the original paper (numbers not given in manuscript)  |  |
| <i>Risk of bias</i>    |  |  |
| Bias                   | Authors' judgement   | Support for judgement  |
| Sequence Generation    | Low risk   | Participants were randomised to 1 of 2 treatment groups (DDAVP or placebo) in blocks of 6 with the use of a random number table with stratification on the basis of previous sternotomy (re-do) or not (primary) |
| Allocation concealment | Unclear risk   | Insufficient information for judgement   |

|  |              |  |
|--|--------------|--|
| Blinding of participants and personnel<br>All outcomes | Low risk     | Only the pharmacist was aware of the solution's identity |
| Blinding of outcome assessors<br>All outcomes          | Low risk     | Blinded personnel were also outcome assessors            |
| Incomplete outcome data<br>All outcomes                | Low risk     | All participants were accounted for in final analysis    |
| Selective outcome reporting                            | Unclear risk | Protocol not available                                   |
| Other sources of bias                                  | Unclear risk | Insufficient information for judgement                   |

### Ozkisacik 2001

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Turkey</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants  | <p><b>Inclusion criteria:</b> undergoing elective CABG</p> <p><b>Exclusion criteria:</b> emergency surgery; haemostatic defect; hypertension; diabetes; renal failure</p> <p><b>Number of participants randomised:</b> 66</p> <p><b>Number of participants analysed:</b> 66</p> <p><b>Age:</b> desmopressin arm: <math>59.0 \pm 11.5</math> years; placebo arm: <math>58.1 \pm 12.1</math> years</p> <p><b>Gender:</b> desmopressin arm: 24 male, 9 female; placebo arm: 23 male, 10 female</p> <p><b>Type of surgery:</b> all undergoing elective CABG</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: <math>73.2 \pm 32.14</math> minutes; placebo arm: <math>65.1 \pm 26.72</math> minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> none</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> none</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not used</p> <p><b>Transfusion protocol:</b> red cells transfused if haematocrit &lt; 28%</p> |
| Interventions | <p><b>Intervention arm:</b> DDAVP (<math>0.3 \mu\text{g/kg}</math> intravenously in 50 mL 0.9% saline) "soon" after heparin reversal over 20 minutes (n = 33)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) "soon" after heparin reversal over 20 minutes (n = 33)</p>   |
| Outcomes      | <p><b>Primary outcome:</b> postoperative blood loss (measured by drain output)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Volume of red cells transfused</li> </ul>   |

**Ozkisacik 2001** (Continued)

|  |   |   |
|--|---|---|
|  | <ul style="list-style-type: none"><li>• Number of participants receiving a red cell transfusion</li><li>• Reoperation due to bleeding</li></ul> |   |
| Notes  |   |   |
| <i>Risk of bias</i>                                    |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Quote: “prospectively randomized and allocated equally”; no further details |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement                                      |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Insufficient information for judgement                                      |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | Insufficient information for judgement                                      |
| Incomplete outcome data<br>All outcomes                | Low risk  | All participants included in final analysis                                 |
| Selective outcome reporting                            | Unclear risk  | Insufficient information for judgement                                      |
| Other sources of bias                                  | Unclear risk  | Insufficient information for judgement                                      |

**Pleym 2004**

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> 2-arm, parallel-group RCT (unclear whether single-centre or multi-centre study)</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Norway</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants | <p><b>Inclusion criteria:</b> stable angina pectoris; elective first-time CABG; taking aspirin</p> <p><b>Exclusion criteria:</b> treatment with heparin or low molecular weight heparin, oral anti-coagulants, NSAIDs or other platelet inhibitors</p> <p><b>Number of participants randomised:</b> 100</p> <p><b>Number of participants analysed:</b> 92</p> <p><b>Age:</b> desmopressin arm: 63.1 ± 8.6 years; placebo arm: 64.4 ± 8 years</p> <p><b>Gender:</b> desmopressin arm: 40 male, 6 female; placebo arm: 36 male, 10 female</p> <p><b>Type of surgery:</b> all undergoing elective CABG</p> <p><b>Duration of surgery:</b> desmopressin arm: 133 ± 27 minutes; placebo arm: 135 ± 31 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 59 ± 16 minutes; placebo arm: 56 ± 20 minutes</p> <p><b>Emergency cases:</b> none</p> |

|  |   |  |
|--|---|--|
|  | <b>Antiplatelet agents:</b> all participants were taking aspirin<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> desmopressin arm: 2 g tranexamic acid 3; placebo arm: 2 g tranexamic acid 8<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> red cell transfusion if haematocrit < 25% |  |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 μg/kg intravenously in 20 mL 0.9% saline) immediately after heparin reversal over 10 minutes (n = 46)<br><b>Comparator arm:</b> placebo (20 mL 0.9% saline) immediately after heparin reversal over 10 minutes (n = 46)   |  |
| Outcomes   | <b>Primary outcome:</b> blood loss postoperatively (measured by drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Number of participants receiving a red cell transfusion</li><li>• Reoperation due to bleeding</li><li>• All-cause mortality</li><li>• Thromboembolic events</li><li>• Clinically important hypotension</li></ul>                       |  |
| Notes  | Volume of blood transfused reported as number of blood product donor exposures per participant. This outcome was not included in the analysis for this review   |  |
| <b>Risk of bias</b>                                    |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>   |
| Sequence Generation                                    | Low risk  | Quote: “The Unit for Applied Clinical Research at the Norwegian University of Science and Technology randomized the patients into two groups by means of a computer program, one group receiving desmopressin and the other group receiving placebo”                                     |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement. Delivered in identical syringes; computer-generated randomised allocation sequence by independent agent  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Quote: “Desmopressin 15 g/mL or placebo was prepared at the hospital pharmacy and delivered in identical 20 mL syringes. The desmopressin group received desmopressin 0.3 g/kg, and the placebo group received a corresponding volume of a 0.9% sodium chloride solution. The injections |

**Pleym 2004** (Continued)

|   |              |   |
|---|--------------|---|
|   |              | were given over 10 min at the end of cardiopulmonary bypass (CPB), immediately after the administration of protamine sulfate to neutralize heparin"<br>Giving DDAVP over 10 minutes is likely to cause facial flushing, resulting in unblinding of personnel, although this may have been masked in the operative setting |
| Blinding of outcome assessors<br>All outcomes | Low risk     | Assessors were blinded  |
| Incomplete outcome data<br>All outcomes       | High risk    | Did not perform an intention-to-treat analysis. Excluded 8 participants in total, including 3 post randomisation for bleeding (deemed surgical)   |
| Selective outcome reporting                   | Unclear risk | No protocol available   |
| Other sources of bias                         | Unclear risk | Imbalance in number of participants treated with tranexamic acid between the 2 groups, although this did not reach statistical significance. Supported by a Norwegian Health Association grant  |

**Reich 1991**

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> adults scheduled to undergo elective myocardial revascularisation or single-valve replacement surgery; left ventricular ejection fraction > 0.40; normal preoperative coagulation profile (prothrombin time, partial thromboplastin time, platelet count, fibrinogen, template bleeding time)<br><b>Exclusion criteria:</b> haemodynamic instability; preoperative heparin therapy within 48 hours; refusal of blood products (Jehovah's Witnesses)<br>Participants on aspirin preparations continued to receive aspirin until the evening before surgery<br><b>Number of participants randomised:</b> 27<br><b>Number of participants analysed:</b> 27<br><b>Age:</b> desmopressin arm: 60 ± 16 years; placebo arm: 55 ± 15 years<br><b>Gender:</b> desmopressin arm: 12 male, 2 female; placebo arm: 9 male, 4 female<br><b>Type of surgery:</b> desmopressin arm: 9 CABG, 5 valve replacements; placebo arm: 8 CABG, 5 valve replacements<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 118 ± 30 minutes; placebo |

|  |   |  |
|--|---|--|
|  | arm: 123 ± 26 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> desmopressin arm: 4; placebo arm: 5<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> all participants<br><b>Transfusion protocol:</b> not reported |  |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 μg/kg intravenously in 0.9% saline (volume not reported)) 15 minutes after heparin reversal over 10 minutes (n = 14)<br><b>Comparator arm:</b> placebo (0.9% saline (volume not reported)) 15 minutes after heparin reversal over 10 minutes (n = 13)   |  |
| Outcomes   | <b>Primary outcome:</b> clinically significant hypotension<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Blood loss postoperatively (measured by drain output)</li><li>• Volume of red cells transfused</li></ul>  |  |
| Notes  |   |  |
| <i>Risk of bias</i>                                    |   |  |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | Insufficient information for judgement.<br>“Patients were randomized to receive a blinded infusion”, but DDAVP was given over 10 minutes, which may have broken blinding |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk  | Insufficient information for judgement.<br>“Patients were randomized to receive a blinded infusion”, but DDAVP was given over 10 minutes, which may have broken blinding |
| Incomplete outcome data<br>All outcomes                | Low risk  | All participants included in final analysis  |
| Selective outcome reporting                            | Unclear risk  | Protocol not available   |
| Other sources of bias                                  | Unclear risk  | Insufficient information for judgement   |

## Reynolds 1993

|                     |  |  |
|---------------------|--|--|
| Methods             | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> paediatric cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered   |  |
| Participants        | <b>Inclusion criteria:</b> paediatric patients ranging in age from 1 day to 16 years of age; scheduled for cardiac operations<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> 112<br><b>Number of participants analysed:</b> 95<br><b>Age:</b> desmopressin arm: 27 ± 43 months; placebo arm: 24 ± 34 months<br><b>Gender:</b> desmopressin arm: 29 male, 24 female; placebo arm: 25 male, 17 female<br><b>Type of surgery</b> <ul style="list-style-type: none"><li>• Desmopressin arm: ASD closure 6, resection subaortic membrane 2, AVR 1, arterial switch 2, AV canal repair 2, biventricular repair 1, Fontan procedure 8, hemi-Fontan 7, VSD closure 8, Rastelli procedure 1, stage 1 palliation for HLHS 11, TOF repair 4</li><li>• Placebo arm: ASD closure 4, Blalock-Taussig 1, RCA-RV fistula closure 1, resection subaortic membrane 1, AVR 0, arterial switch 1, AV canal repair 2, biventricular repair 1, Fontan procedure 7, hemi-Fontan 6, VSD closure 5, Rastelli procedure 2, stage 1 palliation for HLHS 5, TOF repair 5, truncus arteriosus repair 1</li></ul> <b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 70 ± 30 minutes; placebo arm: 82 ± 36 minutes<br><b>Emergency cases:</b> not reported<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |  |
| Interventions       | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 0.9% saline (volume not reported)) 5 minutes after heparin reversal over 15 minutes (n = 53)<br><b>Comparator arm:</b> placebo (0.9% saline (volume not reported)) 5 minutes after heparin reversal over 15 minutes (n = 42)  |  |
| Outcomes            | <b>Primary outcome:</b> blood loss in first 24 hours postoperatively (measured by estimating blood loss in surgical sponges, volume of suction drainage and drain output)<br><b>Secondary outcome:</b> volume of red cells transfused  |  |
| Notes               |  |  |
| <b>Risk of bias</b> |  |  |
| <b>Bias</b>         | <b>Authors' judgement</b>  | <b>Support for judgement</b>           |
| Sequence Generation | Unclear risk   | Insufficient information for judgement |

**Reynolds 1993** (Continued)

|  |              |  |
|--|--------------|--|
| Allocation concealment                                 | Unclear risk | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Low risk     | Only the pharmacist was not blinded to participants' group assignment  |
| Blinding of outcome assessors<br>All outcomes          | Low risk     | Quote: "only pharmacist was not blinded to patient's group assignment"   |
| Incomplete outcome data<br>All outcomes                | High risk    | No intention-to-treat analysis. 17 of 112 participants missing, although they were accounted for - 7 did not receive study drug, 4 had incomplete data, 3 died (non-hemorrhagic), 2 returned to OR, 1 did not have blood available |
| Selective outcome reporting                            | Unclear risk | Protocol not available   |
| Other sources of bias                                  | High risk    | Supported in part by a grant from the Rorer Corporation (a manufacturer of DDAVP)  |

**Rocha 1988**

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Spain</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> &gt; 18 years old; valvular heart disease or atrial septal defect</p> <p><b>Exclusion criteria:</b> emergency surgery; known haemostatic defect; uncontrolled hypertension; renal insufficiency; patients undergoing CABG</p> <p><b>Number of participants randomised:</b> 100</p> <p><b>Number of participants analysed:</b> 100</p> <p><b>Age:</b> desmopressin arm: 55 ± 13 years; placebo arm: 53 ± 12 years</p> <p><b>Gender:</b> desmopressin arm: 19 male, 31 female; placebo arm: 25 male, 25 female</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: MVR 19, mitral commissurotomy 4, mitral annuloplasty 0, AVR 16, mitral and AVR 3, MVR and tricuspid annuloplasty 4, mitral and AVR plus tricuspid annuloplasty 0, closure of atrial septal defect 4</li> <li>Placebo arm: MVR 16, mitral commissurotomy 6, mitral annuloplasty 2, AVR 18, mitral and AVR 4, MVR and tricuspid annuloplasty 1, mitral and AVR plus tricuspid annuloplasty 2, closure of atrial septal defect 1</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 93 ± 43 minutes; placebo arm: 94 ± 40 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> |

|               |  |
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|               | <b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported   |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 50)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 50)  |
| Outcomes      | <b>Primary outcome:</b> blood loss intraoperatively, 24 hours postoperatively, and total blood loss (measured by estimating blood loss in surgical sponges and drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Volume of red cells transfused</li> <li>• Reoperation due to bleeding</li> <li>• All-cause mortality</li> <li>• Thromboembolic events up to 3 days postoperatively</li> </ul> |
| Notes         | Blood loss reported as mL/m <sup>2</sup> , so reported narratively and not included in meta-analysis. Volume of red cells transfused reported in mL, so converted to units, based on the assumption than 300 mL is equivalent to 1 unit  |

### *Risk of bias*

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Unclear risk       | Insufficient information for judgement  |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk       | Insufficient information for judgement  |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk       | Insufficient information for judgement  |
| Incomplete outcome data<br>All outcomes                | Low risk           | Reported all outcomes as planned; all participants analysed   |
| Selective outcome reporting                            | Unclear risk       | No protocol available   |
| Other sources of bias                                  | Unclear risk       | DDAVP supplied by Ferring but it is unclear if this was free of charge or if Ferring had a role in study design |

|               |  |
|---------------|--|
| Methods       | <p><b>Type of study:</b> single-centre, 4-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Spain</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants  | <p><b>Inclusion criteria:</b> &gt; 18 years old; valvular or coronary artery disease</p> <p><b>Exclusion criteria:</b> emergency surgery; known haemostatic defect; hepatic or renal insufficiency; previous exposure to study drugs; use of other techniques for blood saving</p> <p><b>Number of participants randomised:</b> 122</p> <p><b>Number of participants analysed:</b> 109</p> <p><b>Age</b></p> <ul style="list-style-type: none"> <li>• Desmopressin (1 dose) arm: <math>56.6 \pm 8.8</math> years</li> <li>• Desmopressin (2 doses) arm: <math>57.3 \pm 7.6</math> years</li> <li>• Aprotinin arm: <math>58.9 \pm 10</math> years</li> <li>• Standard care arm: <math>56.3 \pm 10.1</math> years</li> </ul> <p><b>Gender</b></p> <ul style="list-style-type: none"> <li>• Desmopressin (1 dose) arm: 14 male, 11 female</li> <li>• Desmopressin (2 doses) arm: 20 male, 8 female</li> <li>• Aprotinin arm: 16 male, 12 female</li> <li>• Standard care arm: 22 male, 6 female</li> </ul> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>• Desmopressin (1 dose) arm: CABG 12, valve replacement 12, combined CABG and valve replacement 1</li> <li>• Desmopressin (2 doses) arm: CABG 16, valve replacement 11, combined CABG and valve replacement 1</li> <li>• Aprotinin arm: CABG 13, valve replacement 14, combined CABG and valve replacement 1</li> <li>• Standard care arm: CABG 14, valve replacement 14</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass</b></p> <ul style="list-style-type: none"> <li>• Desmopressin (1 dose) arm: <math>122.4 \pm 34.4</math> minutes</li> <li>• Desmopressin (2 doses) arm: <math>131.6 \pm 39.3</math> minutes</li> <li>• Aprotinin arm: <math>127.3 \pm 45.4</math> minutes</li> <li>• Standard care arm: <math>121.3 \pm 36.2</math> minutes</li> </ul> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> none</p> <p><b>Thrombocytopenia:</b> none</p> <p><b>Antifibrinolytics:</b> all participants in the aprotinin arm were treated with aprotinin. No other participants were treated with an antifibrinolytic agent</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |
| Interventions | <p><b>Intervention arm 1 (DDAVP 1 dose):</b> DDAVP (<math>0.3 \mu\text{g/kg}</math> intravenously in 50 mL 0.9% saline) immediately after heparin reversal over 20 minutes (n = 25)</p> <p><b>Intervention arm 2 (DDAVP 2 doses):</b> DDAVP (<math>0.3 \mu\text{g/kg}</math> intravenously in 50 mL 0.9% saline) immediately after heparin reversal and again 6 hours postoperatively over 20 minutes (n = 28)</p> <p><b>Intervention arm 3 (aprotinin):</b> aprotinin 2 million KIU within 30 minutes after</p>   |

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|  | induction of anaesthesia followed by a continuous infusion of 500,000 KIU/h until participant left the operating room, and an additional bolus of 2 million KIU aprotinin in the pump prime by replacement of crystalloid solution (n = 28)<br><b>Comparator arm (standard care):</b> standard care (n = 28)                               |  |
| Outcomes   | <b>Primary outcome:</b> postoperative blood loss (measured by drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>● Volume of red cells transfused</li><li>● Reoperation due to bleeding</li><li>● All-cause mortality</li><li>● Thromboembolic events</li><li>● Clinically significant hypotension</li></ul> |  |
| Notes  | Single dose of DDAVP arm used for comparison with placebo for review. Blood loss and total volume of blood transfused reported as mL/m <sup>2</sup> , so reported narratively and not included in meta-analysis.   |  |
| <i><b>Risk of bias</b></i>                             |  |  |
| <b>Bias</b>  | <b>Authors’ judgement</b>  | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk   | Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk   | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | High risk  | Open label   |
| Blinding of outcome assessors<br>All outcomes          | High risk  | Open label   |
| Incomplete outcome data<br>All outcomes                | High risk  | Quote: “Of the total number of patients admitted to the study, 13 (4 in the placebo group and 9 in the treatment groups) were excluded from subsequent analysis because they did not complete the study” |
| Selective outcome reporting                            | Unclear risk   | No protocol available  |
| Other sources of bias                                  | Unclear risk   | Desmopressin supplied by Ferring and aprotinin supplied by Bayer but it is unclear if this was free or if either company had a role in study design  |

## Salmenpera 1991

|                        |   |  |
|------------------------|---|--|
| Methods                | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Finland<br><b>Registration:</b> not prospectively registered   |  |
| Participants           | <b>Inclusion criteria:</b> first-time CABG procedure; bleeding history unremarkable; normal preoperative blood coagulation tests<br><b>Exclusion criteria:</b> people who had received acetylsalicylic acid or heparin within 5 days<br><b>Number of participants randomised:</b> 30<br><b>Number of participants analysed:</b> 30<br><b>Age:</b> desmopressin arm: 57 ± 9 years; placebo arm: 59 ± 5 years<br><b>Gender:</b> desmopressin arm: 14 male, 1 female; placebo arm: 14 male, 1 female<br><b>Type of surgery:</b> all participants undergoing first-time CABG<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 94 ± 19 minutes; placebo arm: 103 ± 23 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 30% |  |
| Interventions          | <b>Intervention arm:</b> DDAVP (0.3 µg/kg via side-port of pulmonary artery catheter introducer in 100 mL 0.9% saline) immediately after sternal closure over 15 minutes (n = 15)<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline via side-port of pulmonary artery catheter introducer) immediately after sternal closure over 15 minutes (n = 15)   |  |
| Outcomes               | <b>Primary outcome:</b> clinically significant hypotension<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Blood loss (method for measurement not reported)</li><li>• Thromboembolic events</li></ul>  |  |
| Notes                  | Blood loss reported as median and range, so this outcome is reported narratively and was not included in meta-analysis  |  |
| <i>Risk of bias</i>    |   |  |
| Bias                   | Authors' judgement  | Support for judgement  |
| Sequence Generation    | Unclear risk  | Insufficient information for judgement   |
| Allocation concealment | Unclear risk  | Insufficient information for judgement<br>Quote: "After sternal closure, patients received, according to their randomisation, in a double-blind fashion, either" |

**Salmenpera 1991** (Continued)

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|--|--------------|---|
| Blinding of participants and personnel<br>All outcomes | Unclear risk | Insufficient information for judgement.<br>Reported to be double-blind, but no details  |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk | Insufficient information for judgement.<br>Reported to be double-blind, but no details  |
| Incomplete outcome data<br>All outcomes                | Low risk     | All participants included in final analysis   |
| Selective outcome reporting                            | Unclear risk | No protocol available   |
| Other sources of bias                                  | High risk    | Double-blind comparison of DDAVP with saline part of a larger trial of DDAVP in patients undergoing CABG: larger trial not published (bleeding outcomes not reported) Supported in part by a grant from the Paulo Foundation, Helsinki, Finland |

**Salzman 1986**

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants | <p><b>Inclusion criteria:</b> undergoing CABG with valvular heart disease, atrial septal defects, or undergoing repeat grafting operations for chronically occluded CABGs</p> <p><b>Exclusion criteria:</b> undergoing primary uncomplicated CABG</p> <p><b>Number of participants randomised:</b> 72</p> <p><b>Number of participants analysed:</b> 70</p> <p><b>Age</b></p> <ul style="list-style-type: none"> <li>• Desmopressin arm: 31-40 years: 2, 41-50 years: 3, 51-60 years: 11, 61-70 years: 8, 71-80 years: 9, &gt; 80 years: 2</li> <li>• Placebo arm: 31-40 years: 3, 41-50 years: 1, 51-60 years: 7, 61-70 years: 11, 71-80 years: 11, &gt; 80 years: 2</li> </ul> <p><b>Gender:</b> desmopressin arm: 21 male, 14 female; placebo arm: 21 male, 14 female</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>• Desmopressin arm: AVR 8, MVR 11, AVR/MVR 0, valve/CABG 5, ASD closure 0, repeat CABG 10, resection of ventricular aneurysm 1</li> <li>• Placebo arm: AVR 13, MVR 6, AVR/MVR 2, valve/CABG 7, ASD closure 1, repeat CABG 6</li> </ul> <p><b>Duration of surgery:</b> desmopressin arm: 373 ± 132 minutes; placebo arm: 392 ± 145 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 144 ± 38 minutes; placebo arm: 159 ± 66 minutes</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> |

|  |   |   |
|--|---|---|
|  | <b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported  |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 $\mu$ g/kg intravenously in 50 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 35)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) immediately after heparin reversal over 15 minutes (n = 35)  |   |
| Outcomes   | <b>Primary outcome:</b> intraoperative blood loss and total blood loss (measured by estimating blood in surgical sponges and suction drainage)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Total volume of red cells transfused</li><li>• Reoperation due to bleeding</li><li>• All-cause mortality</li><li>• Thromboembolic events</li><li>• Clinically significant hypotension</li></ul> |   |
| Notes  |   |   |
| <i><b>Risk of bias</b></i>                             |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk  | Insufficient information for judgement  |
| Allocation concealment                                 | Low risk  | Series of sealed envelopes  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk  | "Double-blind", but no details given  |
| Blinding of outcome assessors<br>All outcomes          | Low risk  | Surgeons asked to comment whether they thought participant was in intervention or placebo cohort - no correlation with actual allocation  |
| Incomplete outcome data<br>All outcomes                | Low risk  | Two participants withdrawn from study - 1 died in operating room before receiving the drug and 1 was withdrawn by surgeon (no reason given) before treatment with drug - not included in analysis |
| Selective outcome reporting                            | Unclear risk  | Protocol not available  |
| Other sources of bias                                  | Low risk  | No other clear risk of bias. Supported by grants from the National Institutes of Health   |

|                     |   |  |
|---------------------|---|--|
| Methods             | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> orthopaedic surgery<br><b>Country:</b> Sweden<br><b>Registration:</b> not prospectively registered  |  |
| Participants        | <b>Inclusion criteria:</b> normal haemostasis; scheduled for elective primary total hip replacement<br><b>Exclusion criteria:</b> secondary procedure; antiplatelet drug within 10 days of surgery; iron-deficient anaemia; diabetes mellitus; rheumatoid disease; any disease requiring steroid treatment; abnormal preoperative coagulation status; abnormal bleeding time<br><b>Number of participants randomised:</b> 80<br><b>Number of participants analysed:</b> 79<br><b>Age:</b> desmopressin arm: 71 ± 9 years; placebo arm: 68 ± 7 years<br><b>Gender:</b> desmopressin arm: 20 male, 19 female; placebo arm: 15 male, 25 female<br><b>Type of surgery:</b> all participants undergoing elective primary total hip replacement surgery<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 27% |  |
| Interventions       | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 50 mL 0.9% saline) post induction of spinal anaesthesia and again 6 hours after first dose over 15 minutes (n = 39)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) post induction of spinal anaesthesia and again 6 hours after first dose over 15 minutes (n = 40)   |  |
| Outcomes            | <b>Primary outcomes</b> <ul style="list-style-type: none"><li>• Blood loss intraoperatively and up to 24 hours postoperatively (measured by estimating blood loss in surgical swabs and drapes; volume in suction bottle; and drain output)</li><li>• Volume of red cells transfused perioperatively and total volume transfused</li></ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• All-cause mortality</li><li>• Thromboembolic events</li><li>• Clinically important hypotension</li></ul>   |  |
| Notes               |   |  |
| <b>Risk of bias</b> |   |  |
| <b>Bias</b>         | <b>Authors' judgement</b>   | <b>Support for judgement</b>           |
| Sequence Generation | Unclear risk  | Insufficient information for judgement |

**Schott 1995** (Continued)

|  |              |  |
|--|--------------|--|
| Allocation concealment                                 | Unclear risk | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Unclear risk | Insufficient information for judgement.<br>“Double-blind” but no details reported  |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk | Insufficient information for judgement.<br>“Double-blind” but no details reported  |
| Incomplete outcome data<br>All outcomes                | Low risk     | One participant excluded as this was an emergency case (fractured neck of femur) and therefore did not meet the inclusion criteria |
| Selective outcome reporting                            | Unclear risk | Protocol not available   |
| Other sources of bias                                  | High risk    | The study was supported by Ferring AB (the manufacturer of DDAVP)  |

**Seezar 1989**

|              |   |
|--------------|---|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> paediatric cardiac surgery</p> <p><b>Country:</b> Canada</p> <p><b>Registration:</b> not prospectively registered</p>  |
| Participants | <p><b>Inclusion criteria:</b> paediatric patients undergoing surgery with cardiac bypass</p> <p><b>Exclusion criteria:</b> not reported</p> <p><b>Number of participants randomised:</b> 60</p> <p><b>Number of participants analysed:</b> 60</p> <p><b>Age:</b> desmopressin arm: 45.9 ± 50.3 months; placebo arm: 64.2 ± 60.1 months</p> <p><b>Gender:</b> desmopressin arm: 17 male, 13 female; placebo arm: 18 male, 12 female</p> <p><b>Type of surgery</b></p> <ul style="list-style-type: none"> <li>Desmopressin arm: ASD 7, VSD 4, TOF 8, Mustard procedure 3, AV canal 1, valvotomy 2, PA conduit 5</li> <li>Placebo arm: ASD 4, VSD 6, TOF 6, Fontan procedure 3, AV canal 2, valvotomy 1, artificial valves 4, PA conduit 4</li> </ul> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 96.4 ± 37.4 minutes; placebo arm: 93.7 ± 47.1 minutes</p> <p><b>Emergency cases:</b> not reported</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |

See [Seear 1989](#) (Continued)

|  |  |  |
|--|--|--|
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 $\mu$ g/kg intravenously in 0.9% saline (volume not reported)) “on conclusion of cardiopulmonary bypass” over 15 minutes (n = 30)<br><b>Comparator arm:</b> placebo (0.9% saline (volume not reported but “equal” to DDAVP volume)) “on conclusion of cardiopulmonary bypass” over 15 minutes (n = 30) |  |
| Outcomes   | <b>Primary outcome:</b> postoperative blood loss (measured by estimating blood loss in surgical sponges and drain output)<br><b>Secondary outcome:</b> all-cause mortality   |  |
| Notes  |  |  |
| <i>Risk of bias</i>                                    |  |  |
| <b>Bias</b>  | <b>Authors’ judgement</b>  | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk   | Insufficient information for judgement   |
| Allocation concealment                                 | Low risk   | Sealed envelopes   |
| Blinding of participants and personnel<br>All outcomes | Low risk   | Only pharmacist aware of treatment allocation  |
| Blinding of outcome assessors<br>All outcomes          | Low risk   | Only pharmacist aware of treatment allocation  |
| Incomplete outcome data<br>All outcomes                | Low risk   | All participants included in final analysis  |
| Selective outcome reporting                            | Unclear risk   | Protocol not available   |
| Other sources of bias                                  | Low risk   | No other clear sources of bias. Supported in part by a grant from the British Columbia Health Care Research Foundation |

Shao 2015

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> endoscopic sinus surgery<br><b>Country:</b> China<br><b>Registration:</b> registered after study commenced (NCT02125188)  |
| Participants | <b>Inclusion criteria:</b> age 18 to 65 years; first-time candidates for 2-side endoscopic sinus surgery; ASA grade 1-2<br><b>Exclusion criteria:</b> history of bleeding disorders; medications that may affect surgical haemostasis; secondary surgery; poorly controlled hypertension; cerebrovascular disease; significant coronary artery disease or arrhythmias; compromised renal or hepatic function; pregnancy<br><b>Number of participants randomised:</b> 90 |

|  |  |   |
|--|--|---|
|  | <b>Number of participants analysed:</b> 90<br><b>Age:</b> desmopressin arm: 45.9 ± 14.9 years; placebo arm: 40.7 ± 17.4 years<br><b>Gender:</b> desmopressin arm: 26 male, 19 female; placebo arm: 24 male, 21 female<br><b>Type of surgery:</b> all undergoing endoscopic sinus surgery<br><b>Duration of surgery:</b> desmopressin arm: 76 ± 20.7 minutes; placebo arm: 82 ± 19.6 minutes<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 µg/kg intravenously in 100 mL 0.9% saline) post anaesthetic induction and preoperatively over 20 minutes (n = 45)<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline) post anaesthetic induction and preoperatively over 20 minutes (n = 45)  |   |
| Outcomes   | <b>Primary outcome:</b> intraoperative blood loss (quality of operative field determined by operating surgeon)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Thromboembolic events</li><li>• Clinically significant hypotension</li></ul>   |   |
| Notes  |  |   |
| <i>Risk of bias</i>                                    |  |   |
| <b>Bias</b>  | <b>Authors’ judgement</b>  | <b>Support for judgement</b>  |
| Sequence Generation                                    | Low risk   | Quote: “Assignment to the groups was performed by computer-generated random numbers”  |
| Allocation concealment                                 | Unclear risk   | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Unclear risk   | Insufficient information on method of blinding. “All of the surgeons were blinded to the patient study groups”                                      |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk   | Insufficient information on method of blinding. Surgeons acted as outcome assessors. “All of the surgeons were blinded to the patient study groups” |

|   |          |  |
|---|----------|--|
| Incomplete outcome data<br>All outcomes | Low risk | All participants included in final analysis  |
| Selective outcome reporting             | Low risk | Primary and secondary outcomes same as trial registration  |
| Other sources of bias                   | Low risk | No other clear sources of bias. Supported by Guangdong Provincial Science and Technology Projects of China |

## Sheridan 1994

|               |  |
|---------------|--|
| Methods       | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> Canada<br><b>Registration:</b> not prospectively registered   |
| Participants  | <b>Inclusion criteria:</b> male; < 70 years old; taking aspirin within previous 7 days; undergoing CABG<br><b>Exclusion criteria:</b> abnormal haematological profile; history of bleeding; repeat coronary bypass surgery; recent heparin intake<br><b>Number of participants randomised:</b> 44<br><b>Number of participants analysed:</b> 44<br><b>Age:</b> desmopressin arm: 56.6 (52.9-60.3) years (mean and range); placebo arm: 61.6 (58.6-64.6) years (mean and range)<br><b>Gender:</b> desmopressin arm: 20 male, 0 female; placebo arm: 24 male, 0 female<br><b>Type of surgery:</b> all undergoing CABG<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> not reported<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> all receiving aspirin<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |
| Interventions | <b>Intervention arm:</b> DDAVP (10 µg/m <sup>2</sup> body surface area intravenously in 20 mL 0.9% saline) "after cardiopulmonary bypass" over 20 minutes (n = 20)<br><b>Comparator arm:</b> placebo (20 mL 0.9% saline) "after cardiopulmonary bypass" over 20 minutes (n = 24)   |
| Outcomes      | <b>Primary outcome:</b> postoperative blood loss (measured by volume of suction drainage and estimated cardiopulmonary bypass residual volume)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Number of participants receiving a red cell transfusion</li> <li>• All-cause mortality</li> </ul>   |

**Sheridan 1994** (Continued)

|  |                           |   |
|--|---------------------------|---|
|  | ● Thromboembolic events   |   |
| Notes  |                           |   |
| <i>Risk of bias</i>                                    |                           |   |
| <b>Bias</b>  | <b>Authors' judgement</b> | <b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk              | Quote: “randomized with restriction in blocks of 10” - exact method unclear |
| Allocation concealment                                 | Unclear risk              | Insufficient information for judgement                                      |
| Blinding of participants and personnel<br>All outcomes | Unclear risk              | Insufficient information for judgement                                      |
| Blinding of outcome assessors<br>All outcomes          | Unclear risk              | Insufficient information for judgement                                      |
| Incomplete outcome data<br>All outcomes                | Low risk                  | All participants included in final analysis                                 |
| Selective outcome reporting                            | Unclear risk              | No protocol available   |
| Other sources of bias                                  | High risk                 | Supported by Ferring Inc (a manufacturer of DDAVP)                          |

**Spyt 1990**

|              |   |
|--------------|---|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group randomised controlled trial<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> UK<br><b>Registration:</b> not prospectively registered  |
| Participants | <b>Inclusion criteria:</b> elective CABG with cardiopulmonary bypass grafting; men age 30 to 70 years and women who were postmenopausal and < 70 years old<br><b>Exclusion criteria:</b> reoperation or emergency surgery; heparin or warfarin within 72 hours of surgery; thrombolytic therapy within 7 days before surgery; no informed consent<br><b>Number of participants randomised:</b> 100<br><b>Number of participants analysed:</b> 98<br><b>Age:</b> desmopressin arm: 58.8 ± 8.8 years; placebo arm: 55 ± 8.4 years<br><b>Gender:</b> desmopressin arm: 42 male, 7 female; placebo arm: 38 male, 11 female<br><b>Type of surgery:</b> all undergoing elective CABG<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 71.4 ± 19 minutes; placebo arm: 74.5 ± 23.3 minutes<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> desmopressin arm: 7; placebo arm: 5 |

|               |   |
|---------------|---|
|               | <b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 30%  |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg in 50 mL 0.9% saline) after heparin reversal over 30 minutes (n = 49)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) after heparin reversal over 30 minutes (n = 49)   |
| Outcomes      | <b>Primary outcome:</b> postoperative blood loss (measured by estimating blood loss from surgical swabs, suction drainage, and drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Volume of red cells transfused</li> <li>• Laboratory measures of haemostasis</li> <li>• Number of participants receiving a red cell transfusion</li> </ul> |
| Notes         | Volume of red cells reported as mean with no standard deviation. This outcome has been reported narratively and was not included in meta-analysis   |

### Risk of bias

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Unclear risk       | Insufficient information for judgement<br>Quote: "double-blind, randomized controlled trial with random allocation of patients after informed consent to receive either desmopressin acetate or placebo"  |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Low risk           | Quote: "Both desmopressin and placebo were supplied in numbered but otherwise identical 1 mL vials, containing 4µg of active drug (Ferring Pharmaceuticals, Feltham, Middlesex, UK). The ten ampoules supplied for each patient were stored in a refrigerator at 4-8°C, then diluted in 50 mL isotonic saline prior to administration. A dose of 0.3µg/kg bodyweight was infused intravenously over 30 minutes through a central line, after completion of cardiopulmonary bypass and following reversal of heparin by protamine" |

**Spyt 1990** (Continued)

|   |              |   |
|---|--------------|---|
| Blinding of outcome assessors<br>All outcomes | Low risk     | Quote: "Both desmopressin and placebo were supplied in numbered but otherwise identical 1 mL vials, containing 4 µg of active drug (Ferring Pharmaceuticals, Feltham, Middlesex, UK). The ten ampoules supplied for each patient were stored in a refrigerator at 4-8°C, then diluted in 50 mL isotonic saline prior to administration. A dose of 0.3 µg/kg bodyweight was infused intravenously over 30 minutes through a central line, after completion of cardiopulmonary bypass and following reversal of heparin by protamine" |
| Incomplete outcome data<br>All outcomes       | Unclear risk | Insufficient information for judgement  |
| Selective outcome reporting                   | Unclear risk | No protocol available   |
| Other sources of bias                         | High risk    | Support and supply of study medication from Ferring Pharmaceuticals (a manufacturer of DDAVP)   |

**Steinlechner 2011**

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> cardiac surgery</p> <p><b>Country:</b> Austria</p> <p><b>Registration:</b> not prospectively registered</p>   |
| Participants | <p><b>Inclusion criteria:</b> elective bioprosthetic AVR because of severe aortic valve stenosis (defined as a mean gradient of 50 mmHg or an indexed effective orifice area of 0.5 cm<sup>2</sup>/m<sup>2</sup> body surface area); platelet dysfunction (collagen/adenosine diphosphate closure time on platelet function analyser-100 &gt; 170 seconds)</p> <p><b>Exclusion criteria:</b> left ventricular ejection fraction &lt; 0.40; body mass index &gt; 40 kg/m<sup>2</sup>; serum creatinine &gt; 1.5 mg/dL; known hypersensitivity towards DDAVP; active endocarditis; multi-valvular disease; antiplatelet therapy within 10 days before surgery; any relevant coronary artery disease; inability to give informed consent; mechanical valves</p> <p><b>Number of participants randomised:</b> 50</p> <p><b>Number of participants analysed:</b> 43</p> <p><b>Age:</b> desmopressin arm: 72 ± 10 years; placebo arm: 73 ± 8 years</p> <p><b>Gender:</b> desmopressin arm: 8 male, 12 female; placebo arm: 7 male, 16 female</p> <p><b>Type of surgery:</b> all undergoing elective bioprosthetic AVR</p> <p><b>Duration of surgery:</b> desmopressin arm: 295 ± 95 minutes; placebo arm: 273 ± 52 minutes</p> <p><b>Duration of cardiopulmonary bypass:</b> desmopressin arm: 89 ± 37 minutes; placebo arm: 79 ± 17 minutes</p> <p><b>Emergency cases:</b> none</p> |

|               |  |
|---------------|--|
|               | <b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused when haemoglobin < 70 g/L in the operating room, or < 80 g/L on the ward |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg in 100 mL 0.9% saline) after induction of anaesthesia over 30 minutes (n = 20)<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline) after induction of anaesthesia over 30 minutes (n = 23)  |
| Outcomes      | <b>Primary outcome:</b> postoperative blood loss (method for measurement not reported)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Volume of red cells transfused</li> <li>• Reoperation for bleeding</li> <li>• All-cause mortality</li> <li>• Thromboembolic events</li> </ul>   |
| Notes         | Volume of red cells transfused reported in mL, so converted into units based on assumption that 300 mL is equivalent to 1 unit   |

*Risk of bias*

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Low risk           | Quote: "This was a 1:1 block-randomized (block sizes of 4)"   |
| Allocation concealment                                 | Low risk           | Quote: "A randomization list was generated with an online program (www.randomization.com) and, for concealment, individually sealed opaque envelopes contained the randomization codes for the study nurses who prepared the study drugs. Patients and treating physicians, nurses at the ward, and laboratory technicians were blinded with respect to the randomization code" |
| Blinding of participants and personnel<br>All outcomes | Low risk           | Study nurses prepared and administered study drugs but were not involved in outcome assessment  |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Quote: "Patients and treating physicians, nurses at the ward, and laboratory technicians were blinded with respect to the ran-  |

|   |              |   |
|---|--------------|---|
|   |              | domization code"  |
| Incomplete outcome data<br>All outcomes | Unclear risk | 7/50 participants excluded: 4 excluded owing to low closure time before administration of DDAVP or placebo; 3 after allocation of study drug (all in the DDAVP arm): 2 for intraoperative situs of porcelain aorta and 1 for requirement of additional CABG |
| Selective outcome reporting             | Unclear risk | Protocol not available  |
| Other sources of bias                   | Unclear risk | Insufficient information for judgement  |

## Temeck 1994

|               |  |
|---------------|--|
| Methods       | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> cardiac surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered  |
| Participants  | <b>Inclusion criteria:</b> undergoing primary cardiac surgery<br><b>Exclusion criteria:</b> not reported<br><b>Number of participants randomised:</b> 83<br><b>Number of participants analysed:</b> 83<br><b>Age:</b> not reported<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> all undergoing primary cardiac surgery. No further information reported<br><b>Duration of surgery:</b> not reported<br><b>Duration of cardiopulmonary bypass:</b> not reported<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> not reported<br><b>Coagulopathy:</b> not reported<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> desmopressin arm: epsilon-aminocaproic acid 8; placebo arm: epsilon-aminocaproic acid 13<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported |
| Interventions | <b>Intervention arm:</b> DDAVP (0.3 µg/kg in 50 mL 0.9% saline) after heparin reversal 15 minutes (n = 40)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) after heparin reversal 15 minutes (n = 43)  |
| Outcomes      | <b>Primary outcome:</b> postoperative blood loss (measured by drain output)<br><b>Secondary outcome:</b> number of participants receiving a red cell transfusion   |

**Temeck 1994** (Continued)

|  |  |  |
|--|--|--|
| Notes  | Blood loss reported separately for mediastinal and pleural blood loss. Mediastinal blood loss figure has been used, as this accounts for approximately 80% of total blood loss at 24 hours |  |
| <i>Risk of bias</i>                                    |  |  |
| <b>Bias</b>  | <b>Authors' judgement</b>  | <b>Support for judgement</b>   |
| Sequence Generation                                    | Unclear risk   | Quote: "A card drawn at random determined which vial was to be used"   |
| Allocation concealment                                 | Unclear risk   | Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Low risk   | Identical appearances of bottles (placebo/DDAVP)   |
| Blinding of outcome assessors<br>All outcomes          | Low risk   | Identical appearances of bottles (placebo/DDAVP)   |
| Incomplete outcome data<br>All outcomes                | High risk  | Table 1 reports that sample sizes may vary due to missing data but does not indicate how many participants are missing from the analysis   |
| Selective outcome reporting                            | High risk  | Total blood loss not reported. Mediastinal and pleural blood loss reported separately  |
| Other sources of bias                                  | High risk  | Imbalance of participant characteristics; 5 participants in the placebo group receiving DDAVP, along with other differences in postoperative management. Rorer Pharmaceuticals supplied the DDAVP used in the study. Unclear if the company had a role in study design |

**Theroux 1997**

|              |  |
|--------------|--|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> orthopaedic surgery<br><b>Country:</b> USA<br><b>Registration:</b> not prospectively registered  |
| Participants | <b>Inclusion criteria:</b> stage IV cerebral palsy and neuromuscular scoliosis; undergoing elective spinal fusion with unit rod instrumentation<br><b>Exclusion criteria:</b> history of bleeding problems; prolonged PT/aPTT; bleeding time > 7 minutes; thrombocytopenia<br><b>Number of participants randomised:</b> 21<br><b>Number of participants analysed:</b> 21 |

|  |  |
|--|--|
|  | <b>Age:</b> desmopressin arm: median 13 (range 10-19) years; placebo arm: median 13 (range 6-18) years<br><b>Gender:</b> not reported<br><b>Type of surgery:</b> all undergoing elective spinal fusion with unit rod instrumentation<br><b>Duration of surgery:</b> desmopressin arm: median 4.5 hours (range 3.45 to 5.0 hours); placebo arm: median 4.3 hours (range 3.45 to 5.15 hours)<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> none<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haemoglobin < 100 g/L |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 µg/kg in 100 mL 0.9% saline) preoperatively (exact timing unclear) over 15 to 20 minutes (n = 10)<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline) preoperatively (exact timing unclear) over 15 to 20 minutes (n = 11)  |
| Outcomes   | <b>Primary outcome:</b> blood loss intraoperatively and in total (intensive care paediatrician estimated blood loss in surgical bandages)<br><b>Secondary outcome:</b> total volume of red cells transfused  |
| Notes  | Trial stopped early after 21/40 participants recruited, as more blood loss in DDAVP arm than in placebo arm. Blood loss reported as percentage of blood volume, so results reported narratively. Transfusion requirements were reported as median and range, so are reported narratively and were not incorporated into meta-analysis  |
| <i>Risk of bias</i>                                    |  |
| <b>Bias</b>  | <b>Authors' judgement</b><br><b>Support for judgement</b>  |
| Sequence Generation                                    | Unclear risk<br>Insufficient information for judgement   |
| Allocation concealment                                 | Unclear risk<br>Insufficient information for judgement   |
| Blinding of participants and personnel<br>All outcomes | Low risk<br>DDAVP and placebo identical in appearance  |
| Blinding of outcome assessors<br>All outcomes          | Low risk<br>Quote: “surgeon, anaesthesiologist and investigator collecting data were unaware of what solution was being administered”  |
| Incomplete outcome data<br>All outcomes                | Low risk<br>Power calculation was 40 participants. Interim analysis at 21 participants prompted termination. All 21 participants were reported on  |

**Theroux 1997** (Continued)

|                             |              |  |
|-----------------------------|--------------|--|
| Selective outcome reporting | Unclear risk | Protocol not available   |
| Other sources of bias       | Unclear risk | Unclear when DDAVP was administered before surgery. Funding was provided by the Nemours Foundation |

**Wingate 1992a**

|                     |  |
|---------------------|--|
| Methods             | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> plastic surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p> <p>2 trials reported in 1 paper. <a href="#">Wingate 1992a</a> reported extensive procedures; <a href="#">Wingate 1992b</a> reported smaller procedures</p>   |
| Participants        | <p><b>Inclusion criteria:</b> spinal cord injury requiring flap reconstruction of pelvic pressure sores</p> <p><b>Exclusion criteria:</b> not reported</p> <p><b>Number of participants randomised:</b> 23</p> <p><b>Number of participants analysed:</b> 23</p> <p><b>Age:</b> not reported</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery:</b> all undergoing flap reconstruction</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> <p><b>Cell salvage:</b> not reported</p> <p><b>Transfusion protocol:</b> not reported</p> |
| Interventions       | <p><b>Intervention arm:</b> DDAVP (0.3 µg/kg in 50 mL 0.9% saline) after induction before operation over 20 minutes (n = 14)</p> <p><b>Comparator arm:</b> placebo (50 mL 0.9% saline) after induction before operation over 20 minutes (n = 9)</p>  |
| Outcomes            | <p><b>Primary outcome:</b> intraoperative blood loss (method for measurement not reported)</p> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Volume of red cells transfused intraoperatively</li> <li>• Number of participants receiving a red cell transfusion intraoperatively and in total</li> </ul>   |
| Notes               |  |
| <b>Risk of bias</b> |  |

Wingate 1992a (Continued)

| Bias   | Authors' judgement | Support for judgement   |
|--|--------------------|---|
| Sequence Generation                                    | Low risk           | Selected according to a random numbers table  |
| Allocation concealment                                 | Unclear risk       | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Low risk           | Pharmacist prepared the study drug. "Neither surgical team nor anesthesiologist [was] aware of treatment" |
| Blinding of outcome assessors<br>All outcomes          | Low risk           | Pharmacist prepared the study drug. "Neither surgical team nor anesthesiologist [was] aware of treatment" |
| Incomplete outcome data<br>All outcomes                | Low risk           | All participants included in final analysis   |
| Selective outcome reporting                            | Unclear risk       | No protocol available   |
| Other sources of bias                                  | Unclear risk       | Insufficient information for judgement  |

Wingate 1992b

|              |  |
|--------------|--|
| Methods      | <p><b>Type of study:</b> single-centre, 2-arm, parallel-group RCT</p> <p><b>Setting:</b> plastic surgery</p> <p><b>Country:</b> USA</p> <p><b>Registration:</b> not prospectively registered</p> <p>2 trials reported in 1 paper. <a href="#">Wingate 1992a</a> reported extensive procedures; <a href="#">Wingate 1992b</a> reported smaller procedures</p>   |
| Participants | <p><b>Inclusion criteria:</b> spinal cord injury requiring flap reconstruction of pelvic pressure sores</p> <p><b>Exclusion criteria:</b> not reported</p> <p><b>Number of participants randomised:</b> 21</p> <p><b>Number of participants analysed:</b> 21</p> <p><b>Age:</b> not reported</p> <p><b>Gender:</b> not reported</p> <p><b>Type of surgery:</b> all undergoing flap reconstruction</p> <p><b>Duration of surgery:</b> not reported</p> <p><b>Duration of cardiopulmonary bypass:</b> N/A</p> <p><b>Emergency cases:</b> none</p> <p><b>Antiplatelet agents:</b> not reported</p> <p><b>Anticoagulants:</b> not reported</p> <p><b>Coagulopathy:</b> not reported</p> <p><b>Thrombocytopenia:</b> not reported</p> <p><b>Antifibrinolytics:</b> not reported</p> |

Wingate 1992b (Continued)

|  |  |   |
|--|--|---|
|  | <b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> not reported   |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 $\mu$ g/kg in 50 mL 0.9% saline) after induction before operation over 20 minutes (n = 8)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) after induction before operation over 20 minutes (n = 13)  |   |
| Outcomes   | <b>Primary outcome:</b> Intraoperative blood loss (method for measurement not reported)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Volume of red cells transfused intraoperatively</li><li>• Number of participants receiving a red cell transfusion intraoperatively and in total</li></ul> |   |
| Notes  |  |   |
| <i><b>Risk of bias</b></i>                             |  |   |
| <b>Bias</b>  | <b>Authors' judgement</b>  | <b>Support for judgement</b>  |
| Sequence Generation                                    | Low risk   | Selected according to a random numbers table  |
| Allocation concealment                                 | Unclear risk   | Insufficient information for judgement  |
| Blinding of participants and personnel<br>All outcomes | Low risk   | Pharmacist prepared the study drug. "Neither surgical team nor anesthesiologist [was] aware of treatment" |
| Blinding of outcome assessors<br>All outcomes          | Low risk   | Pharmacist prepared the study drug. "Neither surgical team nor anesthesiologist [was] aware of treatment" |
| Incomplete outcome data<br>All outcomes                | Low risk   | All participants included in final analysis   |
| Selective outcome reporting                            | Unclear risk   | No protocol available   |
| Other sources of bias                                  | Unclear risk   | Insufficient information for judgement  |

Wong 2003

|         |   |
|---------|---|
| Methods | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> hepatic surgery<br><b>Country:</b> Hong Kong<br><b>Registration:</b> not prospectively registered |
|---------|---|

|                        |   |  |
|------------------------|---|--|
| Participants           | <b>Inclusion criteria:</b> adults scheduled for hepatectomy<br><b>Exclusion criteria:</b> coronary artery disease; congenital or acquired coagulation disorders other than liver cirrhosis; blood sodium level < 130 mmol/L; NSAID or aspirin ingestion within 7 days of scheduled surgery; history of thrombovascular disorders or pulmonary thromboembolism<br><b>Number of participants randomised:</b> 60<br><b>Number of participants analysed:</b> 59<br><b>Age:</b> desmopressin arm: 47.4 ± 11.3 years; placebo arm: 54.9 ± 11.8 years<br><b>Gender:</b> desmopressin arm: 20 male, 10 female; placebo arm: 17 male, 13 female<br><b>Type of surgery:</b> all undergoing hepatectomy<br><b>Duration of surgery:</b> desmopressin arm: median 405 (range 210-800) minutes; placebo arm: median 435 (range 180-780) minutes<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> none<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> not reported<br><b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cell transfusion if haematocrit < 30% |  |
| Interventions          | <b>Intervention arm:</b> DDAVP (0.3 µg/kg in 50 mL 0.9% saline) after induction of anaesthesia over 20 minutes (n = 30)<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) after induction of anaesthesia over 20 minutes (n = 29)   |  |
| Outcomes               | <b>Primary outcome:</b> blood loss intraoperatively and in total (measured by estimating blood loss in surgical swabs and drain output)<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Total volume of red cells transfused</li><li>• Number of participants receiving a red cell transfusion</li><li>• Laboratory measures of haemostasis</li></ul>  |  |
| Notes                  | Blood loss reported as median and range, so outcome reported narratively and not included in meta-analysis  |  |
| <i>Risk of bias</i>    |   |  |
| Bias                   | Authors' judgement  | Support for judgement  |
| Sequence Generation    | Unclear risk  | Insufficient information for judgement   |
| Allocation concealment | Low risk  | Quote: "Patient randomization was by drawing a sealed envelope specifying a prescription for either desmopressin or placebo, which was then prepared by an independent investigator and blinded to the |

Wong 2003 (Continued)

|  |              |   |
|--|--------------|---|
|  |              | patient, attending anesthesiologist and surgeon"  |
| Blinding of participants and personnel<br>All outcomes | Low risk     | [DDAVP or placebo] "... was then prepared by an independent investigator and blinded to the patient, attending anesthesiologist and surgeon"  |
| Blinding of outcome assessors<br>All outcomes          | Low risk     | [DDAVP or placebo] "... was then prepared by an independent investigator and blinded to the patient, attending anesthesiologist and surgeon"  |
| Incomplete outcome data<br>All outcomes                | High risk    | One participant excluded due to excess bleeding (surgical damage to inferior vena cava). This exclusion was not prespecified and is likely to result in a significant change in the effect estimate |
| Selective outcome reporting                            | Unclear risk | No protocol available   |
| Other sources of bias                                  | Unclear risk | Insufficient information for judgement  |

Zohar 2001

|              |  |
|--------------|--|
| Methods      | <b>Type of study:</b> single-centre, 2-arm, parallel-group RCT<br><b>Setting:</b> orthopaedic surgery<br><b>Country:</b> Israel<br><b>Registration:</b> not prospectively registered   |
| Participants | <b>Inclusion criteria:</b> ASA physical status 1-3; undergoing elective total knee replacement<br><b>Exclusion criteria:</b> severe ischaemic heart disease (New York Heart Association grade III or IV); chronic renal failure; liver cirrhosis; bleeding disorders; anticoagulant therapy<br><b>Number of participants randomised:</b> 40<br><b>Number of participants analysed:</b> 40<br><b>Age:</b> desmopressin arm: 72 ± 5 years; placebo arm: 71 ± 5 years<br><b>Gender:</b> desmopressin arm: 3 male, 17 female; tranexamic acid arm: 8 male, 12 female<br><b>Type of surgery:</b> all undergoing total knee replacement<br><b>Duration of surgery:</b> desmopressin arm: 128 ± 15 minutes; tranexamic acid arm: 133 ± 13 minutes<br><b>Duration of cardiopulmonary bypass:</b> N/A<br><b>Emergency cases:</b> none<br><b>Antiplatelet agents:</b> not reported<br><b>Anticoagulants:</b> none<br><b>Coagulopathy:</b> none<br><b>Thrombocytopenia:</b> not reported<br><b>Antifibrinolytics:</b> all participants in tranexamic acid arm treated with tranexamic acid; no participants in DDAVP arm treated with an antifibrinolytic agent |

|  |   |   |
|--|---|---|
|  | <b>Cell salvage:</b> not reported<br><b>Transfusion protocol:</b> red cells transfused if haematocrit < 27%   |   |
| Interventions  | <b>Intervention arm:</b> DDAVP (0.3 $\mu$ g/kg (diluent and volume not reported) 30 minutes before deflation of tourniquet (speed of administration not reported). Followed by a constant infusion of intravenous saline until 12 hours after surgery (volume not reported) (n = 20)<br><b>Comparator arm:</b> tranexamic acid (15 mg/kg) 30 minutes before deflation of tourniquet (speed of administration not reported). Followed by a constant infusion of tranexamic acid 10 mg/kg until 12 hours after surgery (volume not reported) (n = 20) |   |
| Outcomes   | <b>Primary outcome:</b> total volume of red cells transfused<br><b>Secondary outcomes</b> <ul style="list-style-type: none"><li>• Blood loss total (measured by drain output)</li><li>• Number of participants receiving a red cell transfusion</li><li>• Thromboembolism</li></ul>   |   |
| Notes  | Blood loss reported separately for first 12 hours and second 12 hours postoperatively. Data from first 12 hours postoperatively used in this review   |   |
| <i><b>Risk of bias</b></i>                             |   |   |
| <b>Bias</b>  | <b>Authors' judgement</b>   | <b>Support for judgement</b>                        |
| Sequence Generation                                    | Low risk  | Computer-generated sequence                         |
| Allocation concealment                                 | Unclear risk  | Insufficient information for judgement              |
| Blinding of participants and personnel<br>All outcomes | High risk   | Participants and personnel not blinded to treatment |
| Blinding of outcome assessors<br>All outcomes          | Low risk  | Outcome assessor blinded to treatment allocation    |
| Incomplete outcome data<br>All outcomes                | Unclear risk  | Three participants lost to follow-up                |
| Selective outcome reporting                            | Unclear risk  | No protocol available                               |
| Other sources of bias                                  | Unclear risk  | Insufficient information for judgement              |

**Abbreviations**

ACBG: aortocoronary bypass graft  
 aPTT: activated partial thromboplastin time  
 ASA: American Society of Anesthesiologists  
 ASD: atrial septal defect  
 AV: atrioventricular  
 AVR: aortic valve replacement

BCPA: bidirectional cavopulmonary anastomosis  
 CABG: coronary artery bypass graft  
 CPB: cardiopulmonary bypass  
 DDAVP: desmopressin; 1-deamino-8-D-arginine vasopressin  
 ECC: extracorporeal circulation  
 GRF: glomerular filtration rate  
 HLHS: hypoplastic left heart syndrome  
 IQR: interquartile range  
 KIU: Kallikrein Inhibitor Unit  
 MA: maximum amplitude  
 MDRD: Modification of Diet in Renal Disease study  
 MVR: mitral valve replacement  
 N/A: not applicable  
 NSAID: non-steroidal anti-inflammatory drug  
 OMC: open mitral commissurotomy  
 PA: pulmonary artery  
 PT: prothrombin time  
 RCA-RV: right coronary artery-right ventricle  
 RCT: randomised controlled trial  
 TOF: tetralogy of Fallot  
 TT: thrombin time  
 TXA: tranexamic acid  
 VSD: ventricular septal defect

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

| Study  | Reason for exclusion  |
|--|---|
| <a href="#">EudraCT Number: 2009-017265-33</a> | Not a RCT   |
| <a href="#">Flordal 1993</a>                   | Not a RCT   |
| <a href="#">Forero 2003</a>                    | Not a RCT   |
| <a href="#">Gandhi 2014</a>                    | Review article  |
| <a href="#">Haith 1993</a>                     | Wrong participant group: procedures rather than participants randomised   |
| <a href="#">Hansen 1980</a>                    | Review article  |
| <a href="#">Hooghiemstra 2012</a>              | Not a RCT   |
| <a href="#">IRCT2013092114728N1</a>            | Trial did not use the intervention of interest, but used intranasal DDAVP |
| <a href="#">IRCT201409304345N3</a>             | Trial did not use the intervention of interest, but used intranasal DDAVP |
| <a href="#">Johnson 1990</a>                   | Not a RCT   |
| <a href="#">Karger 2012</a>                    | Not a RCT   |

(Continued)

|                                  |  |
|----------------------------------|--|
| <a href="#">Keyl 2011</a>        | Not a RCT  |
| <a href="#">Kim 2015</a>         | Not a RCT  |
| <a href="#">Lozano 1999</a>      | Not a RCT  |
| <a href="#">Mannucci 1994</a>    | Review article   |
| <a href="#">Mirmansoori 2016</a> | Trial did not use the intervention of interest, but used intranasal DDAVP  |
| <a href="#">Myrvang 2011</a>     | Review article   |
| <a href="#">NCT00835211</a>      | Wrong participant group, used healthy volunteers   |
| <a href="#">NCT01218074</a>      | Trial did not use the intervention of interest, but was a comparison of thromboelastography with combination thromboelastography and platelet aggregometry |
| <a href="#">NCT01382134</a>      | Wrong participant group, used healthy volunteers   |
| <a href="#">NCT01606072</a>      | Not a RCT  |
| <a href="#">NCT01623206</a>      | Not a RCT  |
| <a href="#">Nilsen 1984</a>      | Wrong participant group, used for participants requiring thromboprophylaxis  |
| <a href="#">Ozal 2002</a>        | Trial did not use the intervention of interest, but used DDAVP versus combination DDAVP and tranexamic acid  |
| <a href="#">Palaia 2001</a>      | Not a RCT  |
| <a href="#">Spiro 1982</a>       | Not a RCT  |
| <a href="#">Stanca 2010</a>      | Trial did not use the intervention of interest, but used intranasal DDAVP  |
| <a href="#">Weinberg 2015</a>    | Not a RCT  |
| <a href="#">Zielske 2003</a>     | Wrong participant group, used healthy volunteers   |
| <a href="#">Zotz 2009</a>        | Review article   |

#### Abbreviation

DDAVP: desmopressin; 1-deamino-8-D-arginine-vasopressin

RCT: randomised controlled trial

## Characteristics of studies awaiting assessment [ordered by study ID]

### Jahangirifard 2017

|               |  |
|---------------|--|
| Methods       | <b>Type of study:</b> single-centre, parallel-group, 2-arm randomised controlled trial (RCT)<br><b>Country where study is being performed:</b> Iran  |
| Participants  | <b>Inclusion criteria:</b> age 20 to 70 years; heart transplant surgery<br><b>Exclusion criteria:</b> history of previous surgery on chest; bleeding disorders or haemophilia; abnormal preoperative coagulation tests or platelet count; contraindications for use of DDAVP (1-deamino-8-D-arginine-vasopressin; desmopressin); history of deep vein thrombosis; "Haematologic disease" (not specified); carotid artery stenosis; chronic obstructive pulmonary disease |
| Interventions | <b>Intervention arm:</b> DDAVP 0.3 µg/kg in 2 mL saline before surgery (route of administration not clear)<br><b>Comparator arm:</b> placebo (2 mL saline) before surgery (route of administration not clear)  |
| Outcomes      | <b>Primary outcome</b> <ul style="list-style-type: none"> <li>Blood loss for 24 hours after surgery</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>Blood transfusion requirements for 24 hours after surgery</li> <li>Fresh frozen plasma (FFP) transfusion requirements for 24 hours after surgery</li> <li>Reoperation to control bleeding within 24 hours of surgery</li> </ul>  |
| Notes         |  |

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

### ISRCTN12845429

|                     |  |
|---------------------|--|
| Trial name or title | DRIVE - Desmopressin for procedures or Radiological InterVEntions  |
| Methods             | <b>Type of study:</b> single-centre, parallel-group, 2-arm RCT<br><b>Country where study is being performed:</b> UK  |
| Participants        | <b>Inclusion criteria:</b> age 18 years and over; platelet count $\leq 100 \times 10^9/L$ ; inpatient on a critical care ward; due to undergo an invasive procedure<br><b>Exclusion criteria:</b> active bleeding; history of ischaemic heart disease (myocardial infarction or angina), stroke, or TIA; admission to ICU with traumatic brain injury or seizures; congenital bleeding disorder; pregnant or breastfeeding; history of anaphylaxis to desmopressin |
| Interventions       | <b>Intervention arm:</b> DDAVP 0.3 µg/kg in 50 mL 0.9% saline infused intravenously preoperatively over 20 minutes<br><b>Comparator arm:</b> placebo (50 mL 0.9% saline) infused intravenously preoperatively over 20 minutes  |
| Outcomes            | <b>Primary outcome</b> <ul style="list-style-type: none"> <li>Proportion of eligible participants randomised and receiving the investigational medicinal product will be assessed by analysis of screening and recruitment data at the end of the study</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>Adherence to protocol measured at 28 days post treatment, measured by analysis of Case Report Forms</li> </ul>                 |

|                     |   |
|---------------------|---|
|                     | <p>at the end of the study</p> <ul style="list-style-type: none"> <li>• Time taken to administer IMP (from randomisation), measured by analysis of Case Report Forms at the end of the study</li> <li>• Difference in change in thrombus formation under flow between DDAVP and placebo before and after IMP, measured by blood tests pretreatment, 30 minutes post treatment, and 120 minutes post treatment</li> <li>• Difference in changes in platelet function analyser (PFA)-200 closure time for adenosine diphosphate (ADP)/collagen and P2Y cartridges between desmopressin and placebo before and after IMP, measured by blood tests pretreatment, 30 minutes post treatment, and 120 minutes post treatment</li> <li>• Difference in changes in thrombin generation between desmopressin and placebo before and after IMP, measured by blood tests pretreatment, 30 minutes post treatment, and 120 minutes post treatment</li> <li>• Bleeding up to 24 hours after administration of IMP, measured by the HEME (Haemorrhage Measurement Tool) Bleeding Assessment at 24 hours</li> <li>• Thromboembolic events up to 28 days after administration of IMP, measured by reviewing participant notes at days 1, 7, and 28</li> <li>• Exposure to blood products (red cell transfusion, platelet transfusion) up to 24 hours after administration of IMP, measured by reviewing participant notes at day 1</li> </ul> |
| Starting date       | February 2017   |
| Contact information | <b>Trial Manager:</b> Miss Emma Laing (emma.laing@nhsbt.nhs.uk)   |
| Notes               | <p><b>Expected number of participants:</b> 40</p> <p><b>Expected completion date:</b> April 2018</p>  |

## NCT00885924

|                     |  |
|---------------------|--|
| Trial name or title | Desmopressin as treatment for postoperative bleeding after cardiac surgery   |
| Methods             | <p><b>Type of study:</b> single-centre, parallel-group, 2-arm RCT</p> <p><b>Country where study is being performed:</b> Norway</p>   |
| Participants        | <p><b>Inclusion criteria:</b> age <math>\geq</math> 18 years; scheduled for cardiac surgery; excessive postoperative bleeding: <math>&gt; 250</math> mL for 1 hour, or <math>&gt; 150</math> mL for 2 hours during first 4 hours</p> <p><b>Exclusion criteria:</b> a medical condition known to influence the haemostatic system; treated with clopidogrel or systemic steroids during the last week before surgery; INR <math>&gt; 1.5</math>; unable to give written informed consent; unstable people who need transfusion limits other than those used in this study</p> |
| Interventions       | <p><b>Intervention arm:</b> DDAVP <math>0.3 \mu\text{g/kg}</math> infused intravenously postoperatively in the event of bleeding over 20 minutes</p> <p><b>Comparator arm:</b> placebo (0.9% saline) infused intravenously postoperatively in the event of bleeding over 20 minutes</p>  |
| Outcomes            | <p><b>Primary outcome</b></p> <ul style="list-style-type: none"> <li>• Transfusion of blood components during postoperative stay</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>• Postoperative haemorrhage during first 16 hours postoperatively</li> <li>• Platelet activation during first 20 hours postoperatively</li> <li>• Activation of coagulation during first 20 hours postoperatively</li> </ul>   |

**NCT00885924** (Continued)

|                     |   |
|---------------------|---|
| Starting date       | March 2009  |
| Contact information | <b>Principal Investigator:</b> Dr Guri Greiff (guri.greiff@gmail.com)   |
| Notes               | <b>Expected number of participants:</b> This trial was stopped because of difficulties with recruitment. 17 participants were recruited. These results are not yet published<br><b>Expected completion date:</b> not reported |

**NCT01982760**

|                     |   |
|---------------------|---|
| Trial name or title | DDAVP in the reduction of post-operative ecchymosis in rhinoplasty  |
| Methods             | <b>Type of study:</b> single-centre, parallel-group, 2-arm RCT<br><b>Country where study is being performed:</b> USA  |
| Participants        | <b>Inclusion criteria:</b> age 18 to 80 years; undergoing rhinoplasty for which nasal bone osteotomy is necessary<br><b>Exclusion criteria:</b> heart disease; renal disease with decreased GFR; liver disease  |
| Interventions       | <b>Intervention arm:</b> DDAVP 0.3 µg/kg infused intravenously preoperatively over 30 minutes<br><b>Comparator arm:</b> standard care   |
| Outcomes            | <b>Primary outcome</b> <ul style="list-style-type: none"> <li>Reduction in ecchymosis and swelling (photographs taken preoperatively, and at days 1 and 8 postoperatively, will be analysed for bruising)</li> </ul> <b>Secondary outcome</b> <ul style="list-style-type: none"> <li>Time it takes for participants to feel comfortable wearing makeup, going out in public, and returning to work</li> </ul> |
| Starting date       | December 2013   |
| Contact information | <b>Principal Investigator:</b> Dr Bahman Guyuron (bahman.guyuron@uhhospitals.org)   |
| Notes               | <b>Expected number of participants:</b> 30<br><b>Expected completion date:</b> July 2015  |

**NCT02084342**

|                     |   |
|---------------------|---|
| Trial name or title | Study of DDAVP combined with TXA on the blood loss and transfusion need during and after scoliosis correction surgery   |
| Methods             | <b>Type of study:</b> parallel-group, 2-arm RCT<br><b>Country where study is being performed:</b> China   |
| Participants        | <b>Inclusion criteria:</b> age 8 to 18 years; with idiopathic scoliosis undergoing posterior scoliosis correction surgery; ASA classification: 1-2 agreed to participate in this study and signed informed consent<br><b>Exclusion criteria:</b> blood disease, such as anaemia or ITP; history of bleeding or ecchymosis; disorders of platelets, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimers; hypertension; |

|                     |  |
|---------------------|--|
|                     | cardiac disease, such as unstable angina, myocardial infarction in previous 6 months, cardiac dysfunction, congenital heart disease, pulmonary heart disease; cerebral ischaemia administered with anticoagulants or non-steroidal anti-inflammatory drugs; hepatic or kidney dysfunction; blood transfusion in previous month |
| Interventions       | <b>Intervention arm:</b> DDAVP 0.3 µg/kg in 100 mL 0.9% saline infused intravenously over 20 minutes before first skin incision<br><b>Comparator arm:</b> placebo (100 mL 0.9% saline) infused intravenously over 20 minutes before first skin incision  |
| Outcomes            | <b>Primary outcome</b> <ul style="list-style-type: none"> <li>• Blood loss during and 3 days after surgery</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li>• Blood transfusion during and 3 days after surgery</li> <li>• Postoperative complications up to 24 weeks after surgery</li> </ul>      |
| Starting date       | December 2013  |
| Contact information | <b>Principal Investigator:</b> Dr Wen Qi Huang   |
| Notes               | <b>Expected number of participants:</b> 60<br><b>Expected completion date:</b> June 2014   |

### Abbreviations

ADP: adenosine diphosphate  
ASA: American Society of Anesthesiologists  
DDAVP: desmopressin (1-deamino-8-D-arginine vasopressin)  
GFR: glomerular filtration rate  
HEME: Haemorrhage Measurement Tool  
ICU: intensive care unit  
IMP: investigational medicinal product  
INR: international normalised ratio  
ITP: immune thrombocytopenic purpura  
PFA: platelet analyser function  
RCT: randomised controlled trial  
TIA: transient ischaemic attack  
TXA: tranexamic acid

## DATA AND ANALYSES

### Comparison 1. Desmopressin vs placebo

| Outcome or subgroup title  | No. of studies | No. of participants | Statistical method                   | Effect size               |
|--|----------------|---------------------|--------------------------------------|---------------------------|
| 1 Red cell volume transfused (intraoperatively)                              | 7              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only            |
| 1.1 Adult cardiac surgery  | 1              | 19                  | Mean Difference (IV, Random, 95% CI) | -0.10 [-1.22, 1.02]       |
| 1.2 Paediatric cardiac surgery   | 1              | 60                  | Mean Difference (IV, Random, 95% CI) | 0.40 [-0.87, 1.67]        |
| 1.3 Orthopaedic surgery  | 3              | 144                 | Mean Difference (IV, Random, 95% CI) | -0.50 [-0.89, -0.11]      |
| 1.4 Vascular surgery   | 1              | 44                  | Mean Difference (IV, Random, 95% CI) | -1.20 [-2.55, 0.15]       |
| 1.5 Plastic surgery  | 1              | 23                  | Mean Difference (IV, Random, 95% CI) | -0.75 [-1.23, -0.27]      |
| 2 Red cell volume transfused (total)   | 23             |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only            |
| 2.1 Cardiac surgery  | 14             | 957                 | Mean Difference (IV, Random, 95% CI) | -0.52 [-0.96, -0.08]      |
| 2.2 Orthopaedic surgery  | 6              | 303                 | Mean Difference (IV, Random, 95% CI) | -0.02 [-0.67, 0.64]       |
| 2.3 Vascular surgery   | 2              | 135                 | Mean Difference (IV, Random, 95% CI) | 0.06 [-0.60, 0.73]        |
| 2.4 Hepatic surgery  | 1              | 59                  | Mean Difference (IV, Random, 95% CI) | -0.47 [-1.27, 0.33]       |
| 3 Red cell volume transfused (children only, total)                          | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only            |
| 4 Number of participants receiving a red cell transfusion (intraoperatively) | 6              | 349                 | Risk Ratio (M-H, Random, 95% CI)     | 0.74 [0.50, 1.09]         |
| 4.1 Cardiac surgery  | 2              | 115                 | Risk Ratio (M-H, Random, 95% CI)     | 0.68 [0.43, 1.10]         |
| 4.2 Plastic surgery  | 2              | 44                  | Risk Ratio (M-H, Random, 95% CI)     | 0.86 [0.45, 1.64]         |
| 4.3 Kidney biopsy  | 1              | 162                 | Risk Ratio (M-H, Random, 95% CI)     | 0.0 [0.0, 0.0]            |
| 4.4 Other  | 1              | 28                  | Risk Ratio (M-H, Random, 95% CI)     | 0.0 [0.0, 0.0]            |
| 5 Number of participants receiving a red cell transfusion (total)            | 25             | 1806                | Risk Ratio (M-H, Random, 95% CI)     | 0.96 [0.86, 1.06]         |
| 5.1 Cardiac surgery  | 17             | 1350                | Risk Ratio (M-H, Random, 95% CI)     | 0.93 [0.82, 1.06]         |
| 5.2 Orthopaedic surgery  | 1              | 20                  | Risk Ratio (M-H, Random, 95% CI)     | 0.86 [0.45, 1.64]         |
| 5.3 Vascular surgery   | 1              | 91                  | Risk Ratio (M-H, Random, 95% CI)     | 1.05 [0.83, 1.34]         |
| 5.4 Paediatric cardiac surgery   | 1              | 60                  | Risk Ratio (M-H, Random, 95% CI)     | 1.17 [0.66, 2.06]         |
| 5.5 Plastic surgery  | 2              | 44                  | Risk Ratio (M-H, Random, 95% CI)     | 0.86 [0.45, 1.64]         |
| 5.6 Hepatic surgery  | 1              | 59                  | Risk Ratio (M-H, Random, 95% CI)     | 0.58 [0.15, 2.21]         |
| 5.7 Kidney biopsy  | 1              | 162                 | Risk Ratio (M-H, Random, 95% CI)     | 0.0 [0.0, 0.0]            |
| 5.8 Maxillofacial surgery  | 1              | 20                  | Risk Ratio (M-H, Random, 95% CI)     | 2.0 [0.88, 4.54]          |
| 6 Blood loss (intraoperative)  | 11             |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only            |
| 6.1 Cardiac surgery  | 2              | 87                  | Mean Difference (IV, Random, 95% CI) | -138.20 [-623.40, 347.01] |
| 6.2 Orthopaedic surgery  | 5              | 224                 | Mean Difference (IV, Random, 95% CI) | -118.24 [-278.43, 41.95]  |
| 6.3 Vascular surgery   | 1              | 44                  | Mean Difference (IV, Random, 95% CI) | -525.0 [-1177.34, 127.34] |
| 6.4 Sinus surgery  | 1              | 90                  | Mean Difference (IV, Random, 95% CI) | -28.0 [-31.70, -24.30]    |
| 6.5 Plastic surgery  | 2              | 44                  | Mean Difference (IV, Random, 95% CI) | -146.02 [-487.86, 195.83] |

|  |    |      |                                       |                           |
|--|----|------|---------------------------------------|---------------------------|
| 7 Blood loss (total)   | 28 |      | Mean Difference (IV, Random, 95% CI)  | Subtotals only            |
| 7.1 Adult cardiac surgery  | 22 | 1358 | Mean Difference (IV, Random, 95% CI)  | -135.24 [-210.80, -59.68] |
| 7.2 Orthopaedic surgery  | 5  | 241  | Mean Difference (IV, Random, 95% CI)  | -285.76 [-514.99, -56.53] |
| 7.3 Vascular surgery   | 1  | 44   | Mean Difference (IV, Random, 95% CI)  | -582.0 [-1264.07, 100.07] |
| 8 Blood loss (children only, total)  | 2  |      | Mean Difference (IV, Random, 95% CI)  | Subtotals only            |
| 8.1 Paediatric cardiac surgery   | 2  | 155  | Mean Difference (IV, Random, 95% CI)  | 1.11 [-12.92, 15.15]      |
| 9 Number of participants with any bleeding (intraoperatively)  | 1  |      | Risk Ratio (M-H, Random, 95% CI)      | Totals not selected       |
| 9.1 Dialysis catheter  | 1  |      | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]            |
| 10 Number of participants with any bleeding (total)  | 1  |      | Risk Ratio (M-H, Random, 95% CI)      | Totals not selected       |
| 10.1 Kidney biopsy   | 1  |      | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]            |
| 11 Reoperation due to bleeding   | 23 | 1783 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.66 [0.40, 1.09]         |
| 11.1 Cardiac surgery   | 19 | 1483 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.64 [0.38, 1.05]         |
| 11.2 Orthopaedic surgery   | 1  | 30   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 11.3 Paediatric cardiac surgery  | 1  | 60   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 6.93 [0.14, 349.88]       |
| 11.4 Dialysis catheter insertion   | 1  | 48   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 11.5 Kidney biopsy   | 1  | 162  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 12 All-cause mortality   | 22 | 1631 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.09 [0.51, 2.34]         |
| 12.1 Cardiac surgery   | 16 | 1239 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.09 [0.48, 2.51]         |
| 12.2 Orthopaedic surgery   | 3  | 171  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 12.3 Vascular surgery  | 1  | 91   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 8.50 [0.52, 138.60]       |
| 12.4 Paediatric cardiac surgery  | 2  | 130  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.13 [0.01, 2.14]         |
| 13 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism) | 29 | 1984 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.36 [0.85, 2.16]         |
| 13.1 Cardiac surgery   | 19 | 1311 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.46 [0.88, 2.42]         |
| 13.2 Orthopaedic surgery   | 6  | 280  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 7.21 [0.14, 363.30]       |
| 13.3 Vascular surgery  | 2  | 141  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.77 [0.23, 2.60]         |
| 13.4 Sinus surgery   | 1  | 90   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 13.5 Kidney biopsy   | 1  | 162  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 14 Myocardial infarction   | 26 | 1704 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.32 [0.70, 2.46]         |
| 14.1 Cardiac surgery   | 16 | 1031 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.52 [0.77, 3.00]         |
| 14.2 Orthopaedic surgery   | 6  | 280  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 14.3 Vascular surgery  | 2  | 141  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.55 [0.11, 2.88]         |
| 14.4 Kidney biopsy   | 1  | 162  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 14.5 Sinus surgery   | 1  | 90   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 15 Stroke  | 19 | 1277 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.95 [0.94, 9.24]         |
| 15.1 Cardiac surgery   | 11 | 733  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.95 [0.94, 9.24]         |
| 15.2 Orthopaedic surgery   | 5  | 201  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 15.3 Vascular surgery  | 1  | 91   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 15.4 Kidney biopsy   | 1  | 162  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 15.5 Sinus surgery   | 1  | 90   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]            |
| 16 Venous thromboembolism  | 20 | 1377 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.77 [0.17, 3.38]         |
| 16.1 Cardiac surgery   | 11 | 754  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.53 [0.11, 2.62]         |

|                                     |    |      |                                       |                     |
|-------------------------------------|----|------|---------------------------------------|---------------------|
| 16.2 Orthopaedic surgery            | 6  | 280  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 7.21 [0.14, 363.30] |
| 16.3 Vascular surgery               | 1  | 91   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 16.4 Kidney biopsy                  | 1  | 162  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 16.5 Sinus surgery                  | 1  | 90   | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 17 Clinically important hypotension | 18 | 1183 | Risk Ratio (M-H, Random, 95% CI)      | 2.32 [1.37, 3.91]   |
| 17.1 Cardiac surgery                | 13 | 762  | Risk Ratio (M-H, Random, 95% CI)      | 2.88 [1.32, 6.30]   |
| 17.2 Orthopaedic surgery            | 2  | 109  | Risk Ratio (M-H, Random, 95% CI)      | 2.05 [0.99, 4.24]   |
| 17.3 Paediatric cardiac surgery     | 1  | 60   | Risk Ratio (M-H, Random, 95% CI)      | 0.94 [0.06, 14.27]  |
| 17.4 Sinus surgery                  | 1  | 90   | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]      |
| 17.5 Kidney biopsy                  | 1  | 162  | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]      |

## Comparison 2. Desmopressin vs placebo (platelet dysfunction)

| Outcome or subgroup title   | No. of studies | No. of participants | Statistical method                    | Effect size               |
|---|----------------|---------------------|---------------------------------------|---------------------------|
| 1 Red cell volume transfused (total)  | 6              | 388                 | Mean Difference (IV, Random, 95% CI)  | -0.65 [-1.16, -0.13]      |
| 2 Number of participants receiving a red cell transfusion (intraoperatively)  | 1              |                     | Risk Ratio (M-H, Random, 95% CI)      | Subtotals only            |
| 3 Number of participants receiving a red cell transfusion (total)   | 5              | 258                 | Risk Ratio (M-H, Random, 95% CI)      | 0.83 [0.66, 1.04]         |
| 4 Blood loss (total)  | 7              | 422                 | Mean Difference (IV, Random, 95% CI)  | -253.93 [-408.01, -99.85] |
| 5 Reoperation due to bleeding   | 6              | 413                 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.39 [0.18, 0.84]         |
| 6 All-cause mortality   | 7              | 422                 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.72 [0.12, 4.22]         |
| 7 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism) | 7              | 422                 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.58 [0.60, 4.17]         |
| 8 Myocardial infarction   | 5              | 277                 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.72 [0.60, 12.37]        |
| 9 Stroke  | 3              |                     | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only            |
| 10 Venous thromboembolism   | 4              | 248                 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.56 [0.06, 5.50]         |
| 11 Clinically important hypotension   | 5              | 315                 | Risk Ratio (M-H, Random, 95% CI)      | 6.58 [1.18, 36.76]        |

### Comparison 3. Desmopressin vs tranexamic acid

| Outcome or subgroup title   | No. of studies | No. of participants | Statistical method                    | Effect size            |
|---|----------------|---------------------|---------------------------------------|------------------------|
| 1 Red cell volume transfused (total)  | 1              |                     | Mean Difference (IV, Random, 95% CI)  | Totals not selected    |
| 1.1 Orthopaedic surgery   | 1              |                     | Mean Difference (IV, Random, 95% CI)  | 0.0 [0.0, 0.0]         |
| 2 Number of participants receiving a red cell transfusion (total)   | 3              | 135                 | Risk Ratio (M-H, Random, 95% CI)      | 2.42 [1.04, 5.64]      |
| 2.1 Cardiac surgery   | 1              | 75                  | Risk Ratio (M-H, Random, 95% CI)      | 1.46 [0.82, 2.59]      |
| 2.2 Orthopaedic surgery   | 2              | 60                  | Risk Ratio (M-H, Random, 95% CI)      | 4.15 [1.58, 10.90]     |
| 3 Blood loss (total)  | 2              | 115                 | Mean Difference (IV, Random, 95% CI)  | 142.81 [79.78, 205.84] |
| 3.1 Cardiac surgery   | 1              | 75                  | Mean Difference (IV, Random, 95% CI)  | 115.0 [35.38, 194.62]  |
| 3.2 Orthopaedic surgery   | 1              | 40                  | Mean Difference (IV, Random, 95% CI)  | 180.0 [86.82, 273.18]  |
| 4 Reoperation due to bleeding   | 1              |                     | Peto Odds Ratio (Peto, Fixed, 95% CI) | Totals not selected    |
| 4.1 Cardiac surgery   | 1              |                     | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]         |
| 5 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism) | 2              |                     | Risk Ratio (M-H, Random, 95% CI)      | Totals not selected    |
| 5.1 Cardiac surgery   | 1              |                     | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 5.2 Orthopaedic surgery   | 1              |                     | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 6 Myocardial infarction   | 2              | 115                 | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 6.1 Cardiac surgery   | 1              | 75                  | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 6.2 Orthopaedic surgery   | 1              | 40                  | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 7 Stroke  | 2              |                     | Risk Ratio (M-H, Random, 95% CI)      | Totals not selected    |
| 7.1 Cardiac surgery   | 1              |                     | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 7.2 Orthopaedic surgery   | 1              |                     | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 8 Venous thromboembolism  | 2              | 115                 | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 8.1 Cardiac surgery   | 1              | 75                  | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |
| 8.2 Orthopaedic surgery   | 1              | 40                  | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]         |

### Comparison 4. Desmopressin vs aprotinin

| Outcome or subgroup title   | No. of studies | No. of participants | Statistical method                    | Effect size         |
|---|----------------|---------------------|---------------------------------------|---------------------|
| 1 Number of participants receiving a red cell transfusion (total) | 1              |                     | Risk Ratio (M-H, Random, 95% CI)      | Totals not selected |
| 1.1 Cardiac surgery   | 1              |                     | Risk Ratio (M-H, Random, 95% CI)      | 0.0 [0.0, 0.0]      |
| 2 Reoperation due to bleeding                                     | 2              |                     | Peto Odds Ratio (Peto, Fixed, 95% CI) | Totals not selected |
| 2.1 Cardiac surgery   | 2              |                     | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 3 All-cause mortality   | 1              | 53                  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 3.1 Cardiac surgery   | 1              | 53                  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |

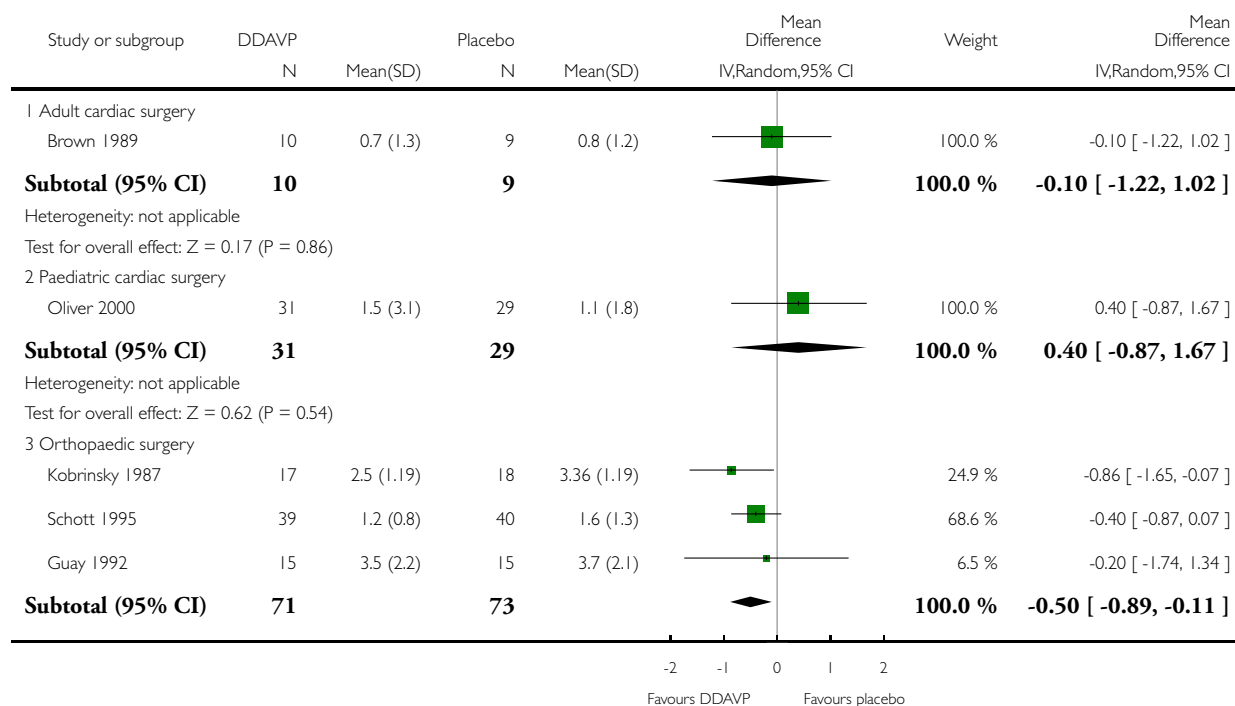
|   |   |     |                                       |                     |
|---|---|-----|---------------------------------------|---------------------|
| 4 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism) | 2 |     | Peto Odds Ratio (Peto, Fixed, 95% CI) | Totals not selected |
| 4.1 Cardiac surgery   | 2 |     | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 5 Myocardial infarction   | 2 | 152 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 5.1 Cardiac surgery   | 2 | 152 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 6 Stroke  | 2 |     | Peto Odds Ratio (Peto, Fixed, 95% CI) | Totals not selected |
| 6.1 Cardiac surgery   | 2 |     | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 7 Venous thromboembolism  | 2 | 152 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 7.1 Cardiac surgery   | 2 | 152 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 8 Clinically significant hypotension  | 1 | 53  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |
| 8.1 Cardiac surgery   | 1 | 53  | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.0 [0.0, 0.0]      |

### Analysis 1.1. Comparison 1 Desmopressin vs placebo, Outcome 1 Red cell volume transfused (intraoperatively).

Review: Desmopressin use for minimising perioperative blood transfusion

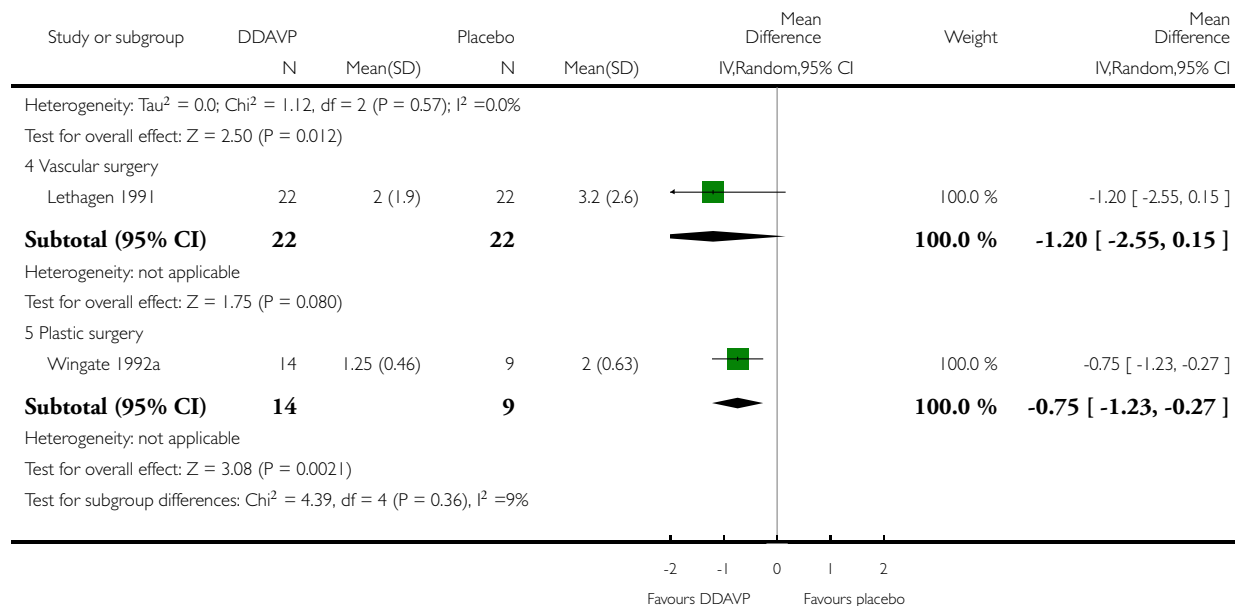
Comparison: 1 Desmopressin vs placebo

Outcome: 1 Red cell volume transfused (intraoperatively)



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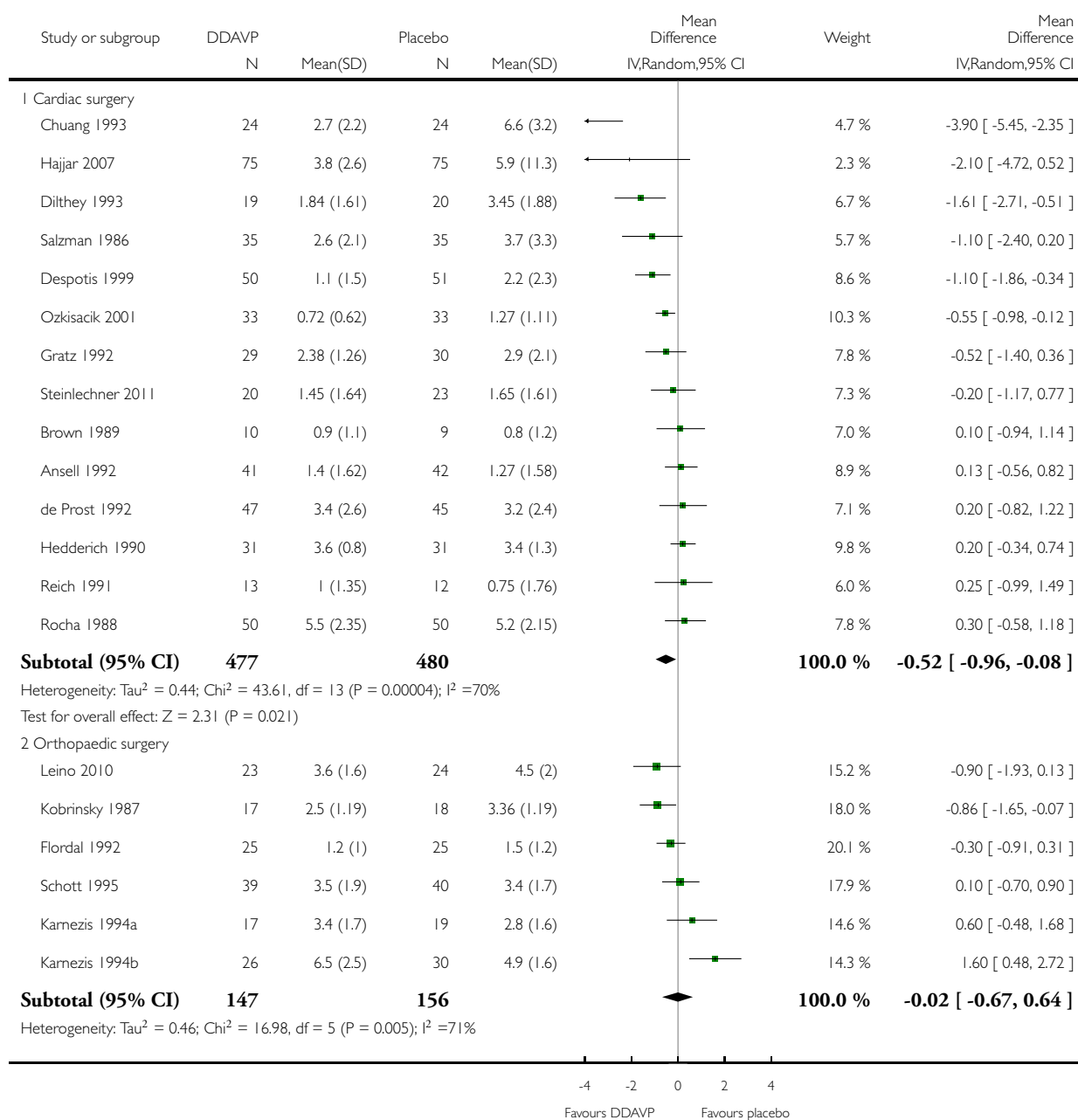


## Analysis 1.2. Comparison 1 Desmopressin vs placebo, Outcome 2 Red cell volume transfused (total).

Review: Desmopressin use for minimising perioperative blood transfusion

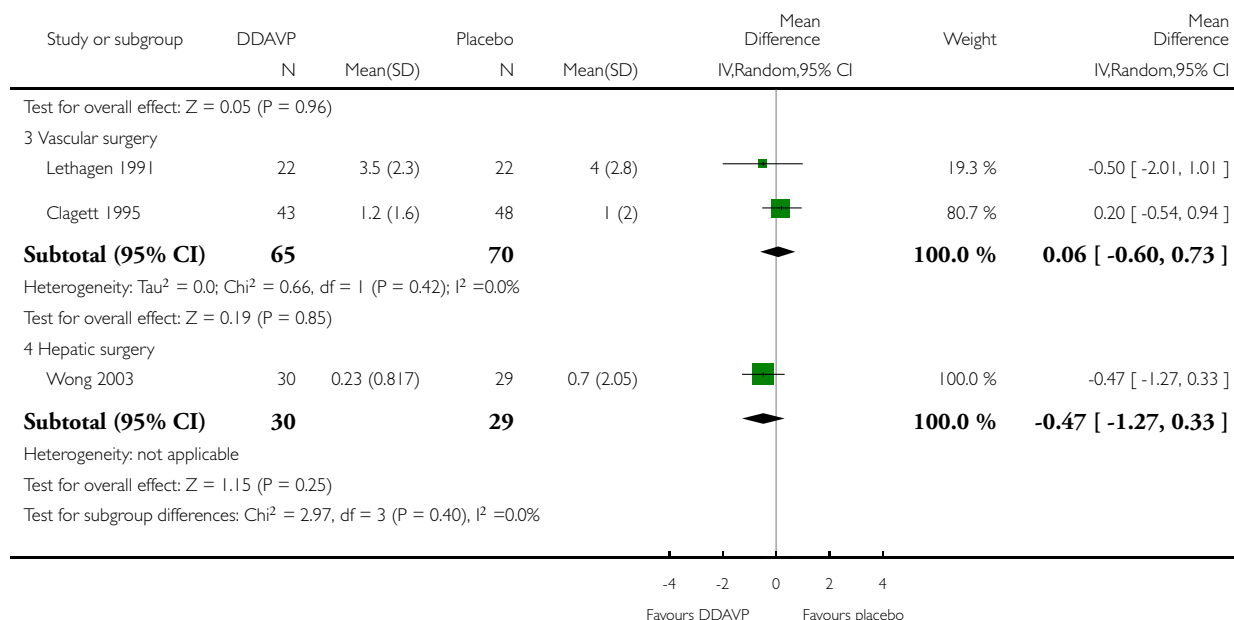
Comparison: 1 Desmopressin vs placebo

Outcome: 2 Red cell volume transfused (total)



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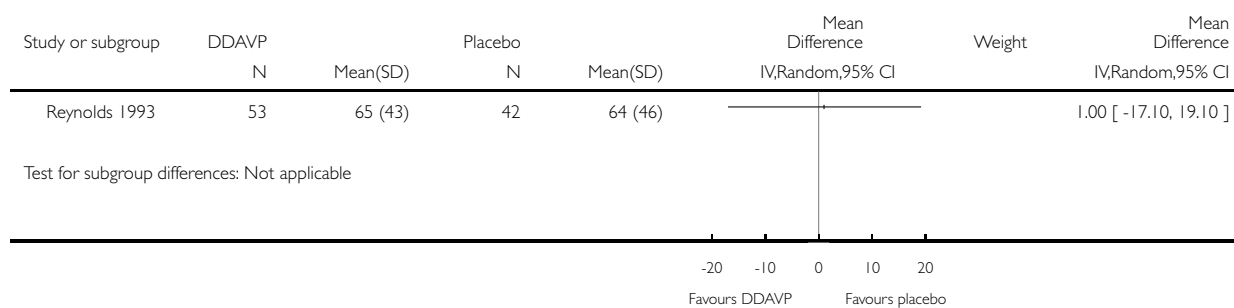


### Analysis 1.3. Comparison 1 Desmopressin vs placebo, Outcome 3 Red cell volume transfused (children only, total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 3 Red cell volume transfused (children only, total)

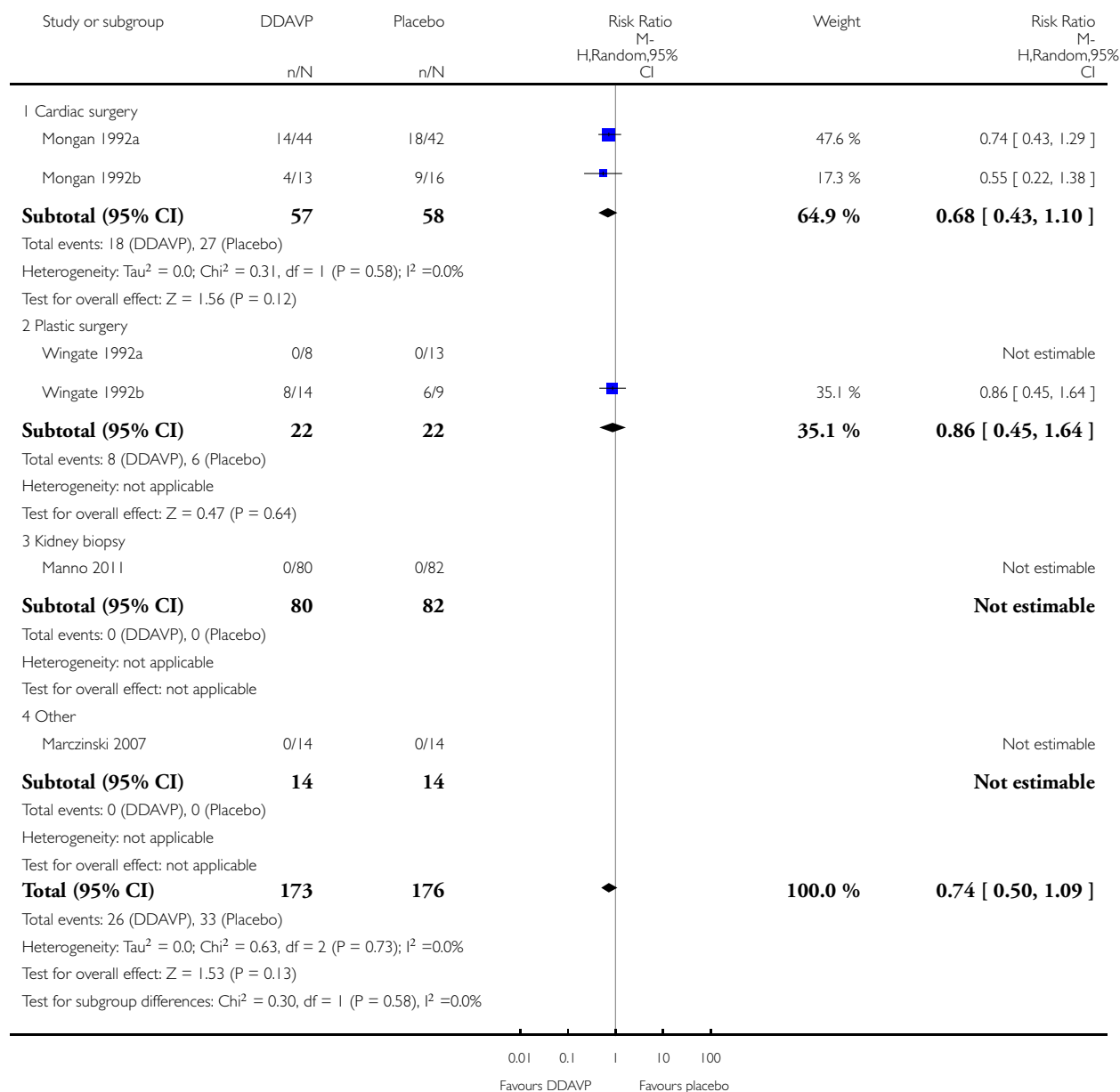


# **Analysis 1.4. Comparison 1 Desmopressin vs placebo, Outcome 4 Number of participants receiving a red cell transfusion (intraoperatively).**

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 4 Number of participants receiving a red cell transfusion (intraoperatively)

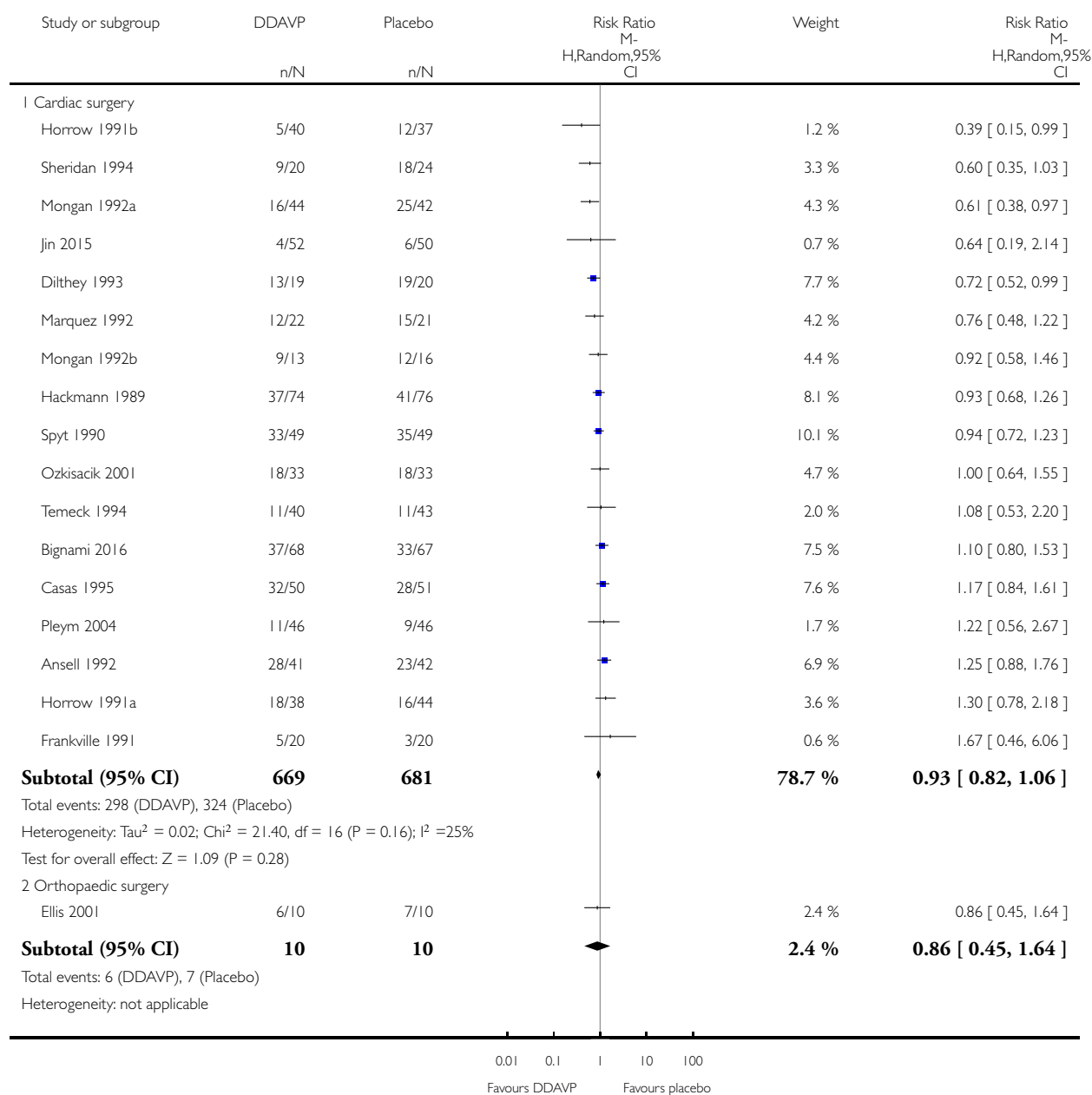


# **Analysis 1.5. Comparison 1 Desmopressin vs placebo, Outcome 5 Number of participants receiving a red cell transfusion (total).**

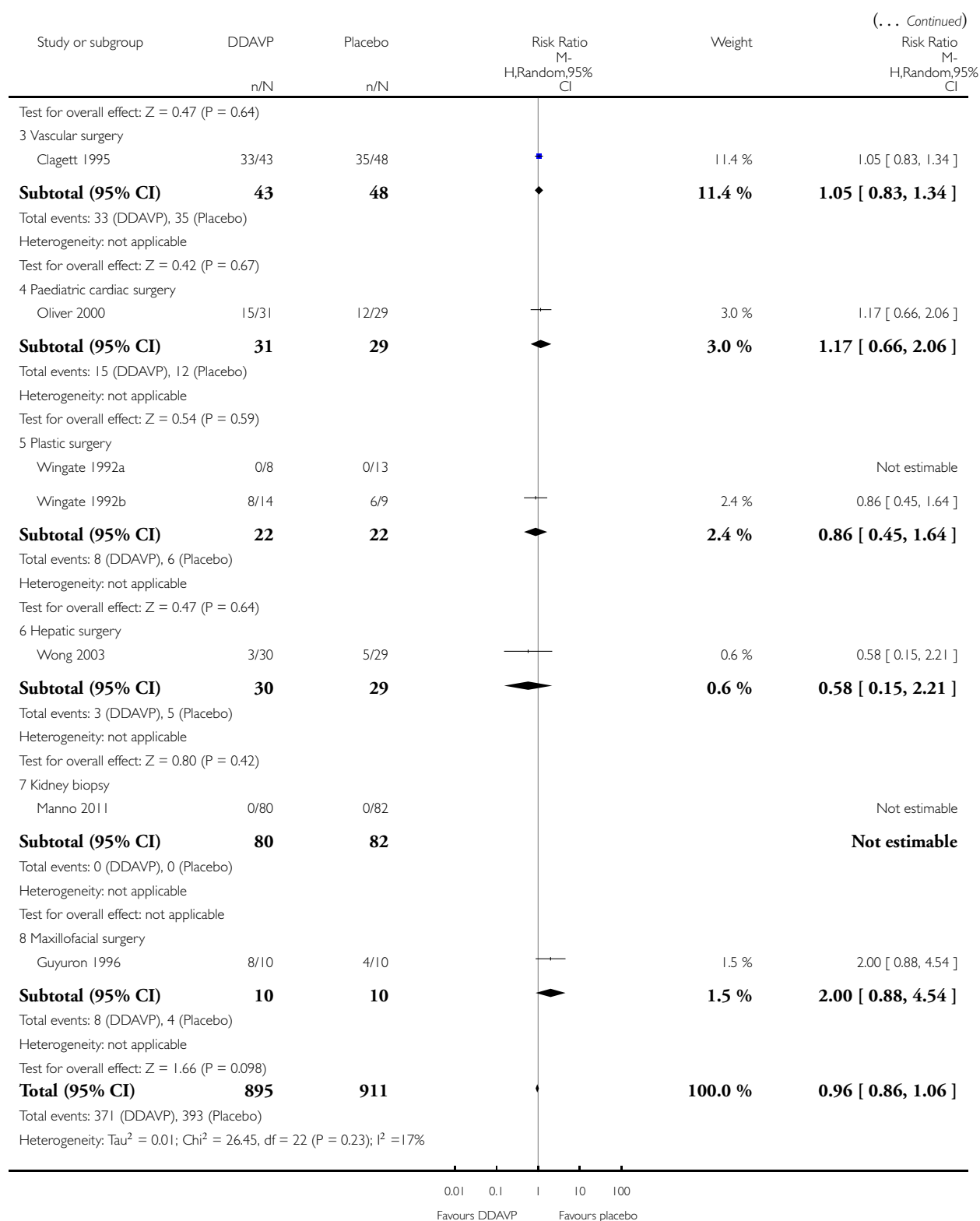
Review: Desmopressin use for minimising perioperative blood transfusion

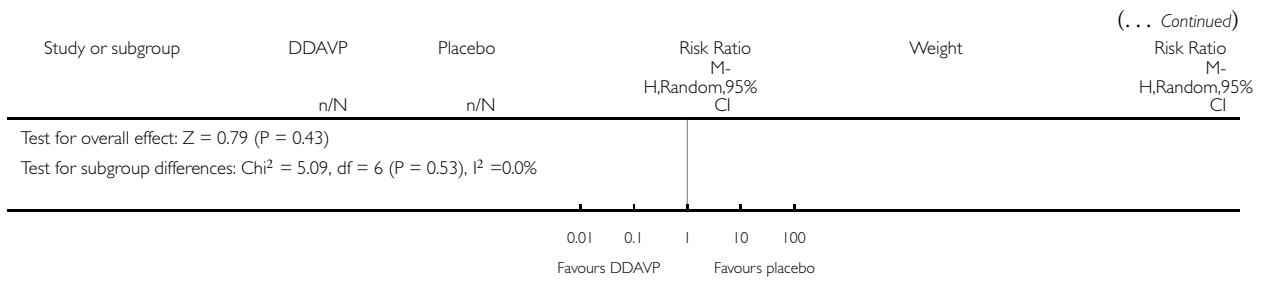
Comparison: 1 Desmopressin vs placebo

Outcome: 5 Number of participants receiving a red cell transfusion (total)



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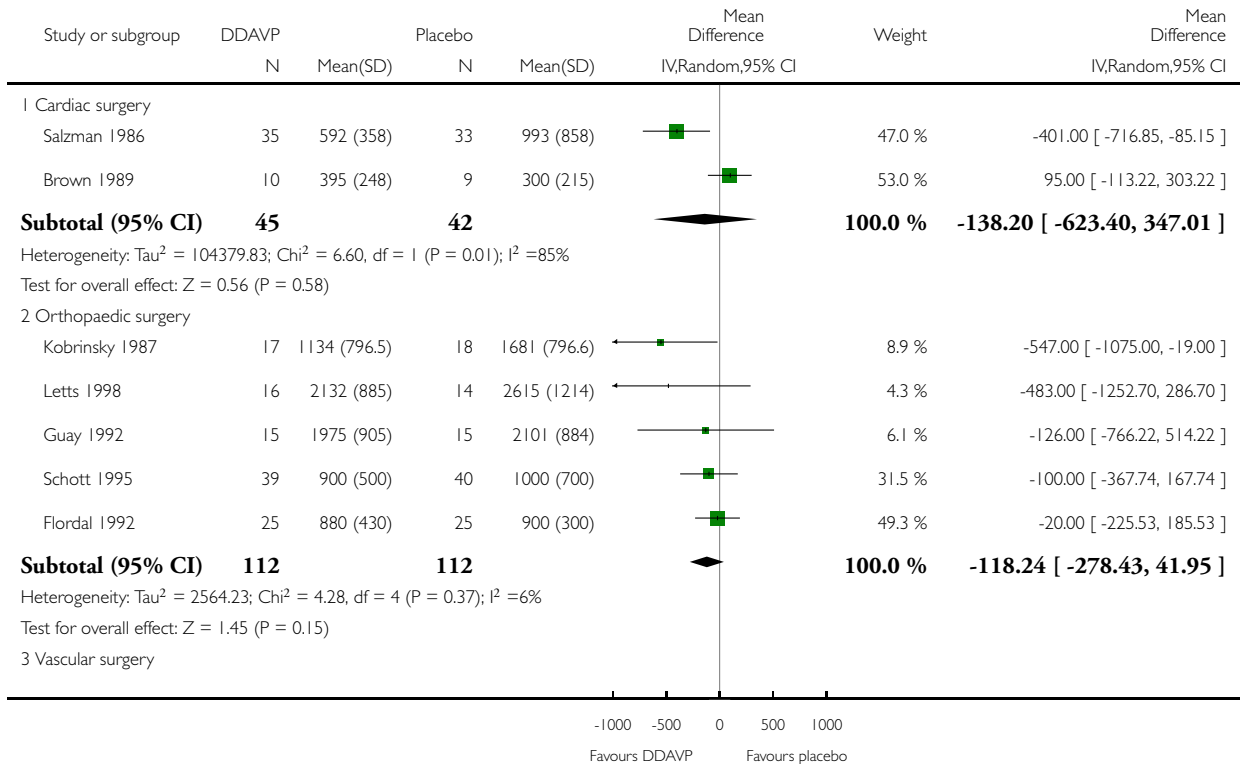


### Analysis 1.6. Comparison 1 Desmopressin vs placebo, Outcome 6 Blood loss (intraoperative).

Review: Desmopressin use for minimising perioperative blood transfusion

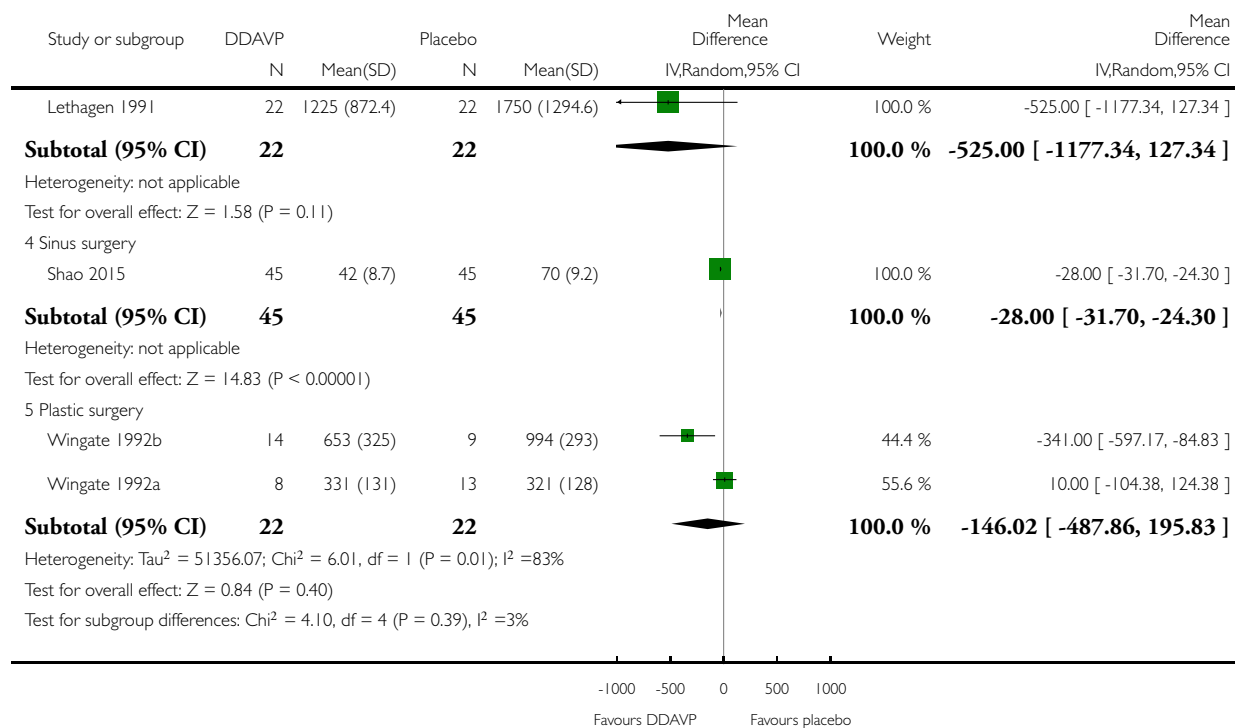
Comparison: 1 Desmopressin vs placebo

Outcome: 6 Blood loss (intraoperative)



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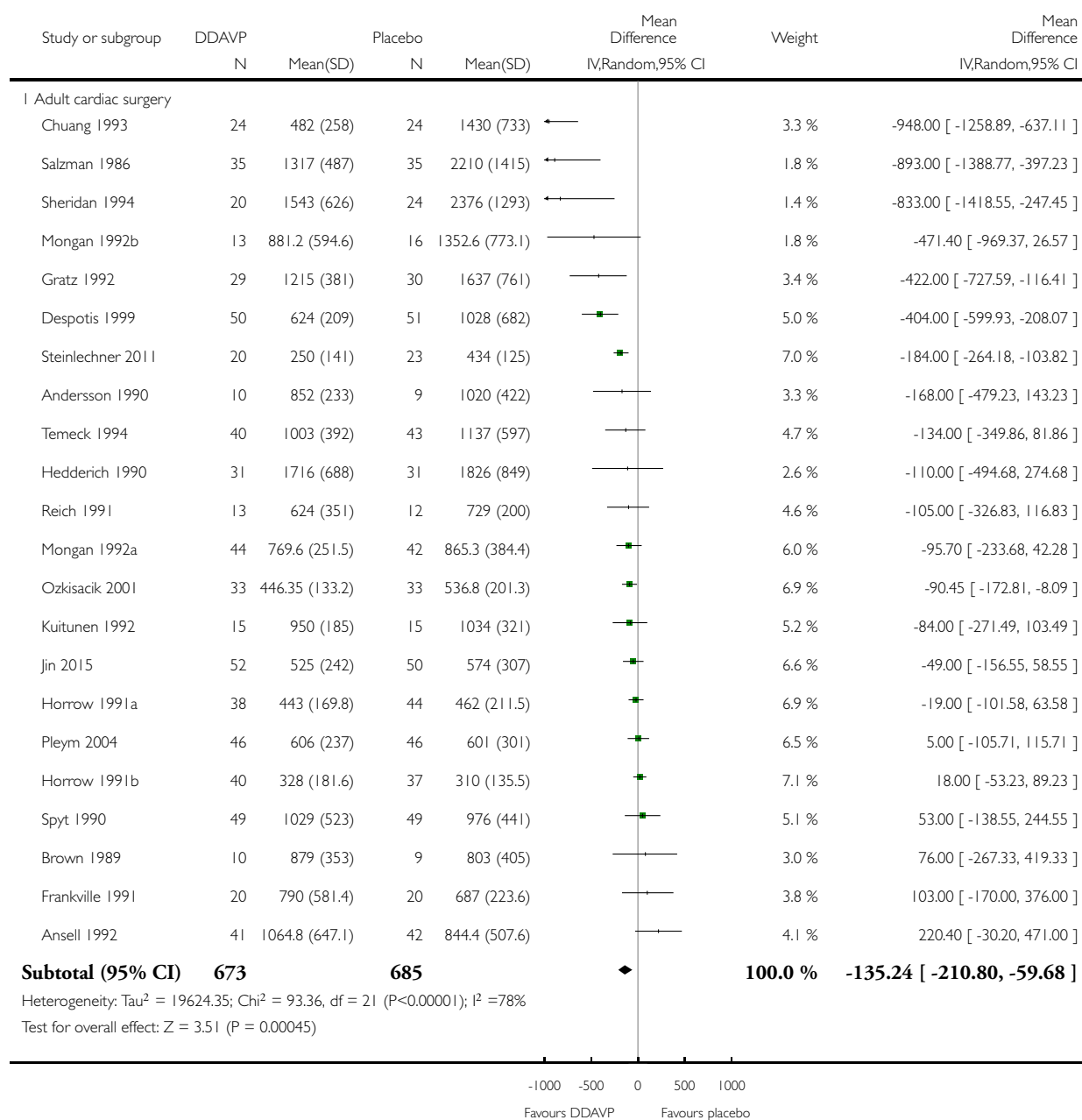


# Analysis 1.7. Comparison 1 Desmopressin vs placebo, Outcome 7 Blood loss (total).

Review: Desmopressin use for minimising perioperative blood transfusion

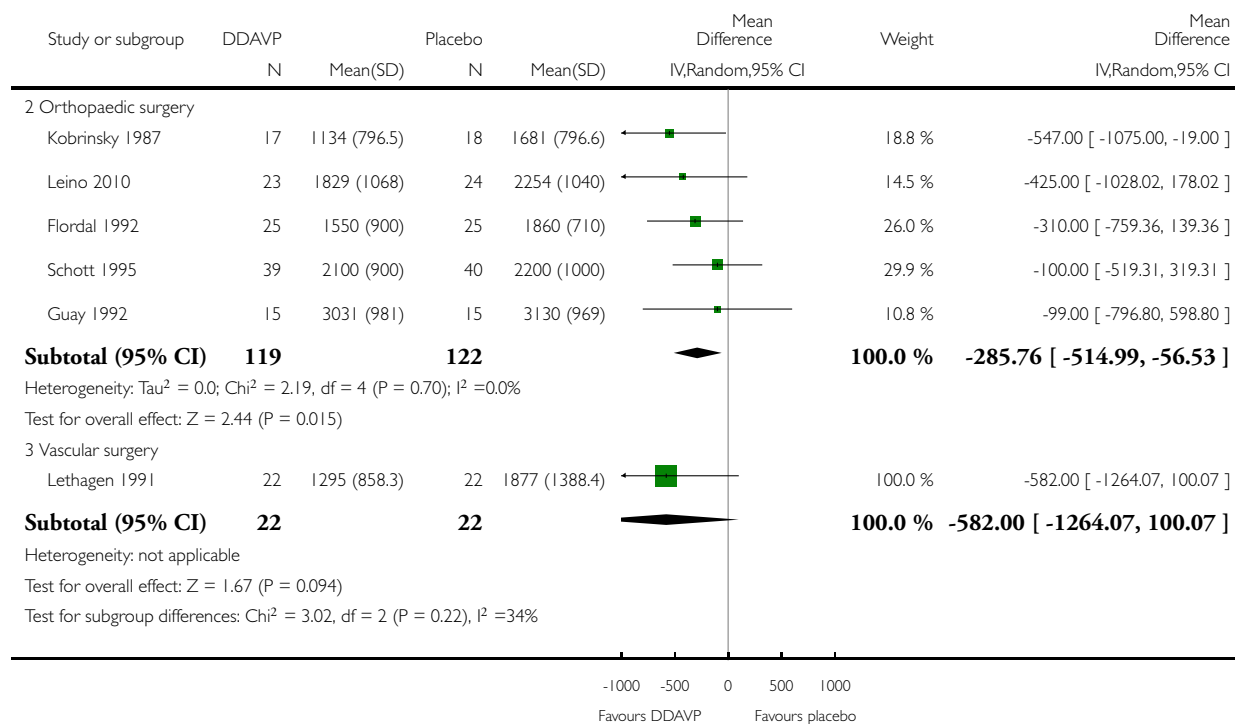
Comparison: 1 Desmopressin vs placebo

Outcome: 7 Blood loss (total)



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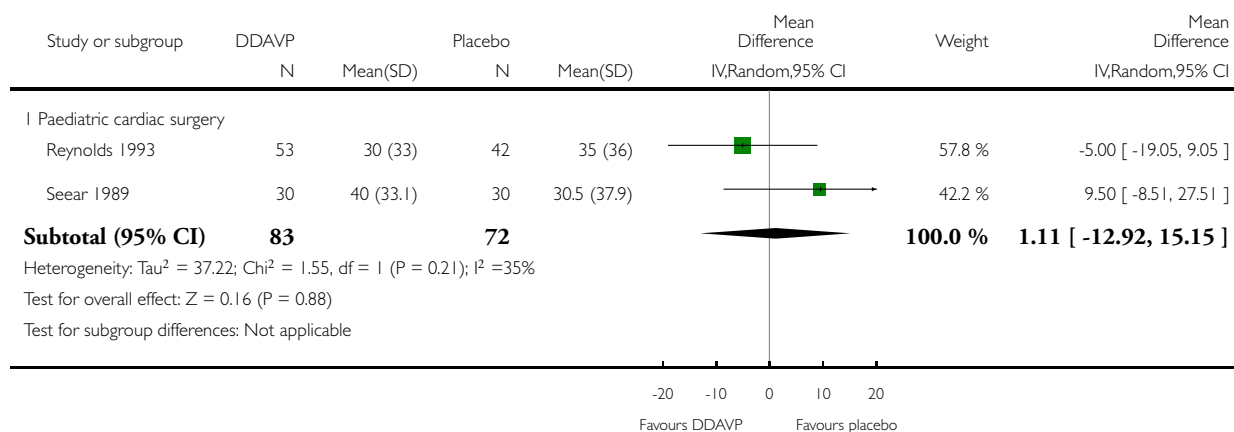


### Analysis 1.8. Comparison 1 Desmopressin vs placebo, Outcome 8 Blood loss (children only, total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 8 Blood loss (children only, total)

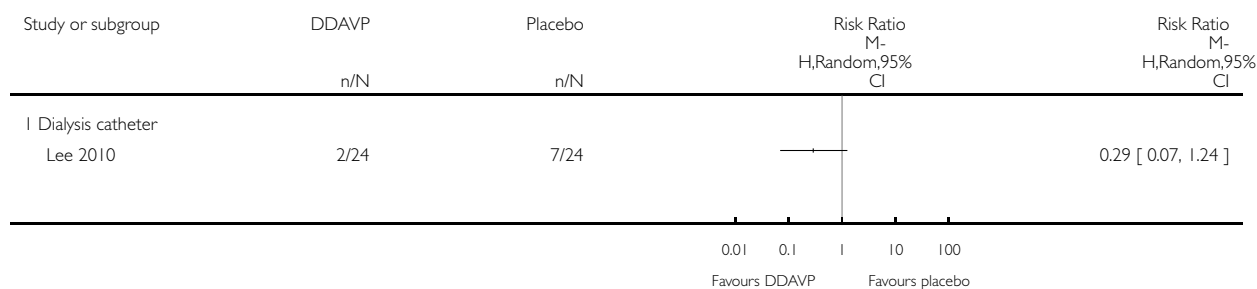


### Analysis 1.9. Comparison 1 Desmopressin vs placebo, Outcome 9 Number of participants with any bleeding (intraoperatively).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 9 Number of participants with any bleeding (intraoperatively)

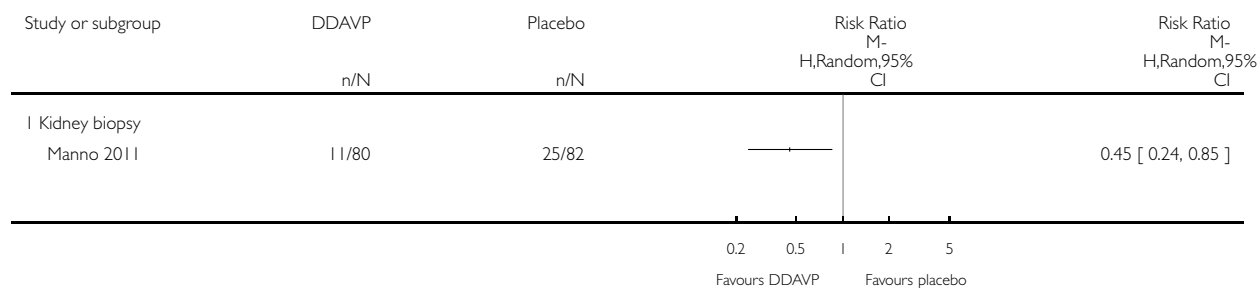


### Analysis 1.10. Comparison 1 Desmopressin vs placebo, Outcome 10 Number of participants with any bleeding (total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 10 Number of participants with any bleeding (total)

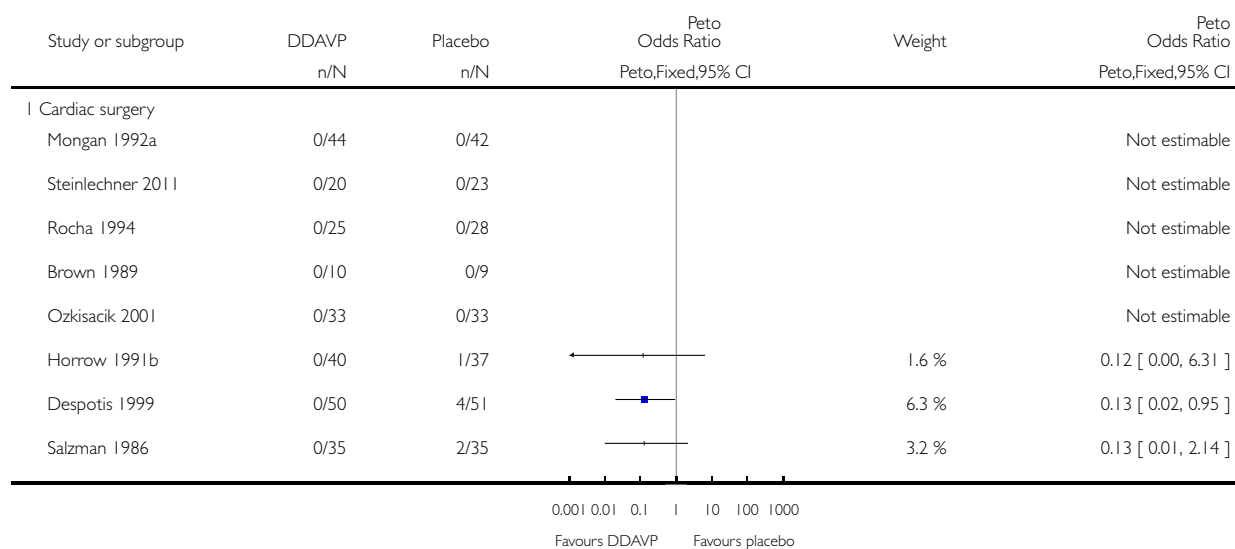


### Analysis 1.11. Comparison 1 Desmopressin vs placebo, Outcome 11 Reoperation due to bleeding.

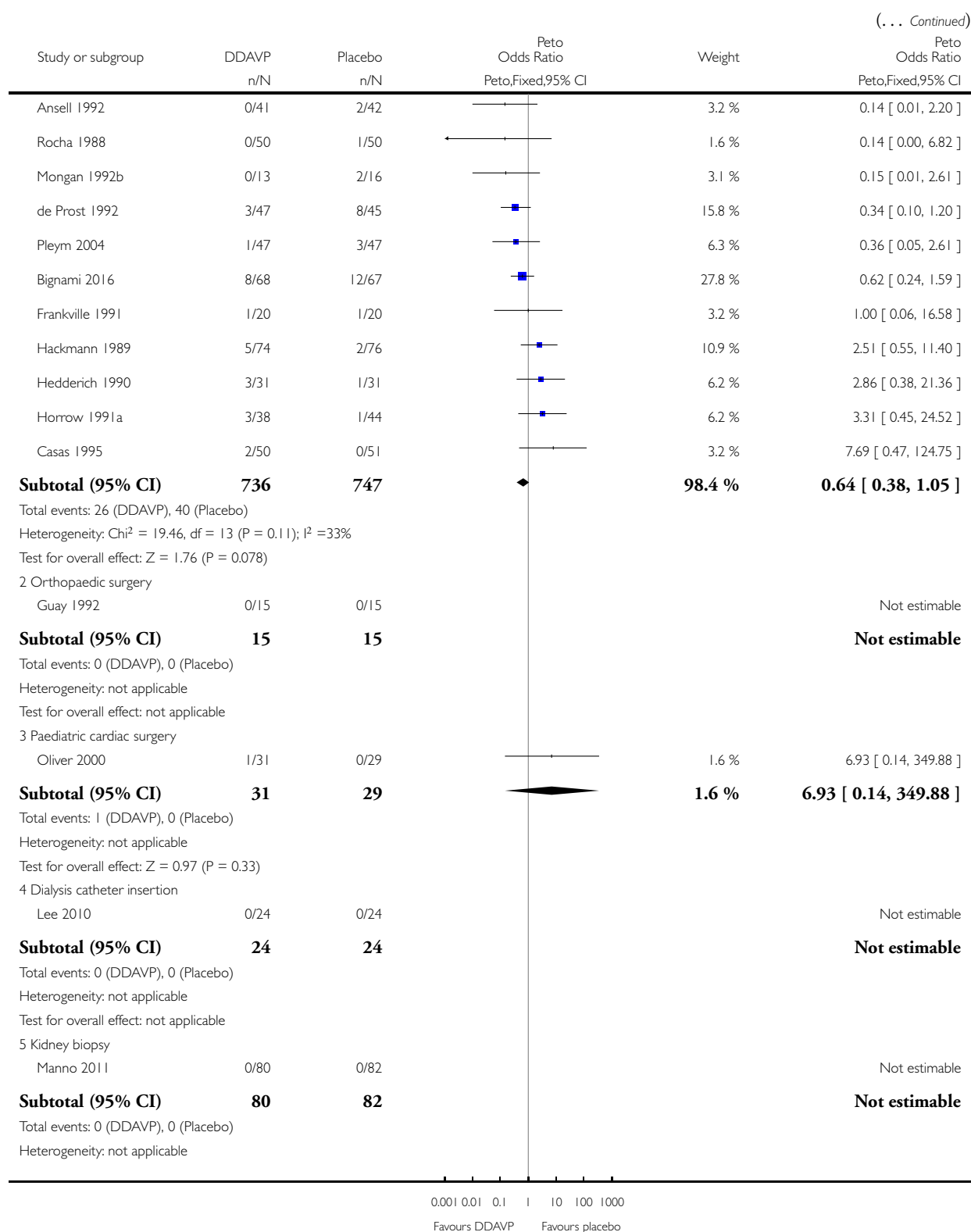
Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

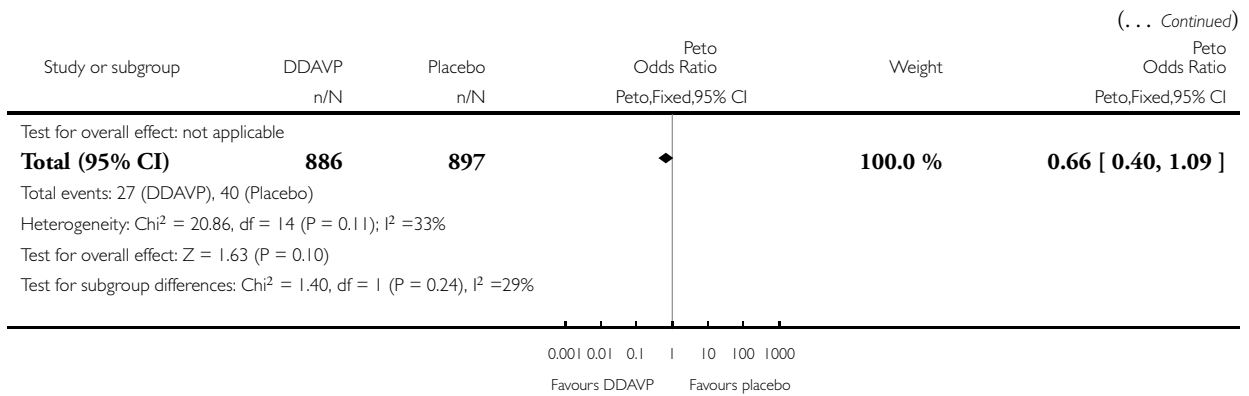
Outcome: 11 Reoperation due to bleeding



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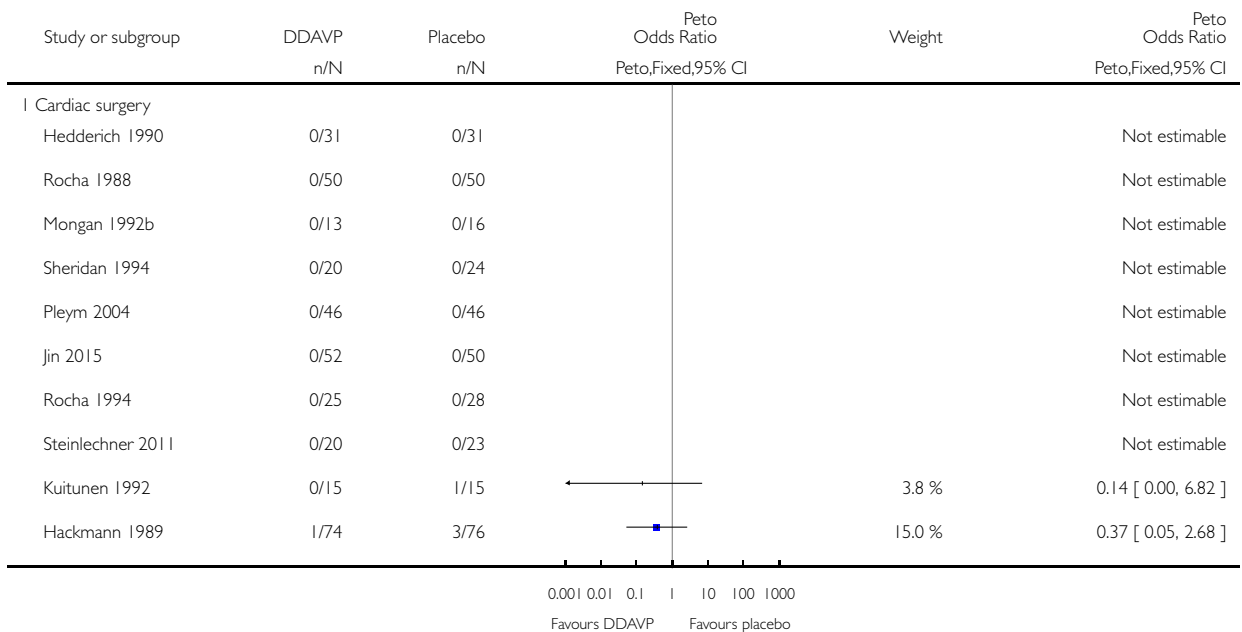


### Analysis 1.12. Comparison 1 Desmopressin vs placebo, Outcome 12 All-cause mortality.

Review: Desmopressin use for minimising perioperative blood transfusion

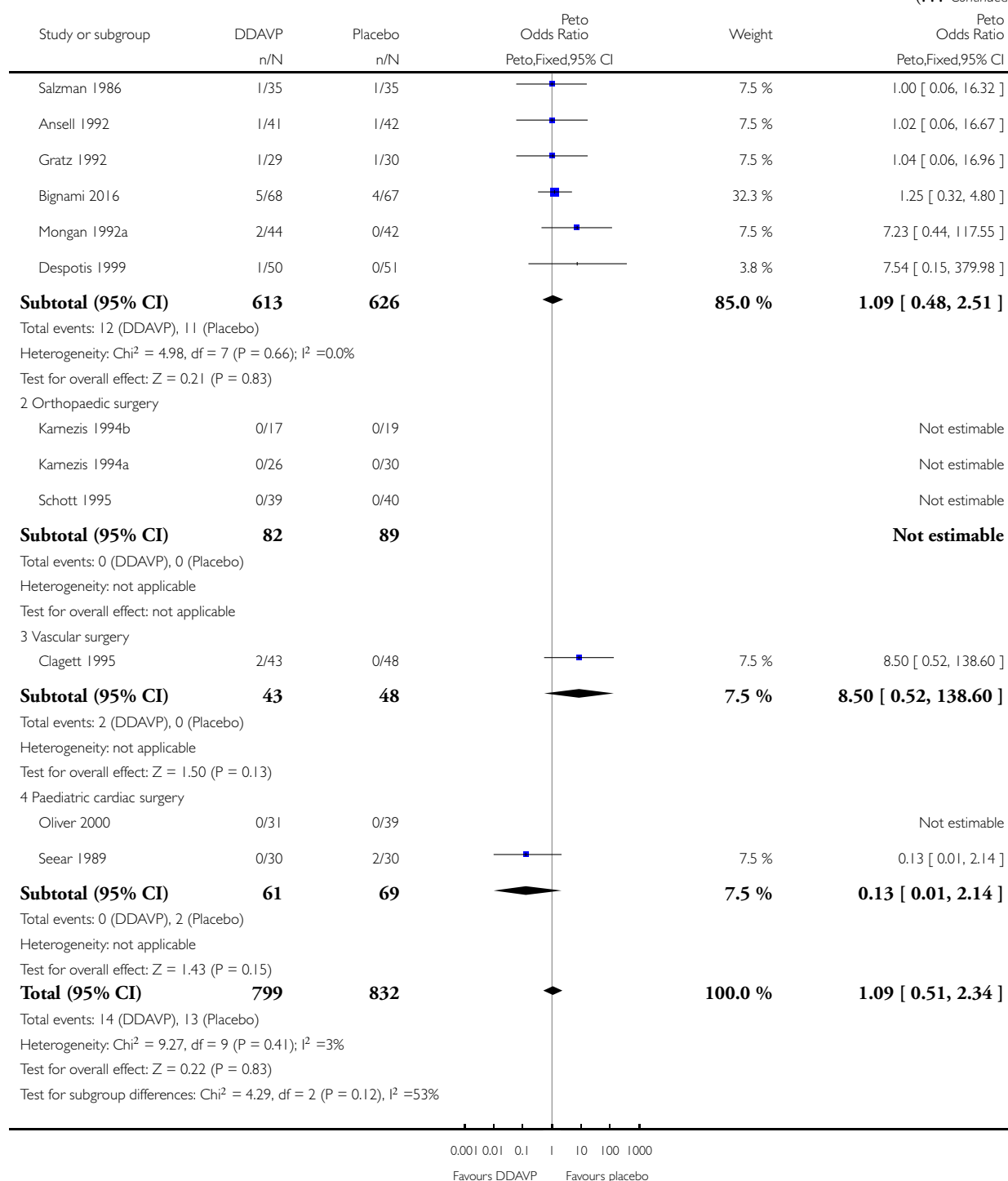
Comparison: 1 Desmopressin vs placebo

Outcome: 12 All-cause mortality



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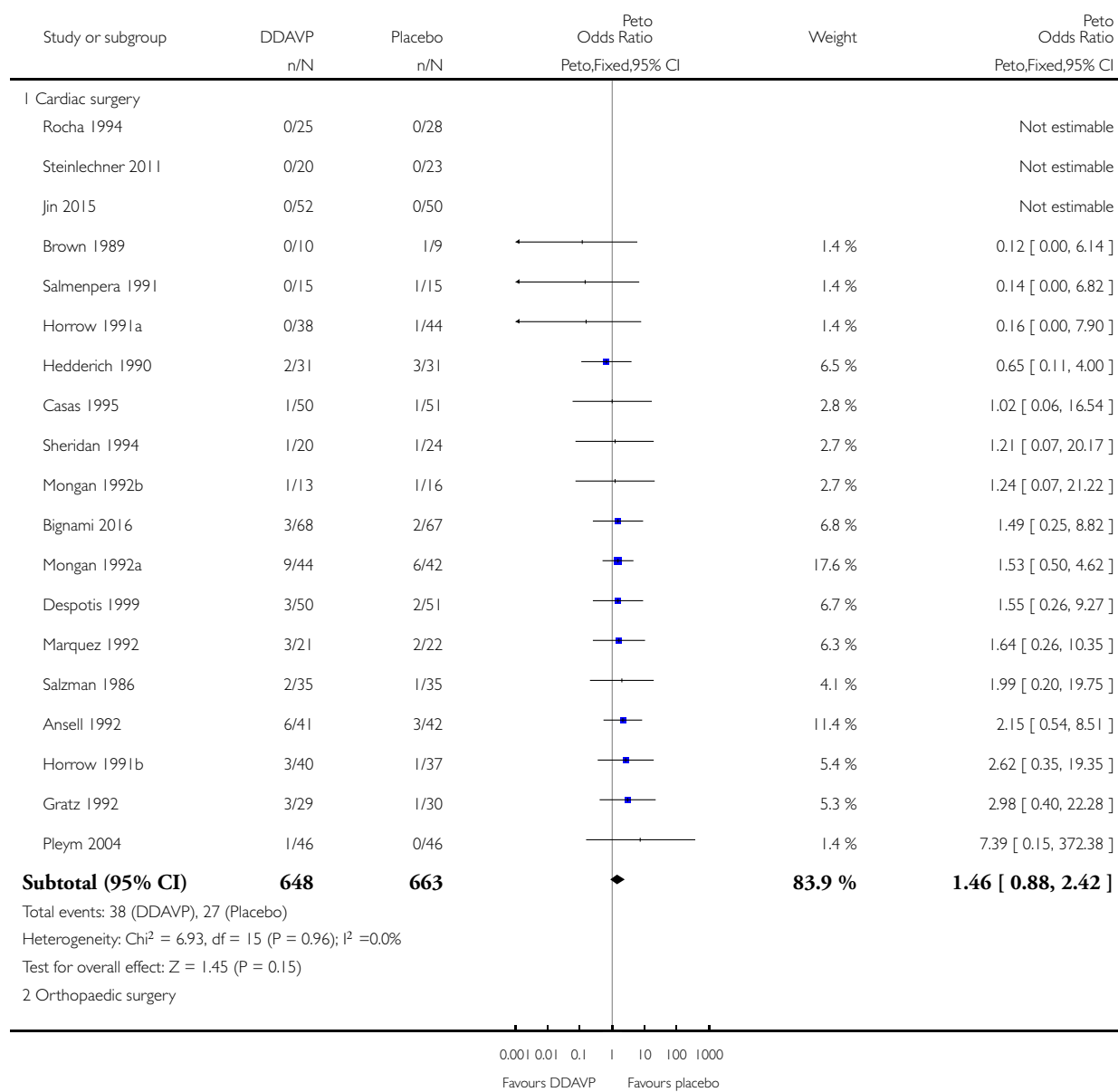


### Analysis 1.13. Comparison 1 Desmopressin vs placebo, Outcome 13 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism).

Review: Desmopressin use for minimising perioperative blood transfusion

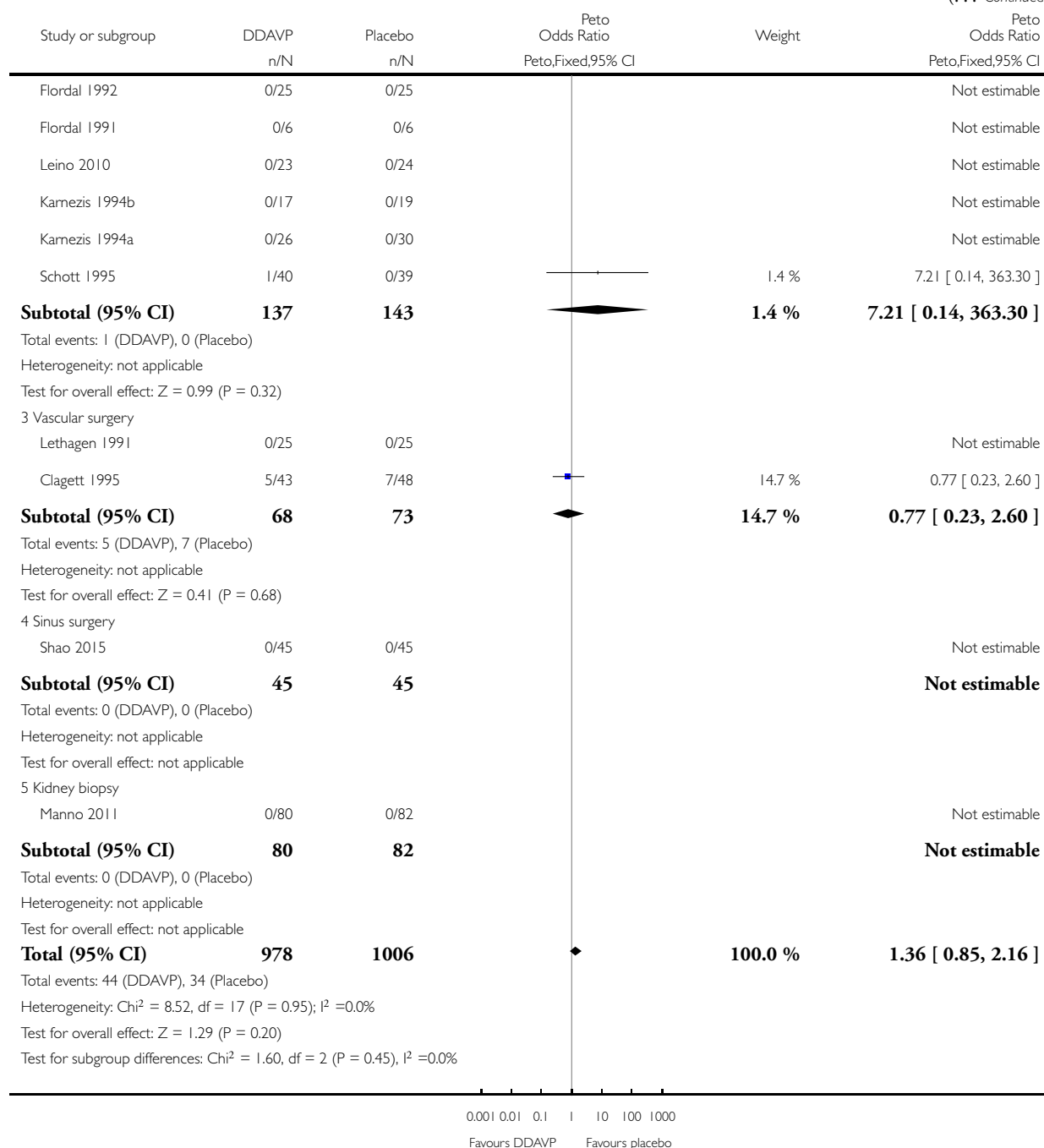
Comparison: 1 Desmopressin vs placebo

Outcome: 13 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)



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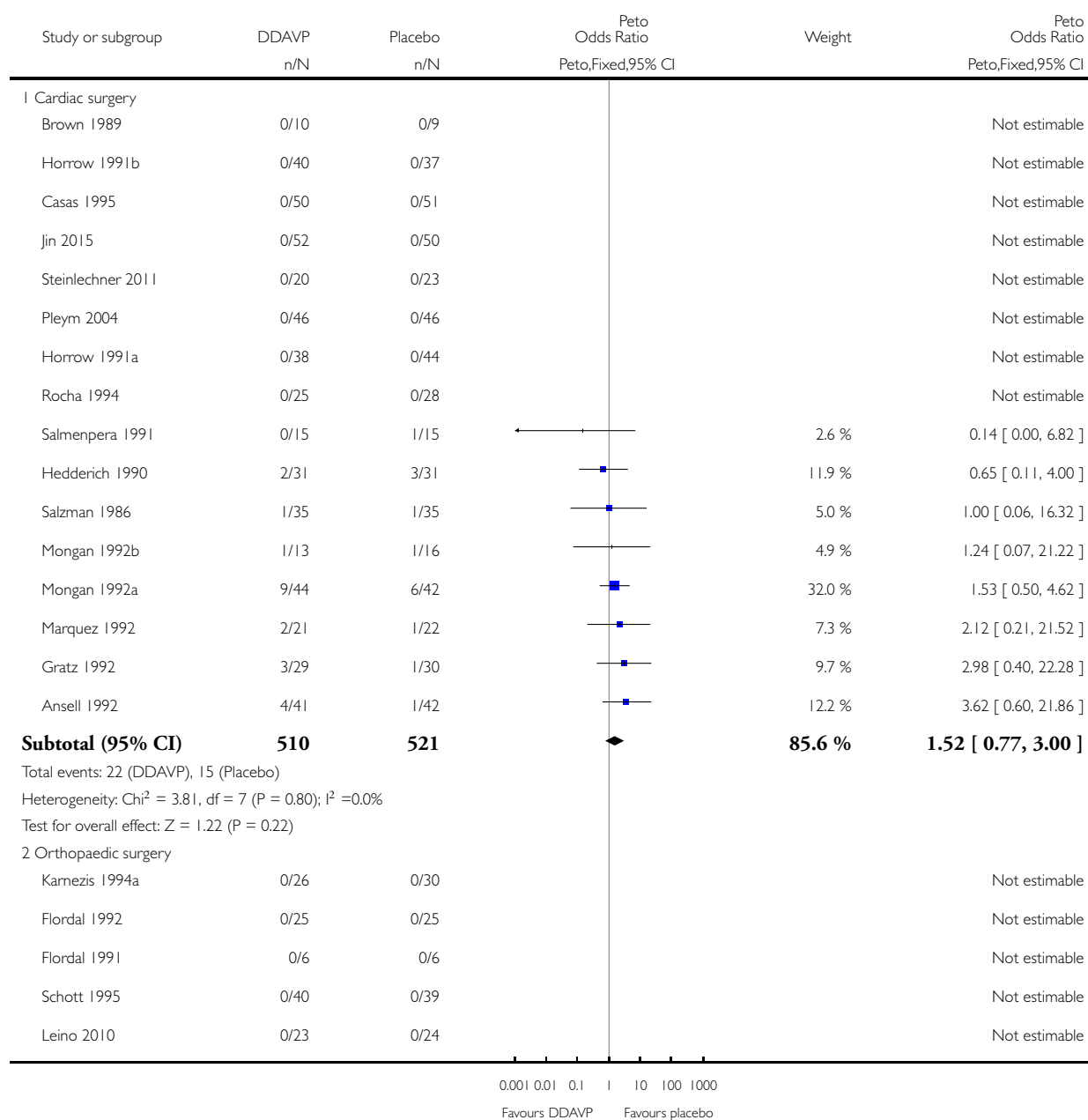


# Analysis 1.14. Comparison 1 Desmopressin vs placebo, Outcome 14 Myocardial infarction.

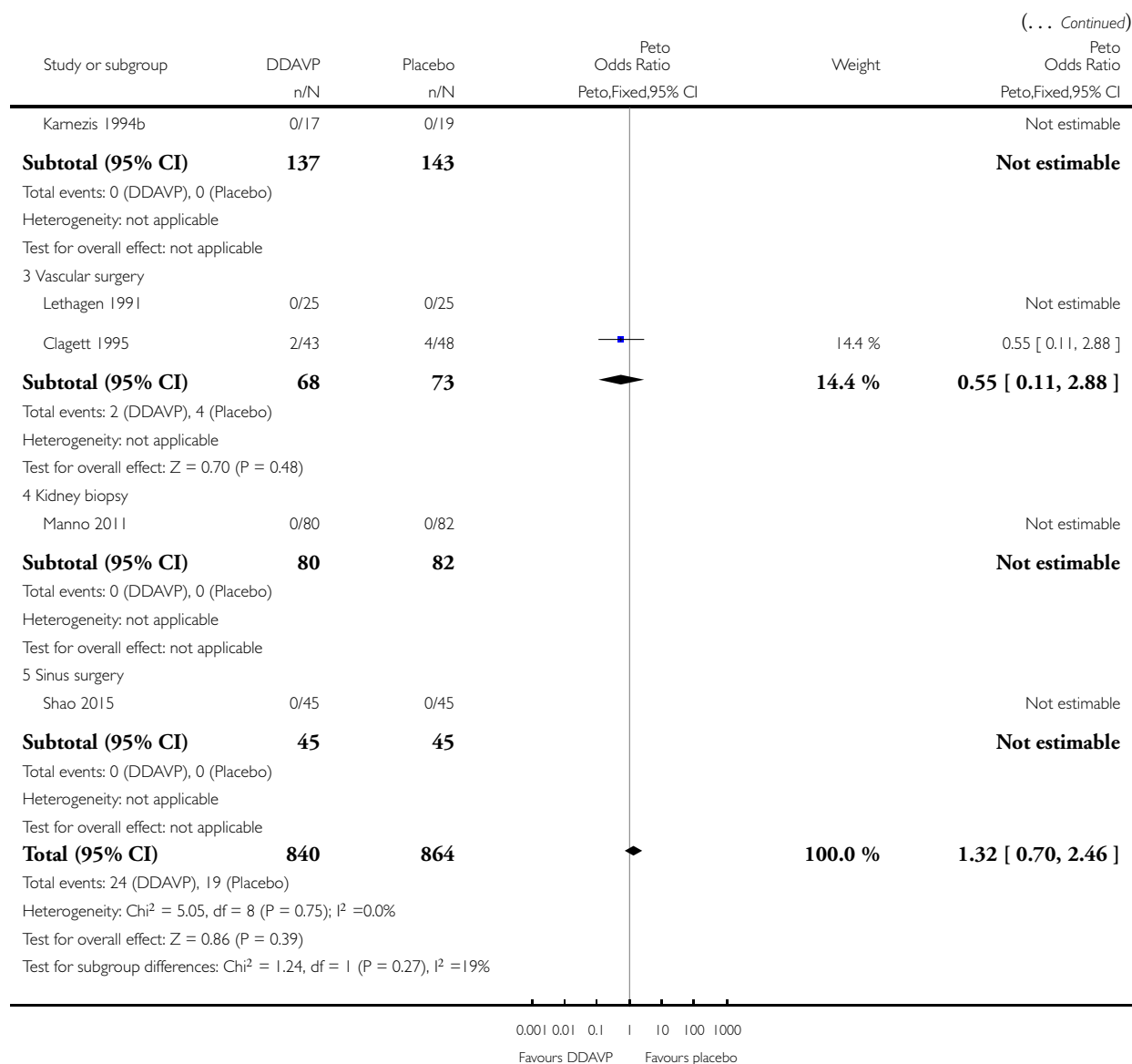
Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 14 Myocardial infarction



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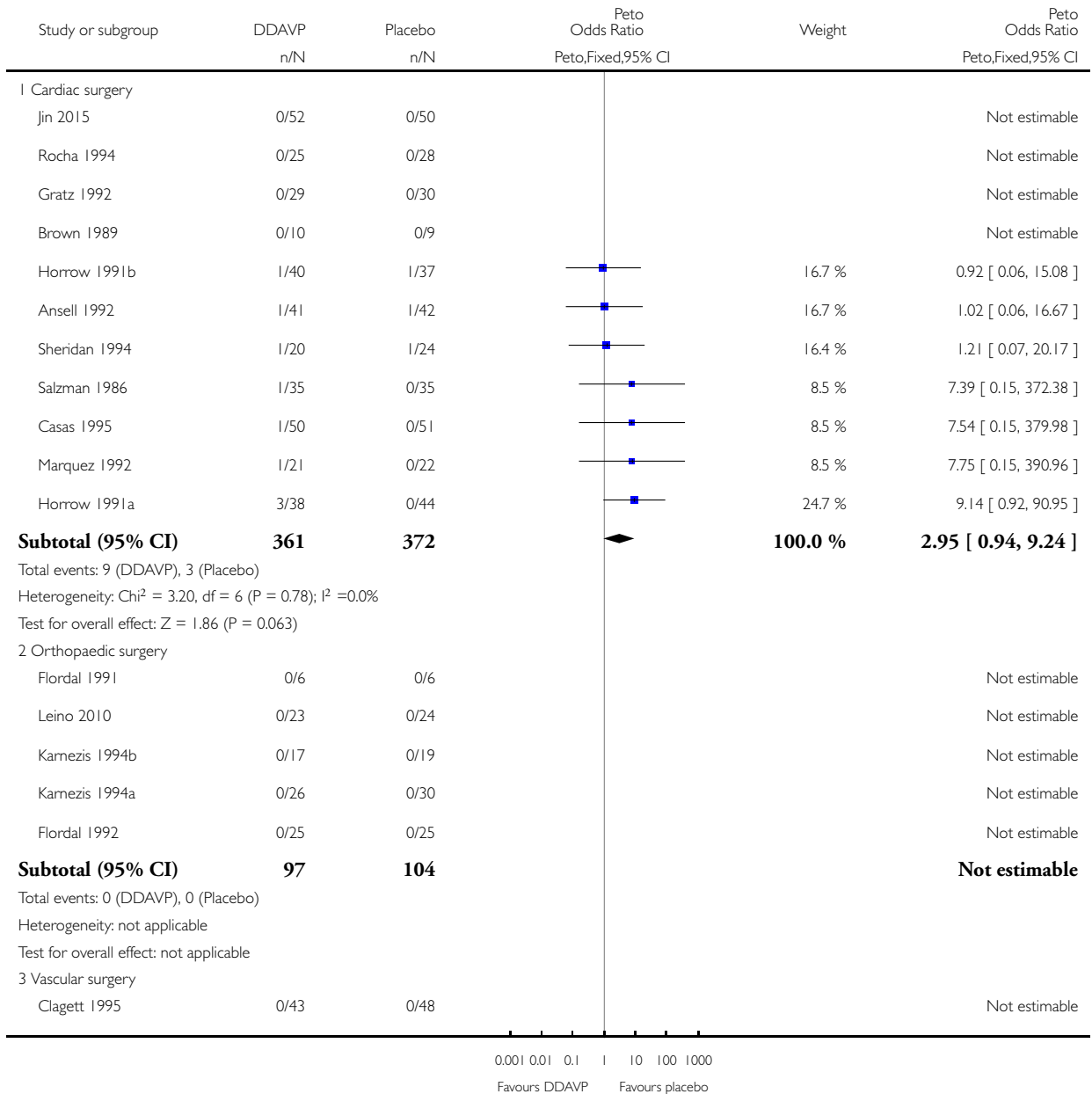


### Analysis 1.15. Comparison 1 Desmopressin vs placebo, Outcome 15 Stroke.

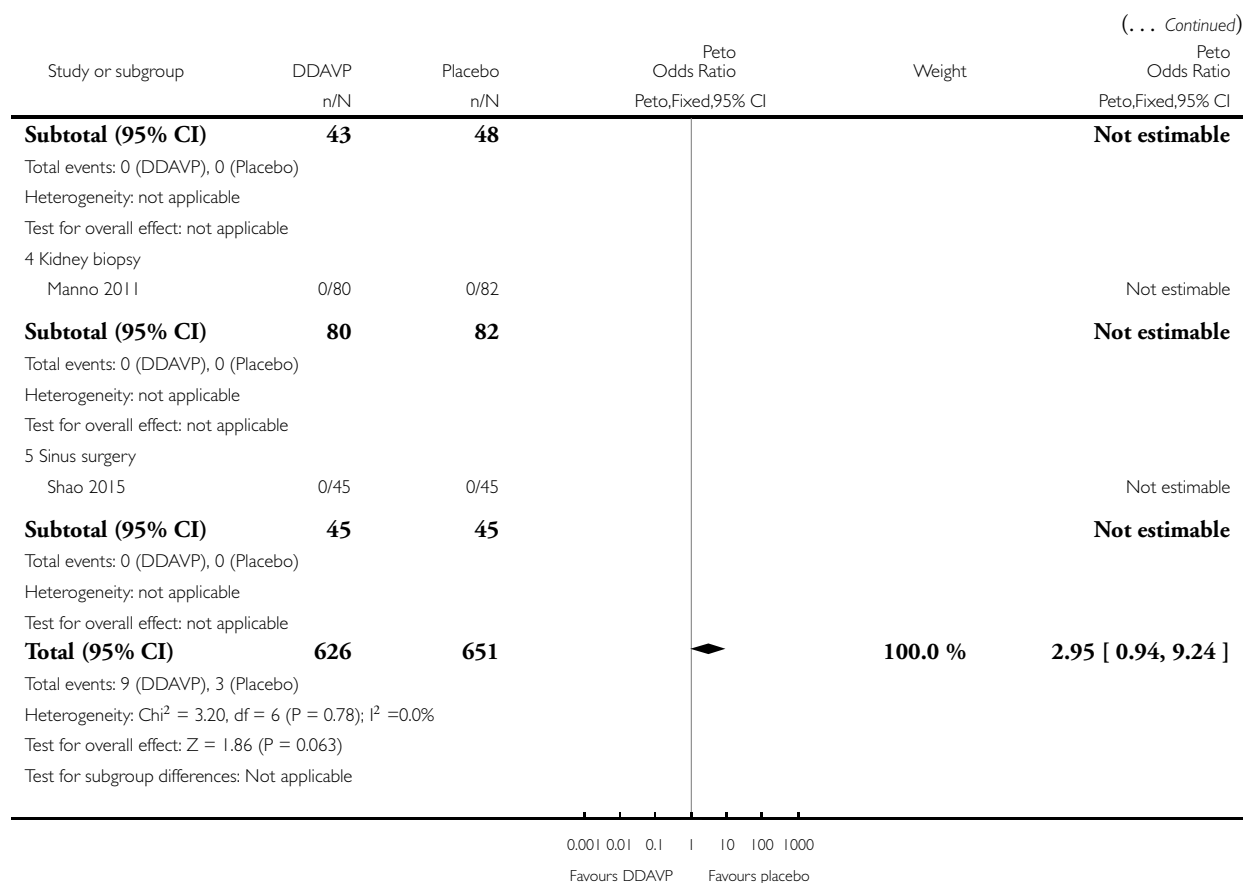
Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 15 Stroke



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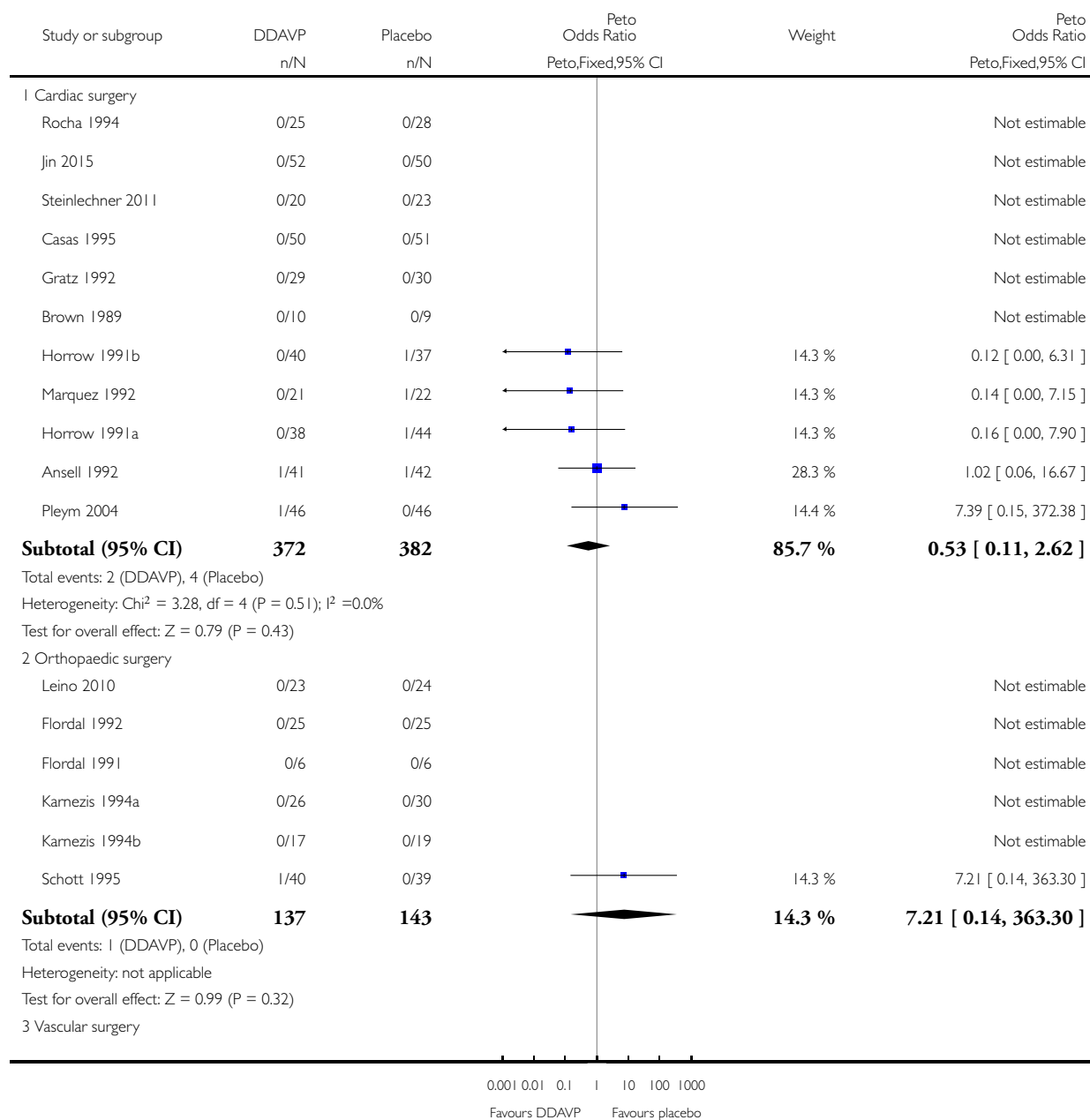


# Analysis 1.16. Comparison 1 Desmopressin vs placebo, Outcome 16 Venous thromboembolism.

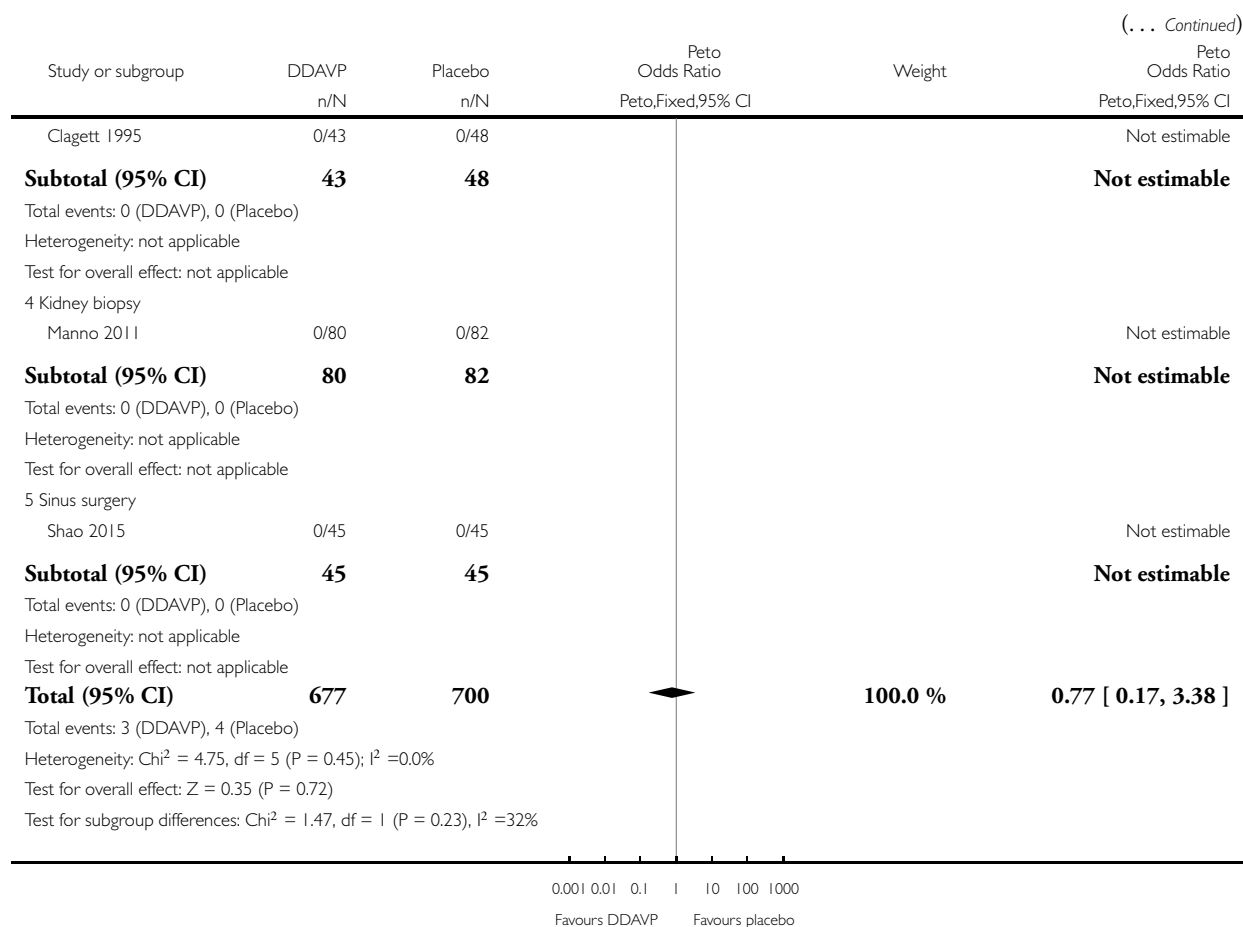
Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 16 Venous thromboembolism



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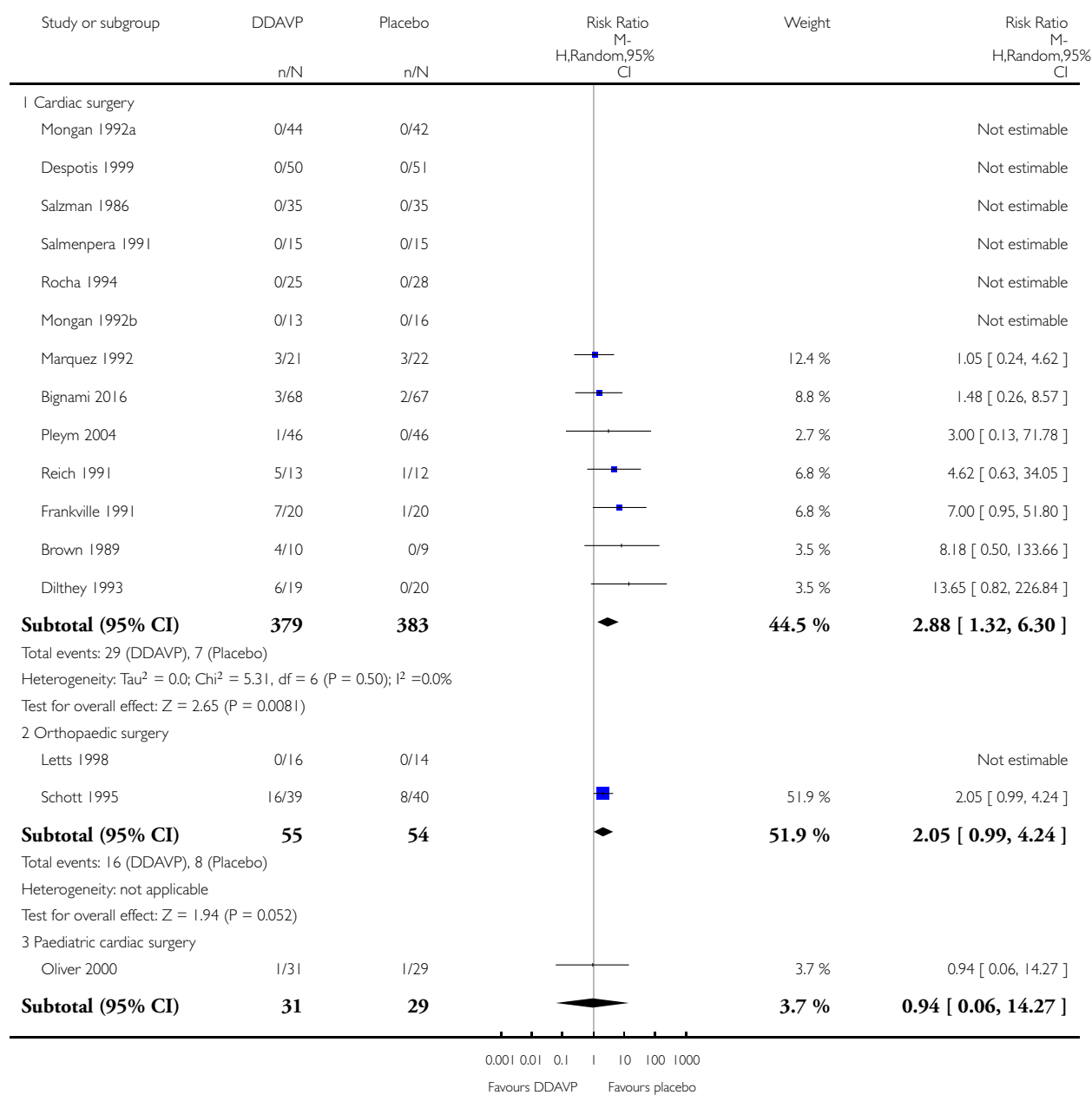


# Analysis 1.17. Comparison 1 Desmopressin vs placebo, Outcome 17 Clinically important hypotension.

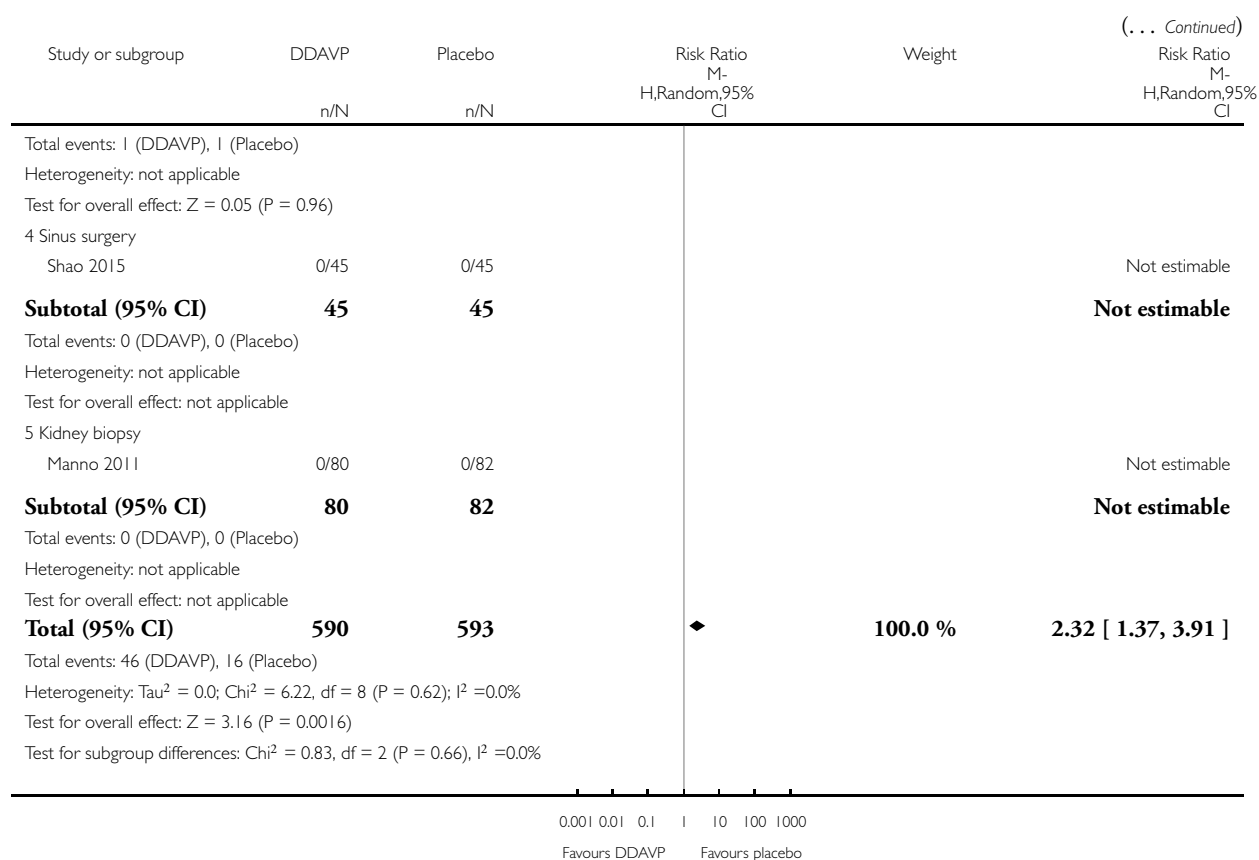
Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 1 Desmopressin vs placebo

Outcome: 17 Clinically important hypotension



(Continued ...)

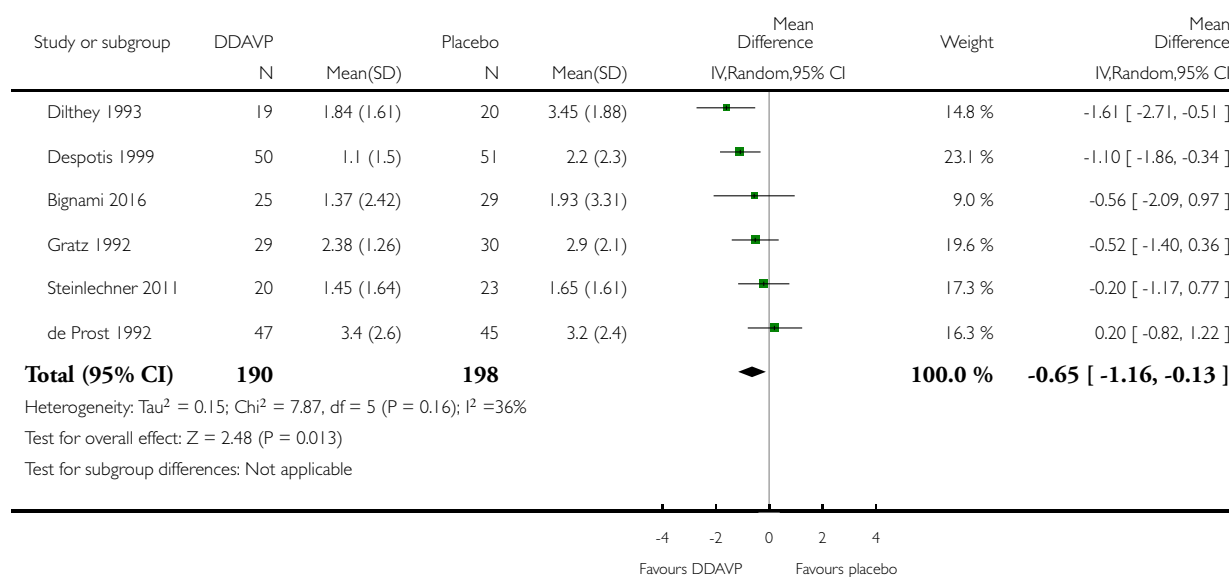


## Analysis 2.1. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 1 Red cell volume transfused (total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 1 Red cell volume transfused (total)

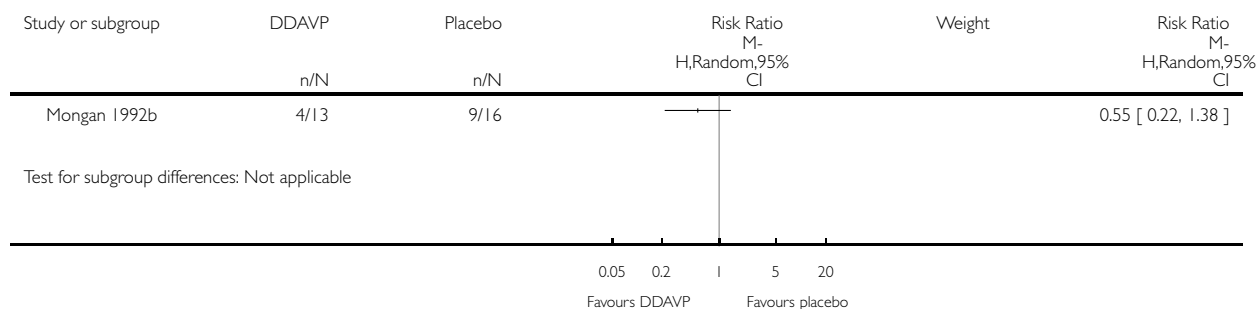


## Analysis 2.2. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 2 Number of participants receiving a red cell transfusion (intraoperatively).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 2 Number of participants receiving a red cell transfusion (intraoperatively)

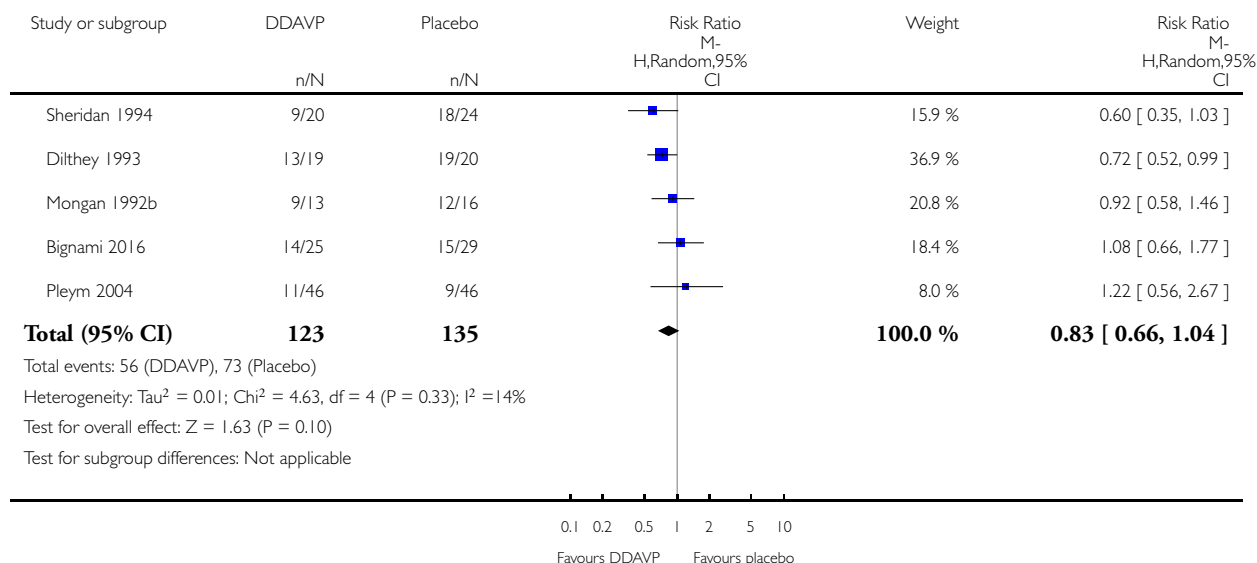


## Analysis 2.3. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 3 Number of participants receiving a red cell transfusion (total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 3 Number of participants receiving a red cell transfusion (total)

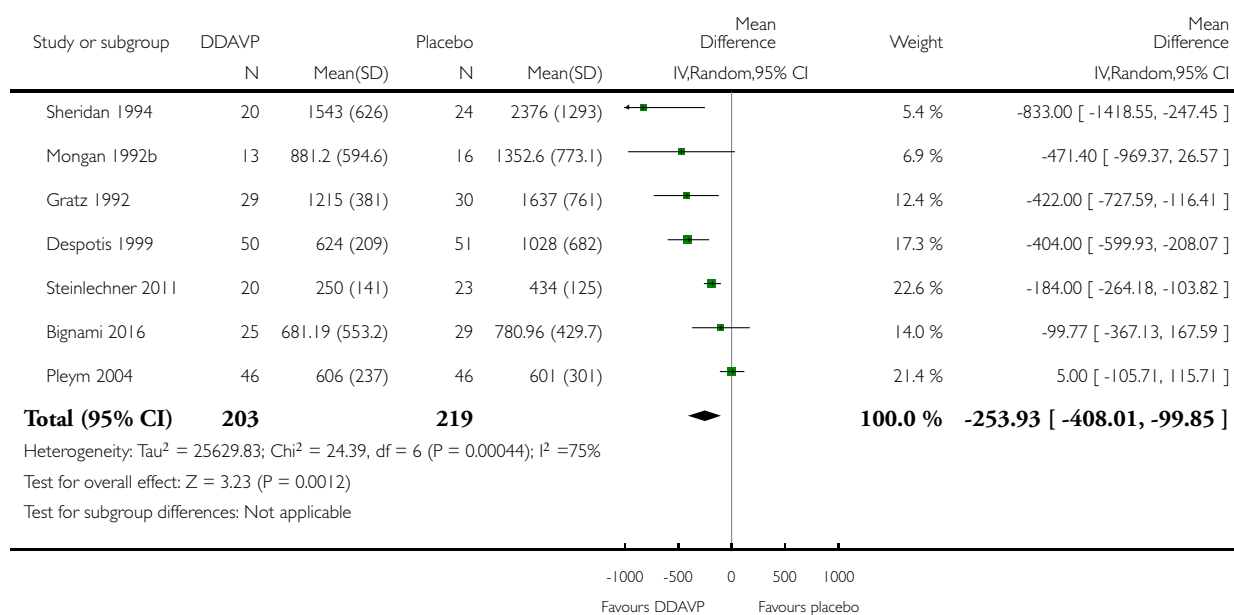


## Analysis 2.4. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 4 Blood loss (total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 4 Blood loss (total)

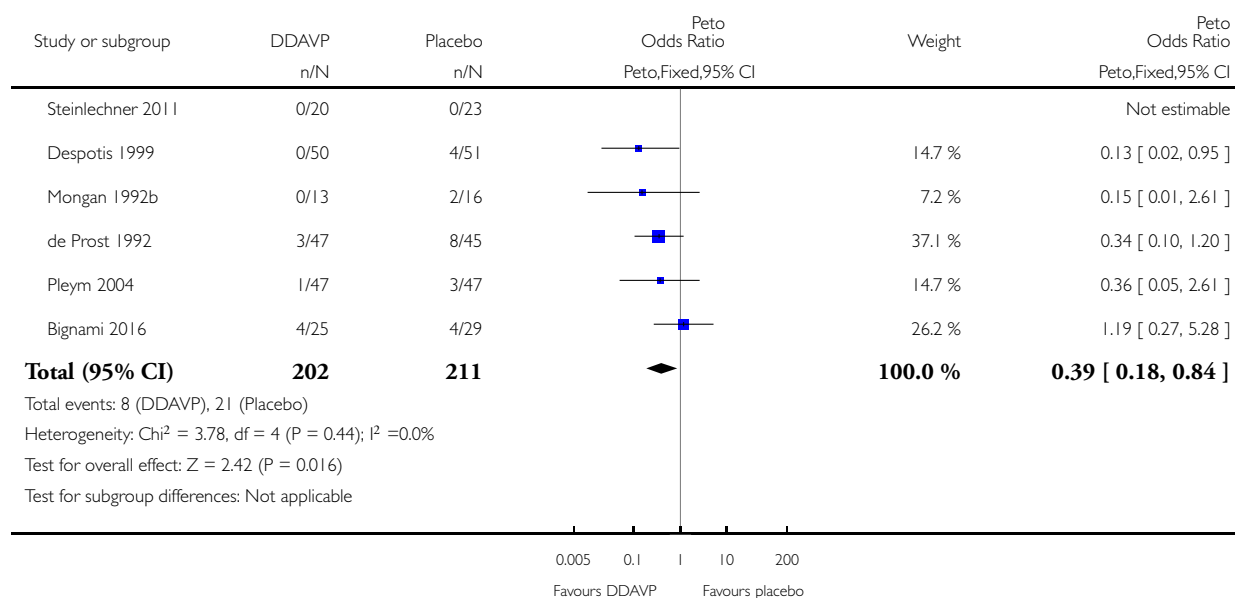


## Analysis 2.5. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 5 Reoperation due to bleeding.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 5 Reoperation due to bleeding

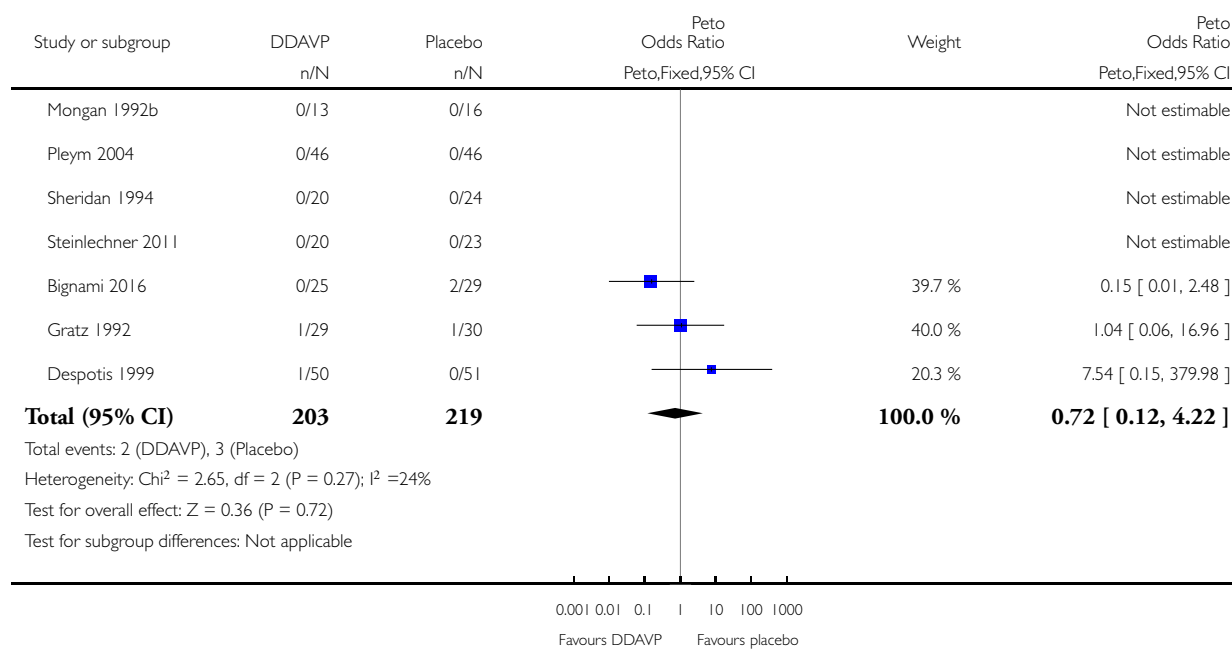


## Analysis 2.6. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 6 All-cause mortality.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 6 All-cause mortality

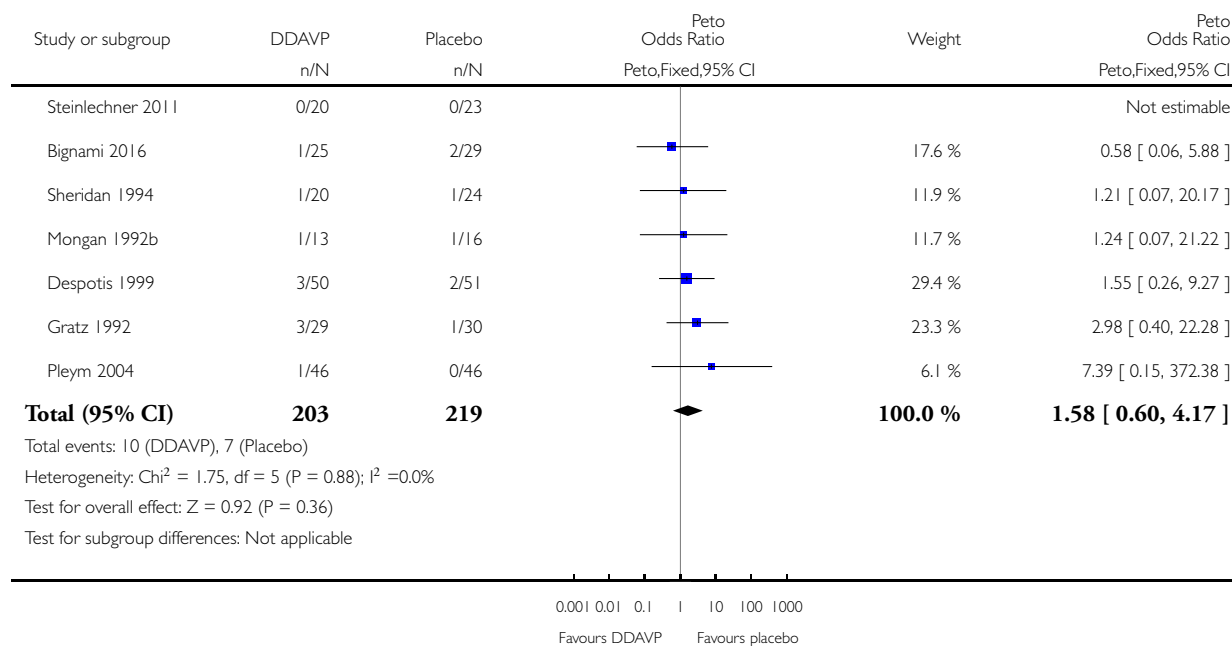


**Analysis 2.7. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 7 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism).**

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 7 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)

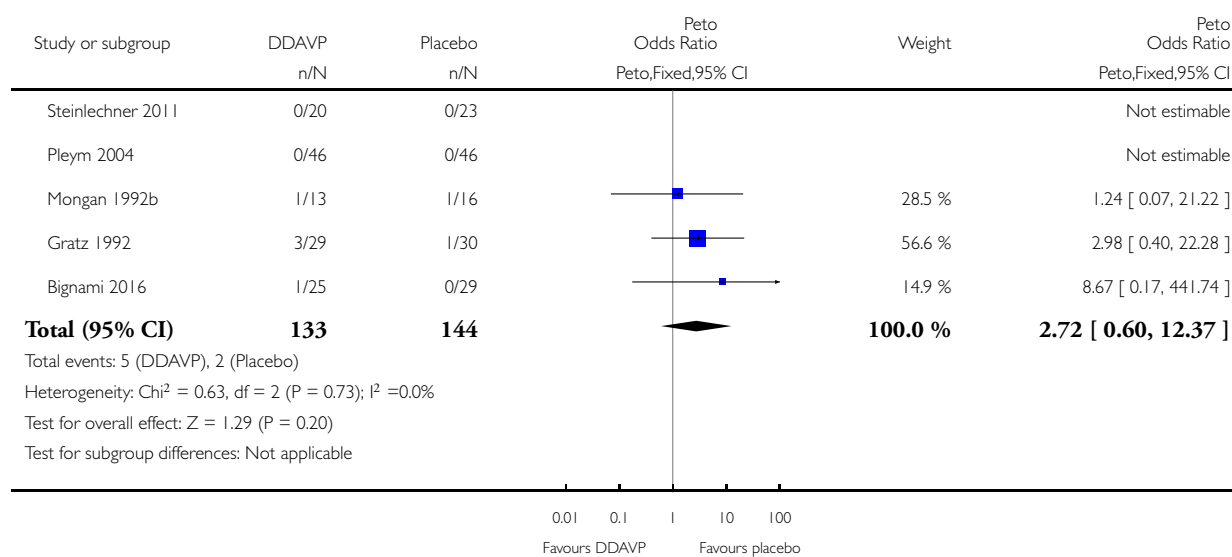


## Analysis 2.8. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 8 Myocardial infarction.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 8 Myocardial infarction

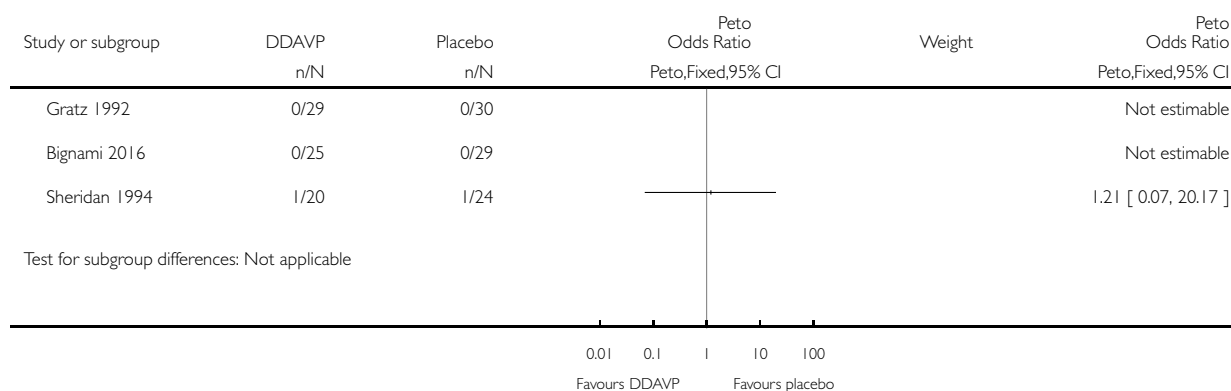


## Analysis 2.9. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 9 Stroke.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 9 Stroke

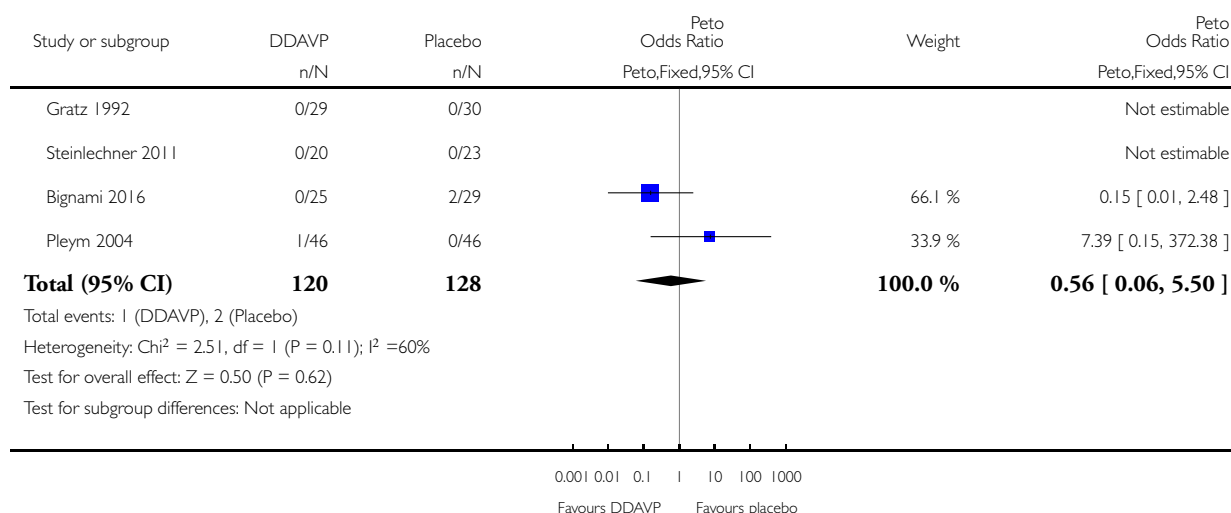


## Analysis 2.10. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 10 Venous thromboembolism.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 10 Venous thromboembolism

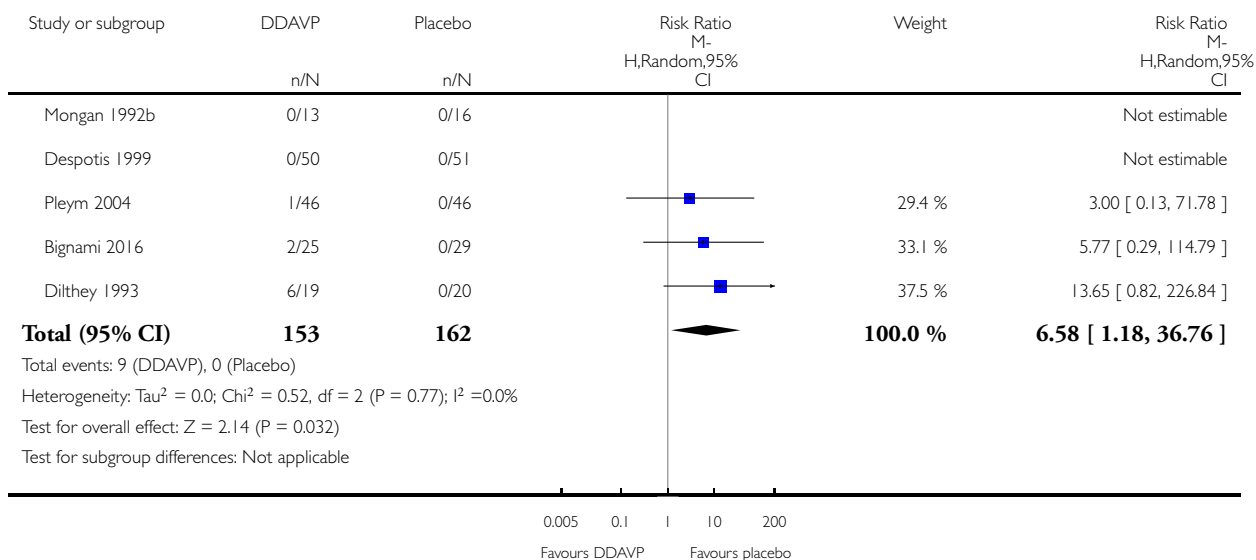


## Analysis 2.11. Comparison 2 Desmopressin vs placebo (platelet dysfunction), Outcome 11 Clinically important hypotension.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 2 Desmopressin vs placebo (platelet dysfunction)

Outcome: 11 Clinically important hypotension

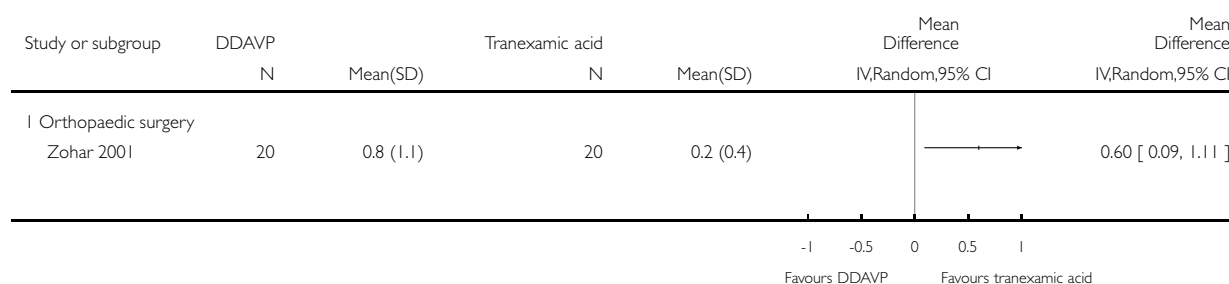


### Analysis 3.1. Comparison 3 Desmopressin vs tranexamic acid, Outcome 1 Red cell volume transfused (total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 1 Red cell volume transfused (total)

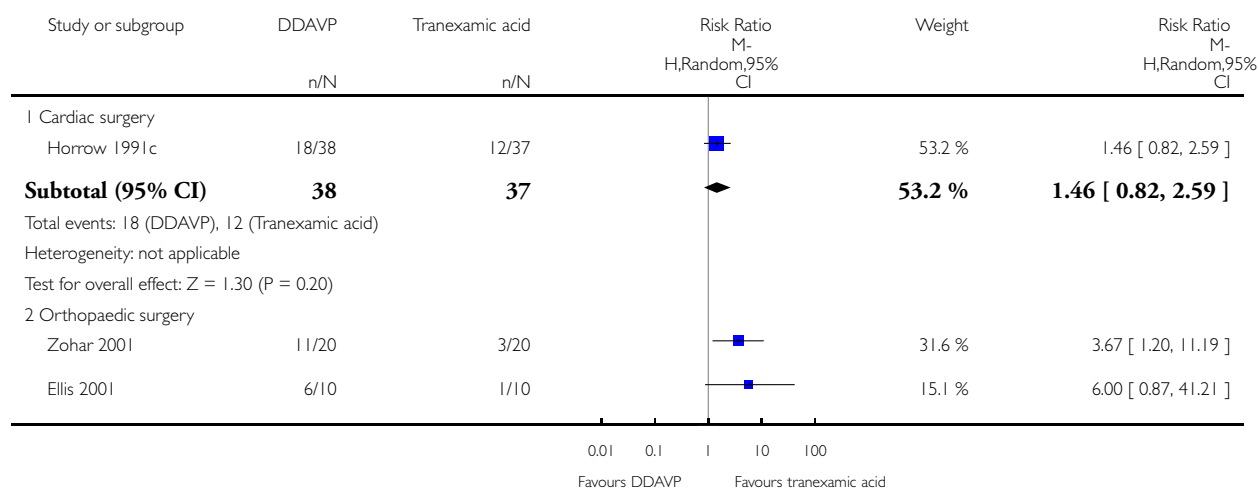


### Analysis 3.2. Comparison 3 Desmopressin vs tranexamic acid, Outcome 2 Number of participants receiving a red cell transfusion (total).

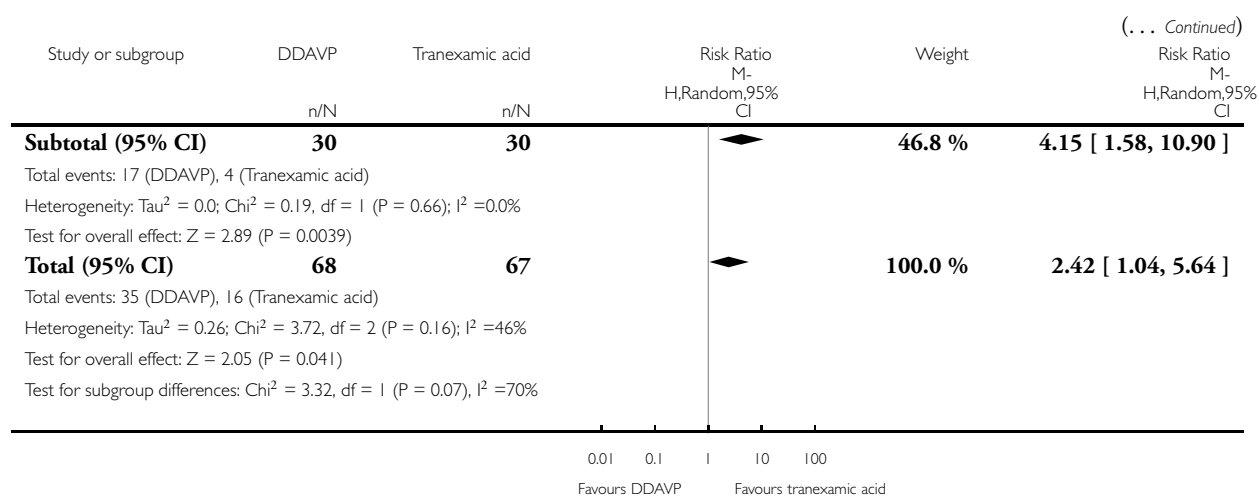
Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 2 Number of participants receiving a red cell transfusion (total)



(Continued ...)

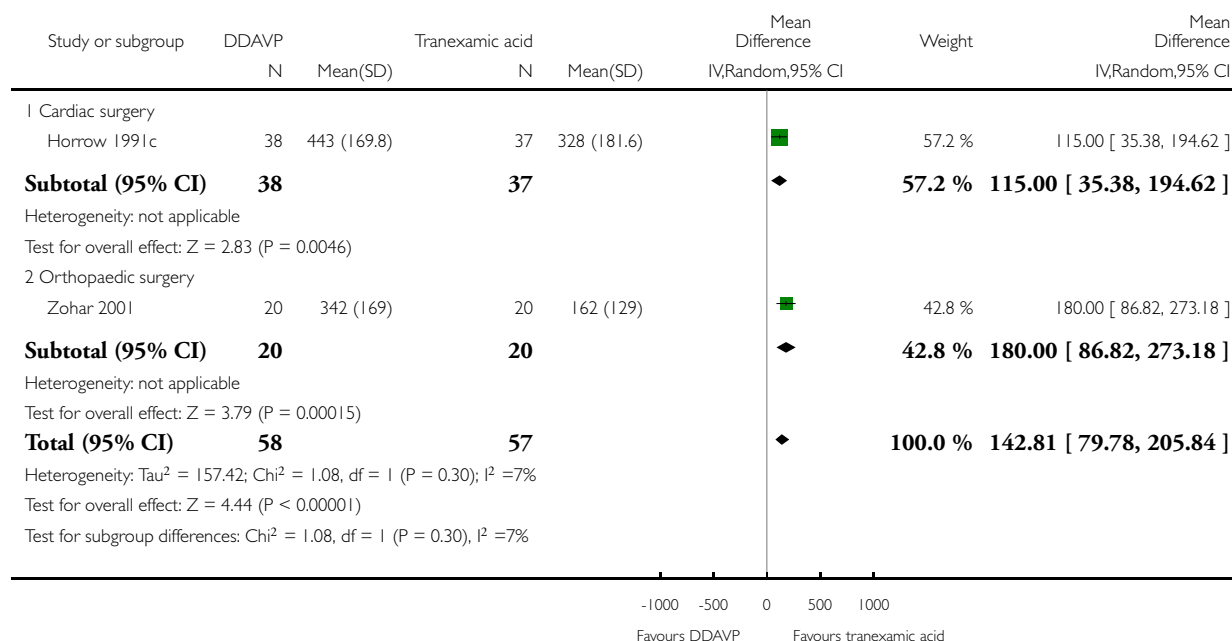


### Analysis 3.3. Comparison 3 Desmopressin vs tranexamic acid, Outcome 3 Blood loss (total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 3 Blood loss (total)

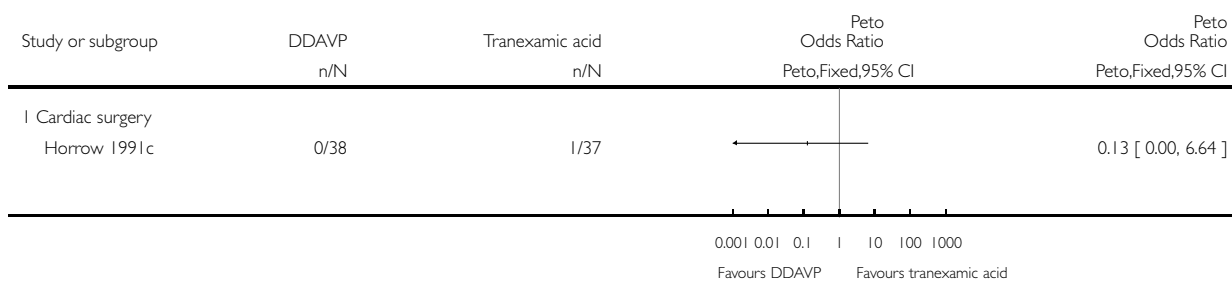


**Analysis 3.4. Comparison 3 Desmopressin vs tranexamic acid, Outcome 4 Reoperation due to bleeding.**

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 4 Reoperation due to bleeding

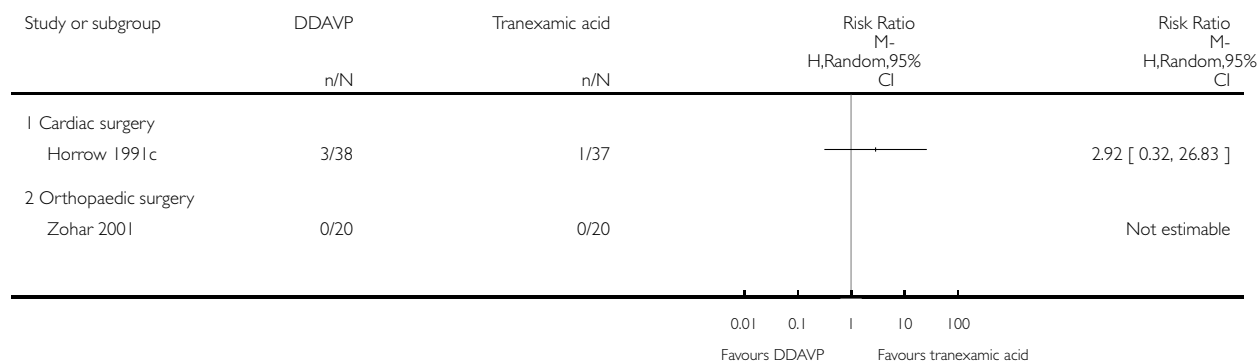


**Analysis 3.5. Comparison 3 Desmopressin vs tranexamic acid, Outcome 5 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism).**

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 5 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)

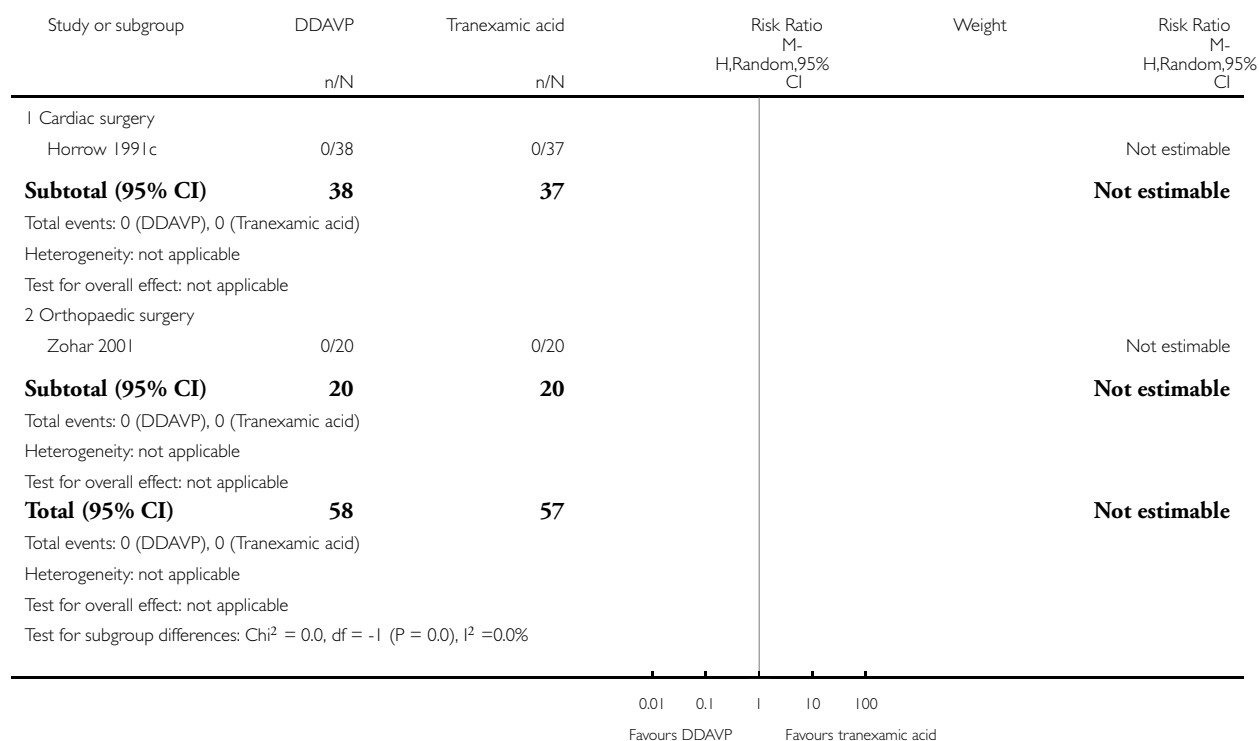


### Analysis 3.6. Comparison 3 Desmopressin vs tranexamic acid, Outcome 6 Myocardial infarction.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 6 Myocardial infarction

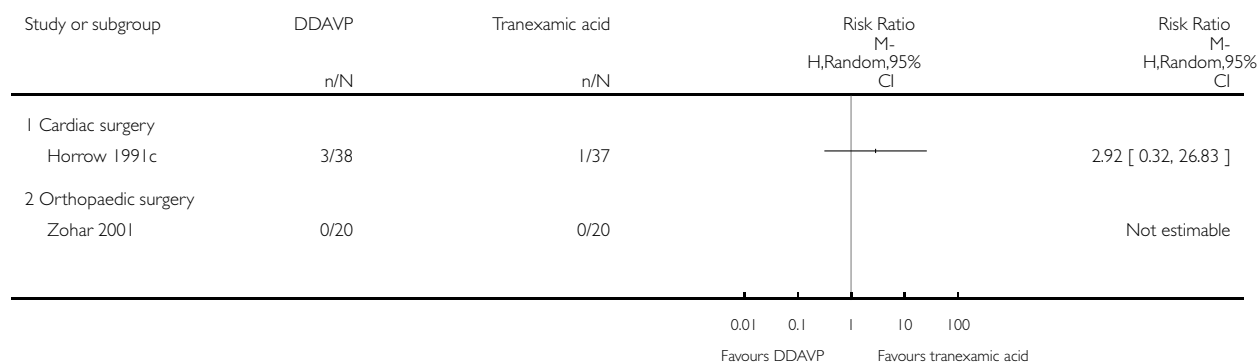


### Analysis 3.7. Comparison 3 Desmopressin vs tranexamic acid, Outcome 7 Stroke.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 7 Stroke

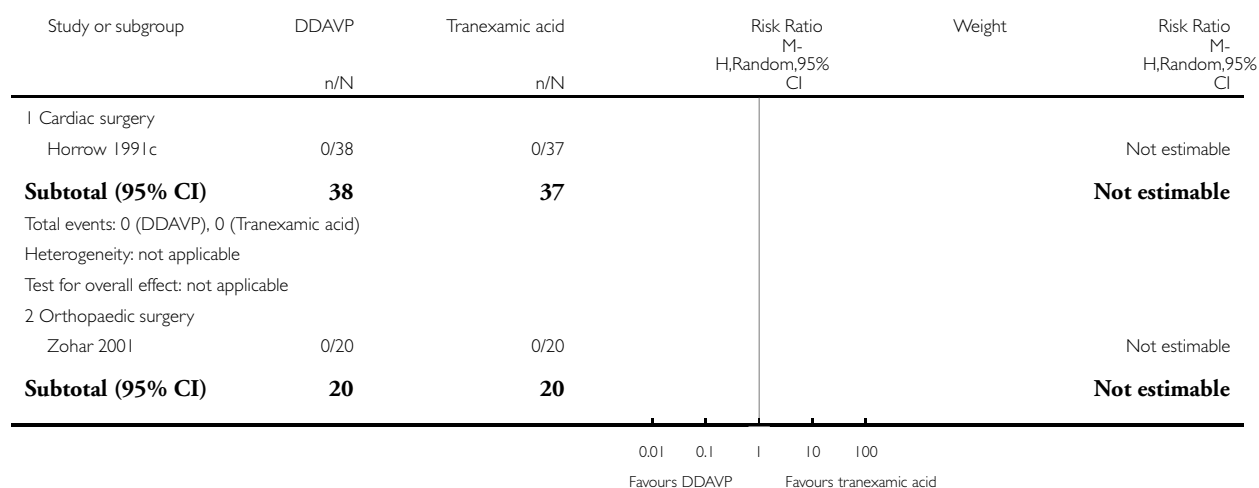


### Analysis 3.8. Comparison 3 Desmopressin vs tranexamic acid, Outcome 8 Venous thromboembolism.

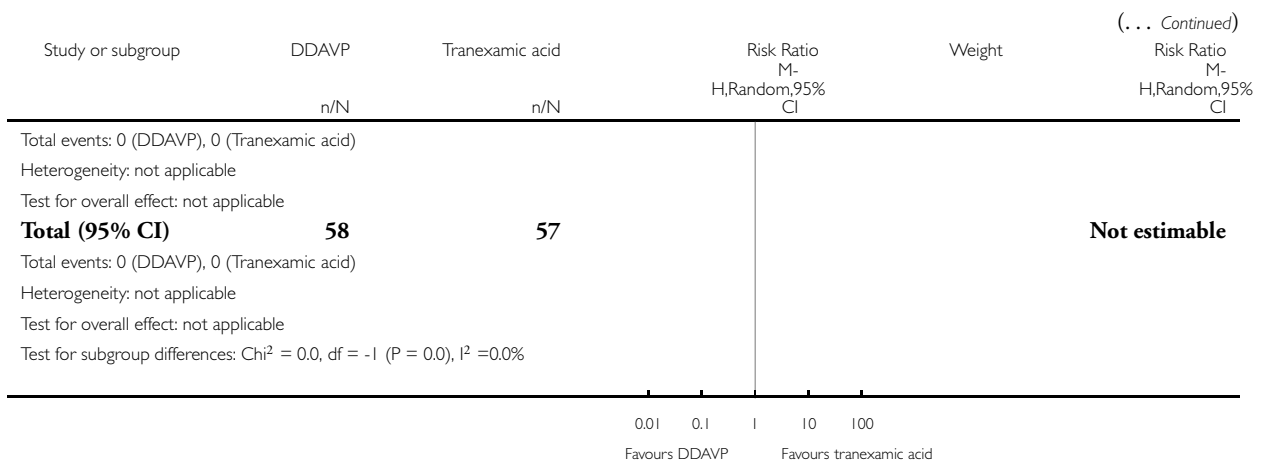
Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 3 Desmopressin vs tranexamic acid

Outcome: 8 Venous thromboembolism



(Continued ...)

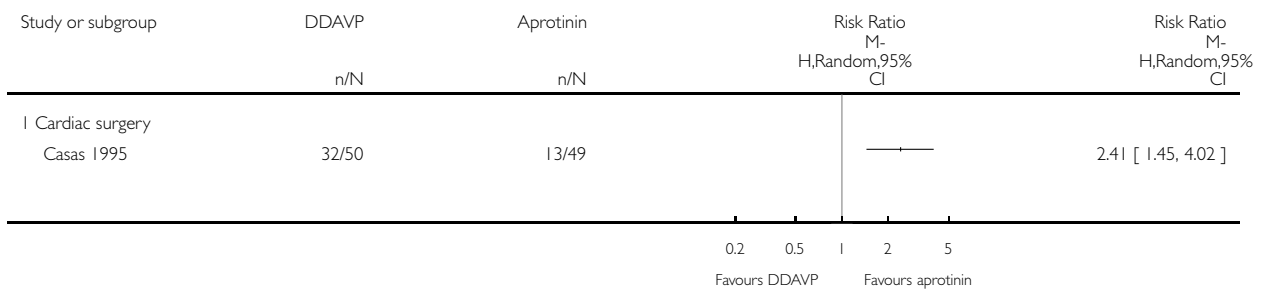


#### Analysis 4.1. Comparison 4 Desmopressin vs aprotinin, Outcome 1 Number of participants receiving a red cell transfusion (total).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 1 Number of participants receiving a red cell transfusion (total)

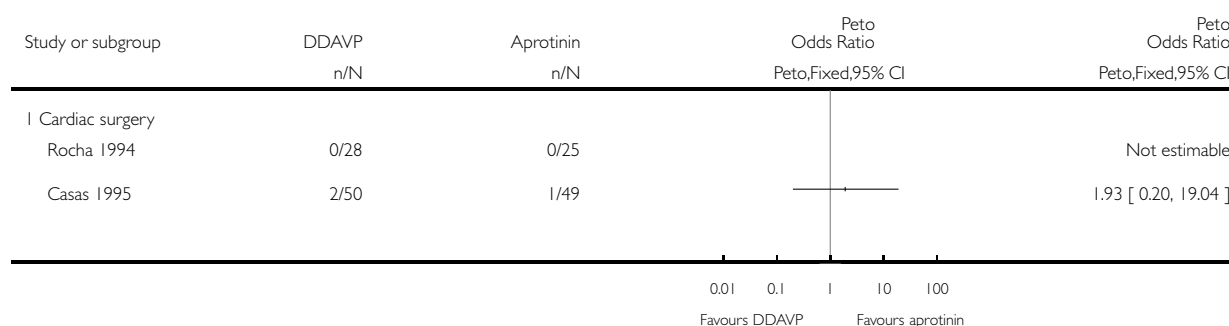


## Analysis 4.2. Comparison 4 Desmopressin vs aprotinin, Outcome 2 Reoperation due to bleeding.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 2 Reoperation due to bleeding

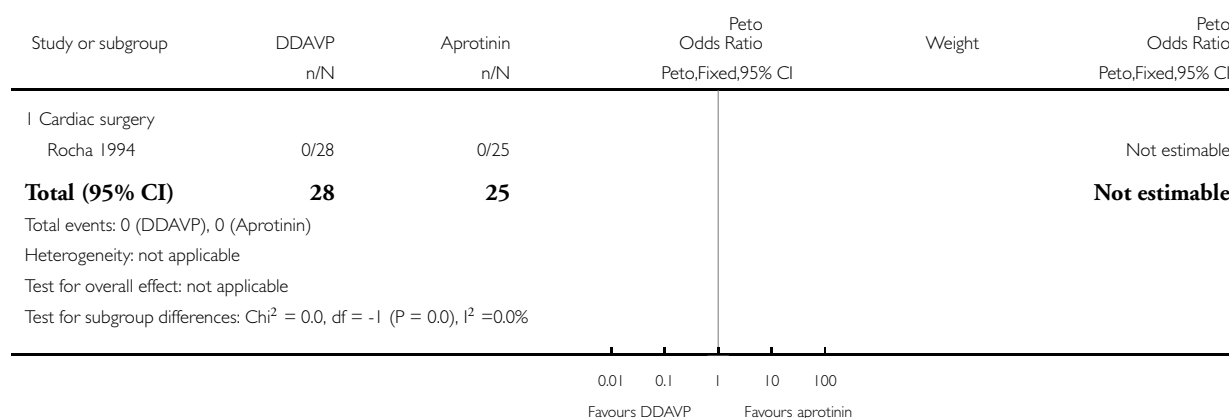


## Analysis 4.3. Comparison 4 Desmopressin vs aprotinin, Outcome 3 All-cause mortality.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 3 All-cause mortality

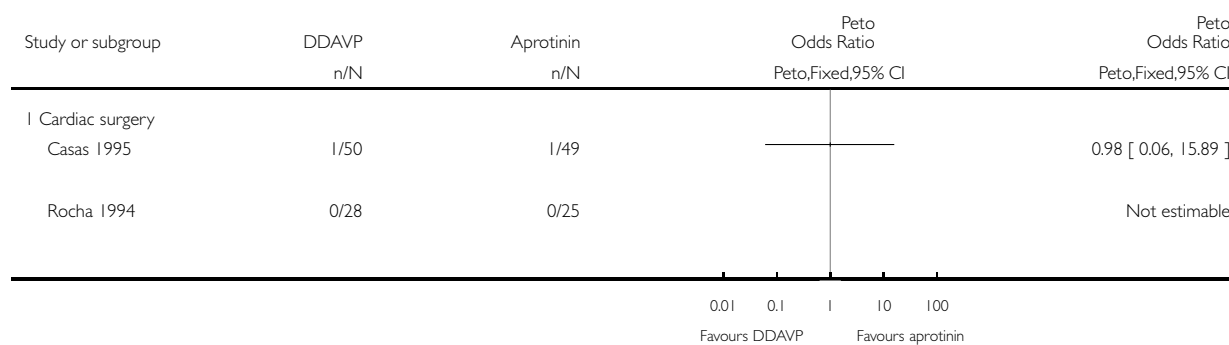


#### Analysis 4.4. Comparison 4 Desmopressin vs aprotinin, Outcome 4 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism).

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 4 All thrombotic events (including myocardial infarction, ischaemic stroke, other arterial thromboembolism, and venous thromboembolism)

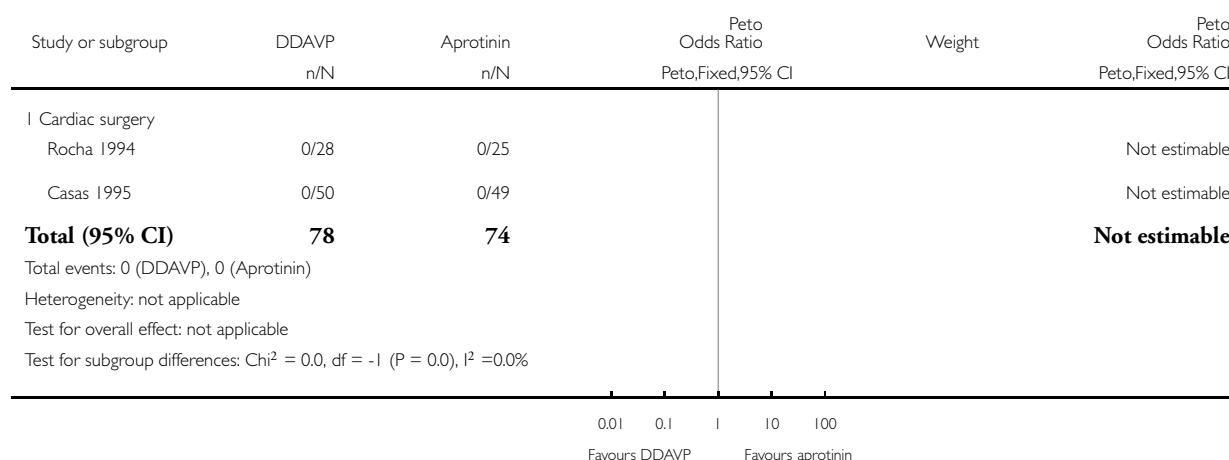


#### Analysis 4.5. Comparison 4 Desmopressin vs aprotinin, Outcome 5 Myocardial infarction.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 5 Myocardial infarction

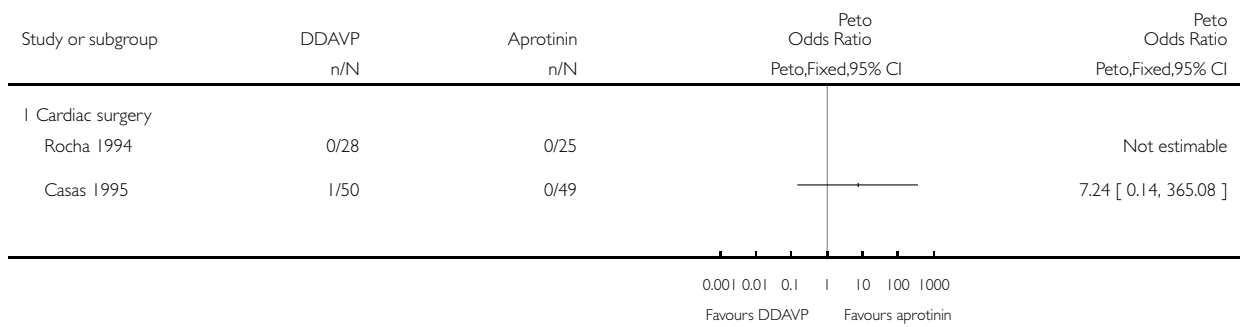


#### Analysis 4.6. Comparison 4 Desmopressin vs aprotinin, Outcome 6 Stroke.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 6 Stroke

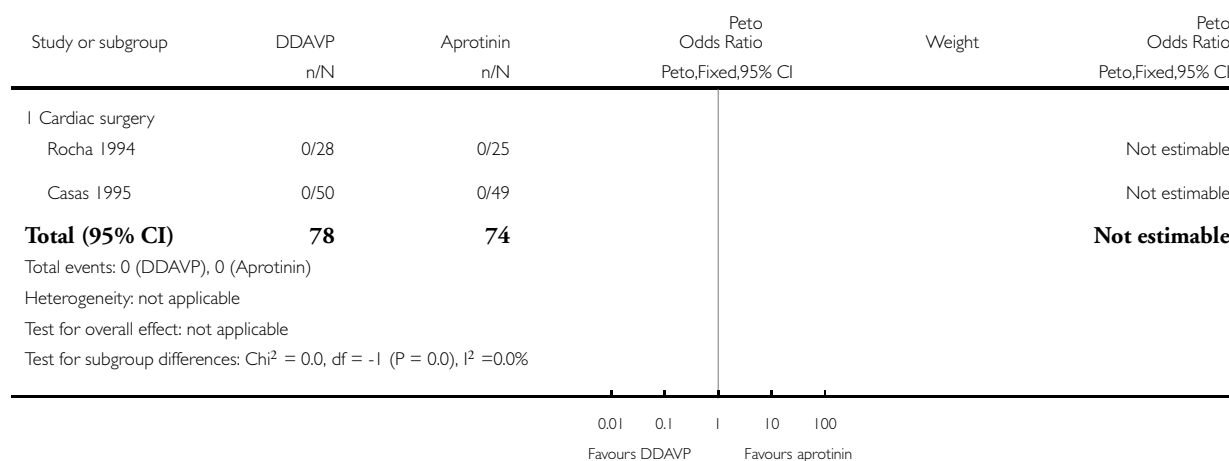


#### Analysis 4.7. Comparison 4 Desmopressin vs aprotinin, Outcome 7 Venous thromboembolism.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 7 Venous thromboembolism

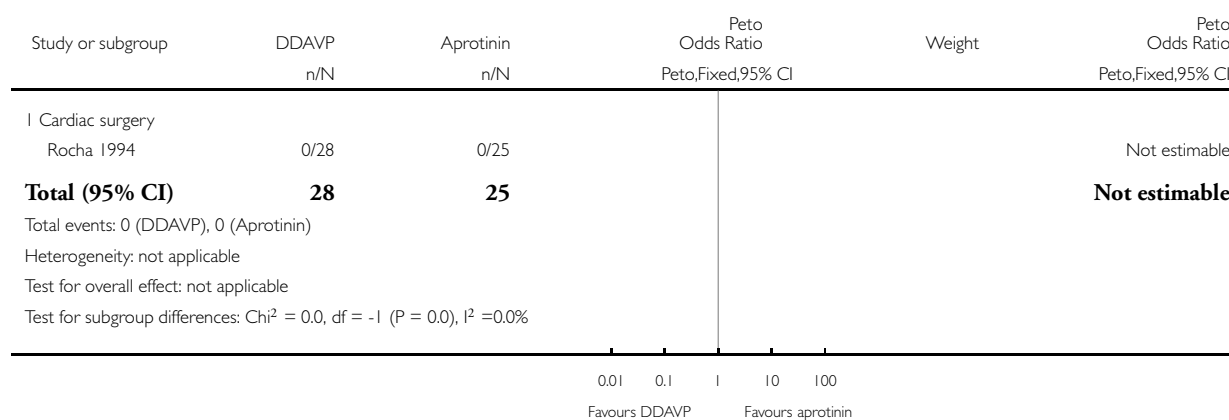


#### Analysis 4.8. Comparison 4 Desmopressin vs aprotinin, Outcome 8 Clinically significant hypotension.

Review: Desmopressin use for minimising perioperative blood transfusion

Comparison: 4 Desmopressin vs aprotinin

Outcome: 8 Clinically significant hypotension



## ADDITIONAL TABLES

Table 1. Study characteristics

| Trial (country)                         | Number of participants | Surgery type | Cases    | Antiplatelet agents or platelet dysfunction (%)    | Anticoagulants (%) | Coagulopathy (%)           | Thrombocytopenia (%) | Antifibrinolytics (%)                 | Transfusion protocol | Timing of blood loss or transfusion assessment (hours) |
|---|------------------------|--------------|----------|--|--------------------|----------------------------|----------------------|---------------------------------------|----------------------|--|
| <a href="#">Aida 1991a</a> (Japan)      | 9                      | Cardiac      | -        | -  | -                  | -                          | -                    | -                                     | -                    | 24   |
| <a href="#">Aida 1991b</a> (Japan)      | 11                     | Cardiac      | -        | -  | -                  | -                          | -                    | -                                     | -                    | 24   |
| <a href="#">Alanay 1999</a> (Turkey)    | 40                     | Orthopaedic  | Elective | -  | -                  | -                          | -                    | -                                     | -                    | 24   |
| <a href="#">Andersson 1990</a> (Sweden) | 19                     | Cardiac      | Elective | 0  | 0                  | -                          | -                    | -                                     | -                    | -  |
| <a href="#">Ansell 1992</a> (USA)       | 83                     | Cardiac      | Elective | -  | -                  | -                          | -                    | DDAVP: 2-4 <sup>a</sup><br>Placebo: 0 | -                    | 24   |
| <a href="#">Bignami 2016</a> (Italy)    | 135                    | Cardiac      | Elective | DDAVP: 38 <sup>b</sup><br>Placebo: 43 <sup>b</sup> | -                  | DDAVP: 1-5<br>Placebo: 1-5 | -                    | 100 <sup>c</sup>                      | Yes                  | 24   |
| <a href="#">Brown 1989</a> (USA)        | 39                     | Cardiac      | Elective | DDAVP: 60 <sup>b</sup><br>Placebo: 50 <sup>b</sup> | -                  | 0                          | -                    | -                                     | -                    | 24   |
| <a href="#">Casas 1995</a> (Spain)      | 149                    | Cardiac      | Elective | DDAVP: 14 <sup>b</sup>                             | 0                  | 0                          | -                    | DDAVP: 0                              | Yes                  | 24   |

**Table 1. Study characteristics** (Continued)

|   |     |                  |          | Placebo:<br>9-8 <sup>b</sup><br>Apro-<br>tinin: 14-<br>6 <sup>b</sup>        |                              |   |   | Placebo:<br>0<br>Apro-<br>tinin: 100 <sup>d</sup>           |     |    |
|---|-----|------------------|----------|--|------------------------------|---|---|---|-----|----|
| <b>Chuang<br/>1993<br/>(China)</b>          | 96  | Cardiac          | -        | -  | -                            | - | - | -   | -   | 24 |
| <b>Clagett<br/>1995<br/>(USA)</b>           | 91  | Vascular         | Elective | 0  | -                            | - | - | -   | -   | 72 |
| <b>de Prost<br/>1992<br/>(France)</b>       | 92  | Cardiac          | -        | 100 <sup>e</sup>   | -                            | - | 0 | DDAVP:<br>4-3 <sup>d</sup><br>Placebo:<br>13-3 <sup>d</sup> | Yes | 24 |
| <b>Despotis<br/>1999<br/>(USA)</b>          | 101 | Cardiac          | Elective | DDAVP:<br>52 <sup>b</sup><br>Placebo:<br>66 <sup>b</sup><br>100 <sup>f</sup> | DDAVP:<br>6<br>Placebo:<br>0 | - | - | DDAVP<br>50 <sup>a</sup><br>Placebo<br>61 <sup>a</sup>      | No  | 24 |
| <b>Dilthey<br/>1993<br/>(Ger-<br/>many)</b> | 39  | Cardiac          | Elective | 100 <sup>b</sup>   | 0                            | 0 | - | 0   | Yes | 24 |
| <b>Ellis<br/>2001<br/>(Israel)</b>          | 30  | Or-<br>thopaedic | Elective | -  | -                            | - | - | DDAVP:<br>0<br>TXA:<br>100 <sup>c</sup>                     | Yes | 72 |
| <b>Flordal<br/>1991<br/>(Sweden)</b>        | 12  | Or-<br>thopaedic | Elective | -  | -                            | - | - | -   | -   | 24 |
| <b>Flordal<br/>1992<br/>(Sweden)</b>        | 50  | Or-<br>thopaedic | Elective | -  | -                            | - | - | -   | -   | -  |
| <b>Frankville<br/>1991<br/>(USA)</b>        | 40  | Cardiac          | Elective | 0  | 0                            | 0 | 0 | -   | -   | 24 |

**Table 1. Study characteristics** (Continued)

|  |     |                |           |  |   |   |   |   |     |   |
|--|-----|----------------|-----------|--|---|---|---|---|-----|---|
| <b>Gratz<br/>1992<br/>(USA)</b>        | 59  | Cardiac        | Elective  | 100 <sup>b</sup>   | - | - | 0 | -                                       | -   | 24                                      |
| <b>Guay<br/>1992<br/>(Canada)</b>      | 30  | Orthopaedic    | Elective  | 0  | 0 | 0 | 0 | -                                       | Yes | 24                                      |
| <b>Guyuron<br/>1996<br/>(USA)</b>      | 20  | Maxillo-facial | Elective  | -  | - | 0 | - | -                                       | -   | 24                                      |
| <b>Hackmann<br/>1989<br/>(Canada)</b>  | 150 | Cardiac        | Elective  | DDAVP:<br>21-6 <sup>b</sup><br>Placebo:<br>14-5 <sup>b</sup> | - | 0 | 0 | -                                       | -   | 24                                      |
| <b>Hajjar<br/>2007<br/>(Brazil)</b>    | 150 | Cardiac        | -         | -  | - | - | - | -                                       | -   | 72                                      |
| <b>Hedderich<br/>1990<br/>(Canada)</b> | 62  | Cardiac        | Elective  | DDAVP:<br>38-7 <sup>b</sup><br>Placebo:<br>41.9 <sup>b</sup> | - | - | - | -                                       | -   | 18 blood<br>loss<br>48 trans-<br>fusion |
| <b>Hemşinli<br/>2012a<br/>(Turkey)</b> | 20  | Cardiac        | Emergency | 100 <sup>b</sup>   | - | - | - | 0                                       | -   | 30                                      |
| <b>Hemşinli<br/>2012b<br/>(Turkey)</b> | 34  | Cardiac        | Emergency | 100 <sup>b</sup>   | - | - | - | 100 <sup>c</sup>                        | -   | 30                                      |
| <b>Hemşinli<br/>2012c<br/>(Turkey)</b> | 28  | Cardiac        | Emergency | 100 <sup>b</sup>   | - | - | - | DDAVP:<br>0<br>TXA:<br>100 <sup>c</sup> | -   | 30                                      |
| <b>Horrow<br/>1991a<br/>(USA)</b>      | 82  | Cardiac        | Elective  | -  | 0 | - | - | 0                                       | Yes | 12                                      |
| <b>Horrow<br/>1991b<br/>(USA)</b>      | 77  | Cardiac        | Elective  | -  | 0 | - | - | 100 <sup>c</sup>                        | Yes | 12                                      |

**Table 1. Study characteristics** (*Continued*)

|  |     |                      |          |                  |   |   |   |   |     |                             |
|--|-----|----------------------|----------|------------------|---|---|---|---|-----|-----------------------------|
| <b>Horrow<br/>1991c<br/>(USA)</b>            | 75  | Cardiac              | Elective | -                | 0 | - | - | DDAVP:<br>0<br>TXA:<br>100 <sup>c</sup> | Yes | 12                          |
| <b>Jin 2015<br/>(China)</b>                  | 102 | Cardiac              | Elective | -                | 0 | 0 | 0 | 100 <sup>c</sup>                        | -   | 6                           |
| <b>Karnezis<br/>1994a<br/>(USA)</b>          | 36  | Or-<br>thopaedic     | Elective | -                | 0 | - | - | -                                       | Yes | 24                          |
| <b>Karnezis<br/>1994b<br/>(USA)</b>          | 56  | Or-<br>thopaedic     | Elective | -                | 0 | - | - | -                                       | Yes | 24                          |
| <b>Kobrin-<br/>sky<br/>1987<br/>(USA)</b>    | 35  | Cardiac              | Elective | 0                | - | - | - | -                                       | -   | 34                          |
| <b>Kuitunen<br/>1992<br/>(Fin-<br/>land)</b> | 30  | Cardiac              | Elective | 0                | 0 | - | - | -                                       | Yes | 16                          |
| <b>Lazarchick<br/>1995<br/>(USA)</b>         | 23  | Not<br>reported      | -        | -                | - | - | - | -                                       | -   | -                           |
| <b>Lee 2010<br/>(South<br/>Korea)</b>        | 48  | Dialysis<br>catheter | Elective | 100 <sup>g</sup> | - | - | 0 | -                                       | -   | -                           |
| <b>Leino<br/>2010<br/>(Fin-<br/>land)</b>    | 71  | Or-<br>thopaedic     | Elective | 0                | 0 | 0 | - | -                                       | Yes | 96                          |
| <b>Lethagen<br/>1991<br/>(Sweden)</b>        | 50  | Vascular             | Elective | 0                | 0 | 0 | - | -                                       | Yes | -                           |
| <b>Letts<br/>1998<br/>(Canada)</b>           | 30  | Or-<br>thopaedic     | Elective | -                | - | - | - | -                                       | -   | Intraop-<br>erative<br>only |

**Table 1. Study characteristics** (*Continued*)

|  |     |  |          |  |                                  |   |   |   |     |    |
|--|-----|--|----------|--|----------------------------------|---|---|---|-----|----|
| <b>Manno<br/>2011<br/>(Italy)</b>                        | 162 | Kidney<br>biopsy                               | Elective | 0  | 0                                | - | - | -   | -   | 72 |
| <b>Marquez<br/>1992<br/>(USA)</b>                        | 65  | Cardiac  | Elective | 0  | 0                                | - | - | -   | Yes | 24 |
| <b>Marczin-<br/>ski<br/>2007<br/>(Nether-<br/>lands)</b> | 28  | Or-<br>thopaedic/<br>Breast/<br>Abdomi-<br>nal | Elective | 0  | 0                                | 0 | 0 | -   | -   | 48 |
| <b>Mongan<br/>1992a<br/>(USA)</b>                        | 86  | Cardiac  | Elective | 0  | 0                                | - | - | -   | Yes | 24 |
| <b>Mongan<br/>1992b<br/>(USA)</b>                        | 29  | Cardiac  | Elective | 100 <sup>h</sup>   | 0                                | - | - | -   | Yes | 24 |
| <b>Oliver<br/>2000<br/>(USA)</b>                         | 60  | Paediatric<br>cardiac                          | Elective | DDAVP:<br>9.7 <sup>b</sup><br>Placebo:<br>3.4 <sup>b</sup>   | DDAVP:<br>6.5<br>Placebo:<br>6.9 | - | - | -   | No  | 24 |
| <b>Ozk-<br/>isacik<br/>2001<br/>(Turkey)</b>             | 66  | Cardiac  | Elective | 0  | -                                | 0 | - | -   | Yes | 24 |
| <b>Pleym<br/>2004<br/>(Nor-<br/>way)</b>                 | 92  | Cardiac  | Elective | 100 <sup>b</sup>   | 0                                | 0 | 0 | DDAVP:<br>6.5 <sup>c</sup><br>Placebo:<br>17.4 <sup>c</sup> | Yes | 16 |
| <b>Reich<br/>1991<br/>(USA)</b>                          | 27  | Cardiac  | Elective | DDAVP:<br>28.6 <sup>b</sup><br>Placebo:<br>38.5 <sup>b</sup> | -                                | 0 | 0 | -   | -   | 24 |
| <b>Reynolds<br/>1993<br/>(USA)</b>                       | 95  | Paediatric<br>cardiac                          | -        | -  | -                                | - | - | -   | -   | 24 |
| <b>Rocha<br/>1988<br/>(Spain)</b>                        | 100 | Cardiac  | Elective | -  | -                                | 0 | 0 | -   | -   | 72 |

**Table 1. Study characteristics** (*Continued*)

|  |     |                       |          |  |   |   |   |  |     |                             |
|--|-----|-----------------------|----------|--|---|---|---|--|-----|-----------------------------|
| <b>Rocha<br/>1994<br/>(Spain)</b>                    | 109 | Cardiac               | Elective | -  | - | 0 | 0 | DDAVP<br>(1): 0<br>DDAVP<br>(2): 0<br>Control:<br>0<br>Apro-<br>tinin: 100<br><i>d</i> | -   | 72                          |
| <b>Salmen-<br/>pera<br/>1991<br/>(Fin-<br/>land)</b> | 30  | Cardiac               | Elective | 0  | 0 | 0 | - | -  | Yes | 16                          |
| <b>Salzman<br/>1986<br/>(USA)</b>                    | 70  | Cardiac               | Elective | -  | - | - | - | -  | -   | 24                          |
| <b>Schott<br/>1995<br/>(Sweden)</b>                  | 79  | Or-<br>thopaedic      | Elective | 0  | 0 | 0 | 0 | -  | Yes | 24                          |
| <b>Seear<br/>1989<br/>(Canada)</b>                   | 60  | Paediatric<br>cardiac | -        | -  | - | - | - | -  | -   | 24                          |
| <b>Shao<br/>2015<br/>(China)</b>                     | 90  | Sinus                 | Elective | 0  | 0 | 0 | 0 | -  | -   | Intraop-<br>erative<br>only |
| <b>Sheridan<br/>1994<br/>(Canada)</b>                | 44  | Cardiac               | Elective | 100 <sup>b</sup>   | 0 | 0 | 0 | -  | -   | 24                          |
| <b>Spyt<br/>1990<br/>(UK)</b>                        | 98  | Cardiac               | Elective | DDAVP:<br>14.3 <sup>b</sup><br>Placebo:<br>10.2 <sup>b</sup> | 0 | - | - | -  | Yes | ~24                         |
| <b>Stein-<br/>lechner<br/>2011<br/>(Austria)</b>     | 43  | Cardiac               | Elective | 100 <sup>g</sup>   | 0 | - | - | -  | Yes | 24                          |

**Table 1. Study characteristics** (Continued)

|  |    |                  |          |   |   |   |   |  |     |                             |
|--|----|------------------|----------|---|---|---|---|--|-----|-----------------------------|
| <b>Temeck<br/>1994<br/>(USA)</b>         | 83 | Cardiac          | Elective | - | - | - | - | DDAVP:<br>20 <sup>a</sup><br>Placebo:<br>30.2 <sup>a</sup> | -   | 24                          |
| <b>Theroux<br/>1997<br/>(USA)</b>        | 21 | Or-<br>thopaedic | Elective | 0 | 0 | 0 | 0 | -  | Yes | 24                          |
| <b>Wingate<br/>1992a<br/>(USA)</b>       | 23 | Plastic          | Elective | - | - | - | - | -  | -   | 24                          |
| <b>Wingate<br/>1992b<br/>(USA)</b>       | 21 | Plastic          | Elective | - | - | - | - | -  | -   | 24                          |
| <b>Wong<br/>2003<br/>(Hong<br/>Kong)</b> | 59 | Hepatic          | Elective | 0 | 0 | 0 | - | -  | Yes | Intraop-<br>erative<br>only |
| <b>Zohar<br/>2001<br/>(Israel)</b>       | 40 | Or-<br>thopaedic | Elective | - | 0 | - | - | DDAVP:<br>0<br>TXA:<br>100 <sup>c</sup>                    | Yes | 12                          |

Blank cells indicate that information was not reported in the original papers

<sup>a</sup>Epsilon-aminocaproic acid

<sup>b</sup>Antiplatelet agents

<sup>c</sup>Tranexamic acid

<sup>d</sup>Aprotinin

<sup>e</sup>Defined as bleeding time greater than 10 seconds

<sup>f</sup>Defined as hemoSTATUS < 60%

<sup>g</sup>Defined as prolonged platelet function analyser-100 closure time

<sup>h</sup>Defined as thromboelastography maximum clot amplitude < 50 mm

**Table 2. Intervention characteristics**

| Trial                     | DDAVP dose(s) (μg/kg) | Timing of dose                                 | Timing summary | Comparator(s) |
|---------------------------|-----------------------|--|----------------|---------------|
| <b>Preoperative DDAVP</b> |                       |  |                |               |
| <b>Alanay 1999</b>        | 0.3                   | Induction of anaesthesia                       | Preoperative   | Placebo       |
| <b>Flordal 1991</b>       | 0.3 (× 2)             | At start of surgery and<br>again after 6 hours | Preoperative   | Placebo       |

**Table 2. Intervention characteristics** (Continued)

|                          |                                    |   |              |                 |
|--------------------------|------------------------------------|---|--------------|-----------------|
| <b>Flordal 1992</b>      | 0.3 (× 2)                          | At start of surgery and again after 6 hours           | Preoperative | Placebo         |
| <b>Guay 1992</b>         | 10 µg/m <sup>2</sup>               | At time of first skin incision                        | Preoperative | Placebo         |
| <b>Guyuron 1996</b>      | 20 µg                              | 30 minutes preoperatively                             | Preoperative | Placebo         |
| <b>Kobrinisky 1987</b>   | 10 µg/m <sup>2</sup>               | Immediately after induction of anaesthesia            | Preoperative | Placebo         |
| <b>Lazarchick 1995</b>   | 0.3                                | After anaesthetic induction                           | Preoperative | Placebo         |
| <b>Lee 2010</b>          | 0.3                                | Not reported  | Preoperative | Placebo         |
| <b>Leino 2010</b>        | 0.4                                | At start of surgery                                   | Preoperative | Placebo         |
|                          |                                    |   |              | DDAVP 0.2 µg/kg |
| <b>Lethagen 1991</b>     | 0.3                                | Immediately before start of operation                 | Preoperative | Placebo         |
| <b>Letts 1998</b>        | 10 µg/m <sup>2</sup>               | Immediately after induction of anaesthesia            | Preoperative | Placebo         |
| <b>Manno 2011</b>        | 0.3                                | 1 hour before biopsy                                  | Preoperative | Placebo         |
| <b>Marczinski 2007</b>   | 15 µg to 45 µg depending on weight | Not reported  | Preoperative | Placebo         |
| <b>Schott 1995</b>       | 0.3 (× 2)                          | Post induction of anaesthesia and again after 6 hours | Preoperative | Placebo         |
| <b>Shao 2015</b>         | 0.3                                | After induction of anaesthesia                        | Preoperative | Placebo         |
| <b>Steinlechner 2011</b> | 0.3                                | After induction of anaesthesia                        | Preoperative | Placebo         |
| <b>Theroux 1997</b>      | 0.3                                | Not reported  | Preoperative | Placebo         |
| <b>Wingate 1992a</b>     | 0.3                                | After induction of anaesthesia                        | Preoperative | Placebo         |
| <b>Wingate 1992b</b>     | 0.3                                | After induction of anaesthesia                        | Preoperative | Placebo         |

**Table 2. Intervention characteristics** (Continued)

|   |       |   |                                |   |
|---|-------|---|--------------------------------|---|
| <b>Wong 2003</b>                              | 0.3   | After induction of anaesthesia  | Preoperative                   | Placebo                                 |
| <b>DDAVP administered at end of operation</b> |       |   |                                |   |
| <b>Aida 1991a</b>                             | 0.3   | 15 minutes after reversal of heparin                                      | End of operation               | Placebo                                 |
| <b>Aida 1991b</b>                             | 0.3   | 15 minutes after reversal of heparin                                      | End of operation               | Placebo                                 |
| <b>Andersson 1990</b>                         | 0.3   | 15 minutes after reversal of heparin                                      | End of operation               | Placebo                                 |
| <b>Ansell 1992</b>                            | 0.3   | Immediately after reversal of heparin                                     | End of operation               | Placebo                                 |
| <b>Bignami 2016</b>                           | 0.3   | In event of excessive bleeding, after reversal of heparin                 | End of operation/postoperative | Placebo                                 |
| <b>Brown 1989</b>                             | 0.3   | Immediately after reversal of heparin                                     | End of operation               | Placebo                                 |
| <b>Casas 1995</b>                             | 0.3   | Immediately after reversal of heparin                                     | End of operation               | Placebo<br>Aprotinin <sup>a</sup>       |
| <b>Chuang 1993</b>                            | 0.3   | 60 minutes after reversal of heparin                                      | End of operation               | Placebo                                 |
| <b>Clagett 1995</b>                           | 20 µg | 15 minutes after heparinisation and before aortic cross-clamp application | End of operation               | Placebo                                 |
| <b>Despotis 1999</b>                          | 0.4   | Unclear   | End of operation               | Placebo                                 |
| <b>Dilthey 1993</b>                           | 0.3   | 5 minutes after reversal of heparin                                       | End of operation               | Placebo                                 |
| <b>Ellis 2001</b>                             | 0.3   | Before removal of tourniquet  | End of operation               | Placebo<br>Tranexamic acid <sup>b</sup> |
| <b>Frankville 1991</b>                        | 0.3   | 5 minutes after reversal of heparin                                       | End of operation               | Placebo                                 |

**Table 2. Intervention characteristics** (Continued)

|                       |     |  |                  |                              |
|-----------------------|-----|--|------------------|------------------------------|
| <b>Gratz 1992</b>     | 0.3 | Immediately after reversal of heparin              | End of operation | Placebo                      |
| <b>Hackmann 1989</b>  | 0.3 | Immediately after reversal of heparin              | End of operation | Placebo                      |
| <b>Hajjar 2007</b>    | 0.3 | Immediately after surgery                          | End of operation | Placebo                      |
| <b>Hedderich 1990</b> | 0.3 | Immediately after reversal of heparin              | End of operation | Placebo                      |
| <b>Horrow 1991a</b>   | 0.3 | Immediately after reversal of heparin              | End of operation | Placebo                      |
| <b>Horrow 1991b</b>   | 0.3 | Immediately after reversal of heparin              | End of operation | Placebo                      |
| <b>Horrow 1991c</b>   | 0.3 | Immediately after reversal of heparin              | End of operation | Tranexamic acid <sup>c</sup> |
| <b>Jin 2015</b>       | 0.3 | Before cardiac rewarming                           | End of operation | Placebo                      |
| <b>Karnezis 1994a</b> | 0.3 | 30 minutes before closure of wound                 | End of operation | Placebo                      |
| <b>Karnezis 1994b</b> | 0.3 | 30 minutes before closure of wound                 | End of operation | Placebo                      |
| <b>Marquez 1992</b>   | 0.3 | Immediately after reversal of heparin              | End of operation | Placebo                      |
|                       |     |  |                  | DDAVP 0.3 µg/kg × 2          |
| <b>Mongan 1992a</b>   | 0.3 | After reversal of heparin and before chest closure | End of operation | Placebo                      |
| <b>Mongan 1992b</b>   | 0.3 | After reversal of heparin and before chest closure | End of operation | Placebo                      |
| <b>Oliver 2000</b>    | 0.3 | 10 minutes after reversal of heparin               | End of operation | Placebo                      |
| <b>Ozkisacik 2001</b> | 0.3 | After reversal of heparin (timing unclear)         | End of operation | Placebo                      |
| <b>Pleym 2004</b>     | 0.3 | Immediately after reversal of heparin              | End of operation | Placebo                      |

**Table 2. Intervention characteristics** (Continued)

|   |                      |   |                  |                              |
|---|----------------------|---|------------------|------------------------------|
| <a href="#">Reich 1991</a>                    | 0.3                  | 15 minutes after reversal of heparin                            | End of operation | Placebo                      |
| <a href="#">Reynolds 1993</a>                 | 0.3                  | 5 minutes after reversal of heparin                             | End of operation | Placebo                      |
| <a href="#">Rocha 1988</a>                    | 0.3                  | Immediately after reversal of heparin                           | End of operation | Placebo                      |
| <a href="#">Rocha 1994</a>                    | 0.3                  | Immediately after reversal of heparin                           | End of operation | Standard care                |
|   |                      |   |                  | Aprotinin <sup>d</sup>       |
|   |                      |   |                  | DDAVP 0.3 µg/kg × 2          |
| <a href="#">Salmenpera 1991</a>               | 0.3                  | Via pulmonary artery catheter immediately after sternal closure | End of operation | Placebo                      |
| <a href="#">Salzman 1986</a>                  | 0.3                  | Immediately after reversal of heparin                           | End of operation | Placebo                      |
| <a href="#">Secar 1989</a>                    | 0.3                  | After reversal of heparin (timing unclear)                      | End of operation | Placebo                      |
| <a href="#">Sheridan 1994</a>                 | 10 µg/m <sup>2</sup> | After reversal of heparin (timing unclear)                      | End of operation | Placebo                      |
| <a href="#">Spyt 1990</a>                     | 0.3                  | After reversal of heparin (timing unclear)                      | End of operation | Placebo                      |
| <a href="#">Temeck 1994</a>                   | 0.3                  | After reversal of heparin (timing unclear)                      | End of operation | Placebo                      |
| <a href="#">Zohar 2001</a>                    | 0.3                  | 30 minutes before deflation of tourniquet                       | End of operation | Tranexamic acid <sup>b</sup> |
| <b>DDAVP administered postoperatively</b>     |                      |   |                  |                              |
| <a href="#">de Prost 1992</a>                 | 0.3                  | Between end of operation and 6 hours postoperatively            | Postoperative    | Placebo                      |
| <a href="#">Kuitunen 1992</a>                 | 0.3                  | Immediately after sternal closure                               | Postoperative    | Placebo                      |
| <b>Timing of DDAVP administration unclear</b> |                      |   |                  |                              |

**Table 2. Intervention characteristics** (Continued)

|                                   |     |              |           |                              |
|-----------------------------------|-----|--------------|-----------|------------------------------|
| <b>Hem<sub>s</sub> inli 2012a</b> | 0.3 | Not reported | Not clear | Standard care                |
| <b>Hem<sub>s</sub> inli 2012b</b> | 0.3 | Not reported | Not clear | Standard care                |
| <b>Hem<sub>s</sub> inli 2012c</b> | 0.3 | Not reported | Not clear | Tranexamic acid <sup>c</sup> |

<sup>a</sup>Aprotinin 2 million KIU in 200 mL preoperatively, 2 million KIU in 200 mL in fluid prime, 500,000 KIU in 50 mL/h from skin incision to skin closure

<sup>b</sup>Tranexamic acid 15 mg/kg 30 minutes before tourniquet removed over 30 minutes, then 10 mg/kg/h until 12 hours after tourniquet deflated

<sup>c</sup>Tranexamic acid 10 mg/kg loading dose after induction of anaesthesia and before first skin incision over 30 minutes, then 1 mg/kg/h for 10 hours

<sup>d</sup>Aprotinin 2 million KIU within 30 minutes after induction of anaesthesia followed by a continuous infusion of 500,000 KIU/h until the patient left the operating room, plus an additional bolus of 2 million KIU aprotinin in the pump prime by replacement of crystalloid solution

**Abbreviation**

KIU: kilounits

**Table 3. DDAVP vs placebo: intraoperative volume of red cells transfused**

| <b>Trial</b>               | <b>Reason not included in meta-analysis</b> | <b>DDAVP arm</b>                    | <b>Placebo arm</b>                  |
|----------------------------|---|-------------------------------------|-------------------------------------|
| <b>Orthopaedic surgery</b> |   |                                     |                                     |
| <b>Leino 2010</b>          | Reported as mean (no standard deviation)    | 0.3 units<br>(n = 23)               | 0.5 units<br>(n = 24)               |
| <b>Letts 1998</b>          | Reported as mean (no standard deviation)    | 4.6 units<br>(n = 16)               | 5.0 units<br>(n = 14)               |
| <b>Theroux 1997</b>        | Reported as median and range                | 51.5 (24 to 98.6) mL/kg<br>(n = 10) | 48.3 (24.5 to 96) mL/kg<br>(n = 11) |

**Table 4. DDAVP vs placebo: total volume of red cells transfused**

| <b>Trial</b>                 | <b>Reason not included in meta-analysis</b>   | <b>DDAVP arm</b>            | <b>Placebo arm</b>          |
|------------------------------|---|-----------------------------|-----------------------------|
| <b>Adult cardiac surgery</b> |   |                             |                             |
| <b>Aida 1991a</b>            | Reported as mL/kg (mean ± standard deviation) | 8.3 ± 5.6 mL/kg<br>(n = 5)  | 10.8 ± 6.3 mL/kg<br>(n = 4) |
| <b>Aida 1991b</b>            | Reported as mL/kg (mean ± standard deviation) | 10.2 ± 6.4 mL/kg<br>(n = 5) | 13.2 ± 6.6 mL/kg<br>(n = 6) |

**Table 4. DDAVP vs placebo: total volume of red cells transfused** (Continued)

|                              |   |   |   |
|------------------------------|---|---|---|
| <b>Alanay 1999</b>           | Reported as median (interquartile range)                  | 1.7 (2.3) units<br>(n = 18)               | 0.6 (1.3) units<br>(n = 22)               |
| <b>Bignami 2016</b>          | Reported as median (interquartile range)                  | 2 (1 to 4) units<br>(n = 68)              | 2 (1 to 3) units<br>(n = 67)              |
| <b>Frankville 1991</b>       | Reported as mean (no standard deviation)                  | 2.4 units<br>(n = 15)                     | 2 units<br>(n = 15)                       |
| <b>Hackmann 1989</b>         | Reported as median (90% confidence interval)              | 2 (1 to 8.5) units<br>(n = 74)            | 2 (1 to 9.8) units<br>(n = 76)            |
| <b>Kuitunen 1992</b>         | Reported as mean (range)                                  | 1.3 (0 to 2) units<br>(n = 15)            | 1.1 (0 to 3) units<br>(n = 15)            |
| <b>Marquez 1992</b>          | Reported as median only                                   | 2 units<br>(n = 21)                       | 2 units<br>(n = 22)                       |
| <b>Mongan 1992a</b>          | Reported as mean only                                     | 0.86 units<br>(n = 44)                    | 1.79 units<br>(n = 42)                    |
| <b>Mongan 1992b</b>          | Reported as mean only                                     | 2.4 units<br>(n = 13)                     | 2.2 units<br>(n = 16)                     |
| <b>Rocha 1994</b>            | Reported as mL/m <sup>2</sup> (mean ± standard deviation) | 740.4 ± 416.3 mL/m <sup>2</sup><br>(n=25) | 662.8 ± 380.7 mL/m <sup>2</sup><br>(n=28) |
| <b>Spyt 1990</b>             | Reported as mean only                                     | 1.38 units<br>(n = 49)                    | 1.30 units<br>(n = 49)                    |
| <b>Orthopaedic surgery</b>   |   |   |   |
| <b>Ellis 2001</b>            | Reported as mean only                                     | 0.7 units<br>(n = 10)                     | 1.1 units<br>(n = 10)                     |
| <b>Theroux 1997</b>          | Reported as median and range                              | 64.8 (30.3 to 123.6) mL/kg<br>(n = 10)    | 64.9 (33.8 to 110) mL/kg<br>(n = 11)      |
| <b>Maxillofacial surgery</b> |   |   |   |
| <b>Guyuron 1996</b>          | Reported as mean (no standard deviation)                  | 0.6 units<br>(n = 10)                     | 0.9 units<br>(n = 10)                     |

Table 5. DDAVP vs placebo: intraoperative blood loss

| Trial                             | Reason not included in meta-analysis            | DDAVP arm                                 | Placebo arm                               |
|-----------------------------------|---|---|---|
| <b>Adult cardiac surgery</b>      |   |   |   |
| <a href="#">Hackmann 1989</a>     | Reported as median (90% confidence interval)    | 200 (0 to 1150) mL<br>(n = 74)            | 200 (0 to 1013) mL<br>(n = 76)            |
| <a href="#">Rocha 1988</a>        | Reported as mL/m <sup>2</sup> body surface area | 131 ± 106 mL/m <sup>2</sup><br>(n = 50)   | 193 ± 137 mL/m <sup>2</sup><br>(n = 50)   |
| <b>Paediatric cardiac surgery</b> |   |   |   |
| <a href="#">Oliver 2000</a>       | Reported as mL/m <sup>2</sup>                   | 49.3 ± 43.7 mL/m <sup>2</sup><br>(n = 31) | 73.6 ± 71.1 mL/m <sup>2</sup><br>(n = 29) |
| <b>Orthopaedic surgery</b>        |   |   |   |
| <a href="#">Leino 2010</a>        | Reported as mean (no standard deviation)        | 1200 mL<br>(n = 23)                       | 1463 mL<br>(n = 24)                       |
| <b>Hepatic surgery</b>            |   |   |   |
| <a href="#">Wong 2003</a>         | Reported as median (range)                      | 832.5 (350 to 2955) mL<br>(n = 30)        | 800 mL (250 to 7128) mL<br>(n = 29)       |
| <b>Other surgery</b>              |   |   |   |
| <a href="#">Marczinski 2007</a>   | Reported as mean and range                      | 251 (2 to 1330) mL<br>(n = 14)            | 504 (50 to 2100) mL<br>(n = 14)           |

Table 6. DDAVP vs placebo: total blood loss

| Trial                        | Reason not included in meta-analysis          | DDAVP arm                  | Placebo arm                |
|------------------------------|---|----------------------------|----------------------------|
| <b>Adult cardiac surgery</b> |   |                            |                            |
| <a href="#">Aida 1991a</a>   | Reported as mL/kg (mean ± standard deviation) | 8.0 ± 1.4 mL/kg<br>(n = 5) | 5.9 ± 1.5 mL/kg<br>(n = 4) |
| <a href="#">Aida 1991b</a>   | Reported as mL/kg (mean ± standard deviation) | 11.3 ± 10 mL/kg<br>(n = 5) | 7.5 ± 4 mL/kg<br>(n = 6)   |
| <a href="#">Alanay 1999</a>  | Reported as median (interquartile range)      | 950 (950) mL<br>(n = 18)   | 975 (811) mL<br>(n = 22)   |

**Table 6. DDAVP vs placebo: total blood loss** (Continued)

|                                   |   |   |   |
|-----------------------------------|---|---|---|
| <b>Bignami 2016</b>               | Reported as median (interquartile range)                                    | 575 (422.5 to 770) mL<br>(n = 68)           | 590 (476.25 to 1013.75) mL<br>(n = 67)      |
| <b>Casas 1995</b>                 | Reported as mL/m <sup>2</sup> body surface area (mean ± standard deviation) | 400 ± 192 mL/m <sup>2</sup><br>(n = 50)     | 489 ± 361 mL/m <sup>2</sup><br>(n = 51)     |
| <b>de Prost 1992</b>              | Reported as mL/m <sup>2</sup> body surface area (mean ± standard deviation) | 582 ± 410 mL/m <sup>2</sup><br>(n = 44)     | 465 ± 303 mL/m <sup>2</sup><br>(n = 37)     |
| <b>Dilthey 1993</b>               | Reported as median (range)  | 1000 (600 to 1800) mL<br>(n = 19)           | 1075 (400 to 1740) mL<br>(n = 20)           |
| <b>Hackmann 1989</b>              | Reported as median (90% confidence interval)                                | 865 (358 to 2495) mL<br>(n = 74)            | 783 (300 to 2219) mL<br>(n = 76)            |
| <b>Hajjar 2007</b>                | Reported as mL/m <sup>2</sup> (mean ± standard deviation)                   | 258 ± 106 mL/m <sup>2</sup><br>(n = 75)     | 526 ± 314 mL/m <sup>2</sup><br>(n = 75)     |
| <b>Hem<sub>s</sub> inli 2012a</b> | Reported as mean (no standard deviation)                                    | 1430 mL<br>(n = 10)                         | 1767 mL<br>(n = 10)                         |
| <b>Hem<sub>s</sub> inli 2012b</b> | Reported as mean (no standard deviation)                                    | 574 mL<br>(n = 16)                          | 535 mL<br>(n = 18)                          |
| <b>Marquez 1992</b>               | Reported as median only   | 1157 mL<br>(n = 21)                         | 1180 mL<br>(n = 22)                         |
| <b>Rocha 1988</b>                 | Reported as mL/m <sup>2</sup> body surface area (mean ± standard deviation) | 458 ± 206 mL/m <sup>2</sup><br>(n = 50)     | 536 ± 304 mL/m <sup>2</sup><br>(n = 50)     |
| <b>Rocha 1994</b>                 | Reported as mL/m <sup>2</sup> body surface area (mean ± standard deviation) | 551.8 ± 324.1 mL/m <sup>2</sup><br>(n = 28) | 438.7 ± 228.1 mL/m <sup>2</sup><br>(n = 25) |
| <b>Salmenpera 1991</b>            | Reported as median (range)  | 1020 (530 to 1155) mL<br>(n = 15)           | 1100 (425 to 1720) mL<br>(n = 15)           |
| <b>Orthopaedic surgery</b>        |   |   |   |
| <b>Flordal 1991</b>               | Reported as mean (no standard deviation)                                    | 1320 mL<br>(n = 6)                          | 1380 mL<br>(n = 6)                          |
| <b>Theroux 1997</b>               | Reported as estimated percentage blood loss: median (range)                 | 147.8% (57% to 428.8%)<br>(n = 10)          | 111.2% (65% to 239.5%)<br>(n = 11)          |
| <b>Maxillofacial surgery</b>      |   |   |   |
| <b>Guyuron 1996</b>               | Reported as mean (range)  | 675 (380 to 1330) mL<br>(n = 10)            | 819 (200 to 1600) mL<br>(n = 10)            |

Table 7. DDAVP vs tranexamic acid: total volume of red cells transfused

| Trial                      | Reason not included in meta-analysis | DDAVP arm             | Tranexamic acid arm   |
|----------------------------|--------------------------------------|-----------------------|-----------------------|
| <b>Orthopaedic surgery</b> |                                      |                       |                       |
| <a href="#">Ellis 2001</a> | Reported as mean only                | 0.7 units<br>(n = 10) | 0.1 units<br>(n = 10) |

Table 8. DDAVP vs tranexamic acid: total blood loss

| Trial                        | Reason not included in meta-analysis     | DDAVP arm           | Tranexamic acid arm |
|------------------------------|--|---------------------|---------------------|
| <b>Adult cardiac surgery</b> |  |                     |                     |
| <a href="#">Hemlin 2012c</a> | Reported as mean (no standard deviation) | 1430 mL<br>(n = 10) | 535 mL<br>(n = 18)  |

Table 9. DDAVP vs aprotinin: total volume of red cells transfused

| Trial                        | Reason not included in meta-analysis  | DDAVP arm                                   | Aprotinin arm                               |
|------------------------------|---|---|---|
| <b>Adult cardiac surgery</b> |   |   |   |
| <a href="#">Rocha 1994</a>   | Reported as mL/m <sup>2</sup> body surface area (mean ± standard deviation) | 740.4 ± 416.3 mL/m <sup>2</sup><br>(n = 25) | 366.1 ± 331.9 mL/m <sup>2</sup><br>(n = 28) |

Table 10. DDAVP vs aprotinin: total blood loss

| Trial                        | Reason not included in meta-analysis  | DDAVP arm                                   | Aprotinin arm                               |
|------------------------------|---|---|---|
| <b>Adult cardiac surgery</b> |   |   |   |
| <a href="#">Casas 1995</a>   | Reported as mL/m <sup>2</sup> body surface area (mean ± standard deviation) | 400 ± 192 mL/m <sup>2</sup><br>(n = 50)     | 195 ± 146 mL/m <sup>2</sup><br>(n = 48)     |
| <a href="#">Rocha 1994</a>   | Reported as mL/m <sup>2</sup> body surface area (mean ± standard deviation) | 551.8 ± 324.1 mL/m <sup>2</sup><br>(n = 25) | 358.5 ± 156.3 mL/m <sup>2</sup><br>(n = 28) |

## APPENDICES

### Appendix I. New search strategy

#### DDAVP COCHRANE REVIEW - SEARCH STRATEGIES, APRIL 2017

##### CENTRAL, the Cochrane Library

#1 MeSH descriptor: [Deamino Arginine Vasopressin] this term only

#2 desmopressin\* or deamino\* or desamino\* or adiuretin\* or stimate or desmotabs or "D-void" or octim or octostim or minurin\* or minirin\* or minrin or desurin or desmospray or defirin or concentraid or desmotab\* or desmogalen or presinex or nocutil or noctisson

#3 DDAVP or DDVAP

#4 #1 or #2 or #3

##### MEDLINE (OvidSP)

1. Deamino Arginine Vasopressin/

2. (desmopressin\* or deamino\* or desamino\* or adiuretin\* or stimate or desmotabs or D-void or octim or octostim or minurin\* or minirin\* or minrin or desurin or desmospray or defirin or concentraid or desmotab\* or desmogalen or presinex or nocutil or noctisson).tw.

3. (DDAVP or DDVAP).tw.

4. 1 or 2 or 3

5. Meta-Analysis.pt.

6. ((meta analy\* or metaanaly\*) and (trials or studies)).ab.

7. (meta analy\* or metaanaly\* or evidence-based).ti.

8. ((systematic\* or evidence-based) adj2 (review\* or overview\*)).tw.

9. (cochrane or embase or cinahl or cinhal or lilacs or citation index or psyclit or psychlit or psycinfo or psychinfo or "web of science" or scopus).ab.

10. Cochrane Database of systematic reviews.jn.

11. ((literature or systematic\* or comprehensive\* or electronic\*) adj2 search\*).ab.

12. (additional adj (papers or articles or sources)).ab.

13. (bibliograph\* or handsearch\* or hand search\* or manual\* search\* or searched or reference list\*).ab.

14. (relevant adj (journals or articles)).ab.

15. or/5-14

16. Review.pt.

17. RANDOMIZED CONTROLLED TRIALS AS TOPIC/

18. selection criteria.ab. or critical appraisal.ti.

19. (data adj (extraction or analys\*)).ab.

20. RANDOMIZED CONTROLLED TRIALS/

21. or/17-20

22. 16 and 21

23. 15 or 22

24. randomized controlled trial.pt.

25. controlled clinical trial.pt.

26. randomi\*.tw.

27. placebo.ab.

28. clinical trials as topic.sh.

29. rando mLy.ab.

30. groups.ab.

31. trial.tw.

32. or/24-31

33. 23 or 32

34. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/

35. (Comment or Editorial).pt.

36. 34 or 35

37. 33 not 36

38. 4 and 37

**PubMed (publications only)**

(desmopressin\* OR deamino\* OR desamino\* OR adiuretin\* OR stimate OR desmotabs OR "D-void" OR octim OR octostim OR minurin\* OR minirin\* OR minrin OR desurin OR desmospray OR defirin OR concentraid OR desmotab\* OR desmogalen OR presinex OR nocutil OR noctisson OR DDAVP OR DDVAP) AND (random\* OR blind\* OR "control group" OR placebo\* OR controlled OR groups OR trial\* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

**Embase (OvidSP)**

1. desmopressin acetate/ or desmopressin/ or desmopressin diacetate/ or "argipressin[1 deamino]"/
2. (desmopressin\* or deamino\* or desamino\* or adiuretin\* or stimate or desmotabs or D-void or octim or octostim or minurin\* or minirin\* or minrin or desurin or desmospray or defirin or concentraid or desmotab\* or desmogalen or presinex or nocutil or noctisson).tw.
3. (DDAVP or DDVAP).tw.
4. 1 or 2 or 3
5. Meta Analysis/
6. Systematic Review/
7. (meta analy\* or metaanalys\*).tw.
8. (systematic adj2 (review\* or overview\* or search\*)).tw.
9. (literature adj2 (review\* or overview\* or search\*)).ti,ab.
10. (cochrane or embase or cinahl or cinhal or lilacs or BIDS or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit).ti,ab.
11. (electronic\* adj (sources or resources or databases)).ab.
12. reference lists.ab.
13. (bibliograph\* or handsearch\* or hand search\* or manual\* search\*).ab.
14. (hand-search\* or handsearch\*).ab.
15. (additional adj (papers or articles or sources)).ab.
16. (relevant adj (journals or articles)).ab.
17. (search term\* or published articles or search strateg\*).ab.
18. or/5-17
19. data extraction.ab.
20. selection criteria.ab.
21. or/19-20
22. review.pt.
23. 21 and 22
24. editorial.pt.
25. 18 or 23
26. 25 not 24
27. Controlled Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
28. Randomized Controlled Trial/
29. Randomization/
30. Single Blind Procedure/
31. Double Blind Procedure/
32. Crossover Procedure/
33. Placebo/
34. (randomized or randomised).tw.
35. RCT.tw.
36. (random\* adj5 (allocat\* or assign\* or divid\* or receiv\*)).tw.
37. single blind\*.tw.
38. double blind\*.tw.
39. ((treble or triple) adj blind\*).tw.
40. (phase III or phase three or "phase 3").ti,ab.
41. (crossover\* or cross over\* or cross-over\* or placebo\*).tw.
42. Prospective Study/
43. or/27-42

44. Case Study/
45. case report\*.tw.
46. (note or editorial).pt.
47. or/44-46
48. 43 not 47
49. 26 or 48
50. limit 49 to embase
51. 4 and 50

#### **CINAHL (ESBSOHost)**

S1 (MH "Desmopressin")

S2 TI ( desmopressin\* or deamino\* or desamino\* or adiuretin\* or stimate or desmotabs or D-void or octim or octostim or minurin\* or minirin\* or minrin or desurin or desmospray or defirin or concentraid or desmotab\* or desmogalen or presinex or nocutil or noctisson or DDVAP or DDAVP ) OR AB ( desmopressin\* or deamino\* or desamino\* or adiuretin\* or stimate or desmotabs or D-void or octim or octostim or minurin\* or minirin\* or minrin or desurin or desmospray or defirin or concentraid or desmotab\* or desmogalen or presinex or nocutil or noctisson or DDVAP or DDAVP )

S3 S1 OR S2

S4 (MH Clinical Trials+)

S5 PT Clinical Trial

S6 TI ((controlled trial\*) or (clinical trial\*)) OR AB ((controlled trial\*) or (clinical trial\*))

S7 TI ((singl\* blind\*) OR (doubl\* blind\*) OR (trebl\* blind\*) OR (tripl\* blind\*) OR (singl\* mask\*) OR (doubl\* mask\*) OR (tripl\* mask\*)) OR AB ((singl\* blind\*) OR (doubl\* blind\*) OR (trebl\* blind\*) OR (tripl\* blind\*) OR (singl\* mask\*) OR (doubl\* mask\*) OR (tripl\* mask\*))

S8 TI randomi\* OR AB randomi\*

S9 MH RANDOM ASSIGNMENT

S10 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))

S11 ( TI (random\* N2 (assign\* or allocat\*)) ) OR ( AB (random\* N2 (assign\* or allocat\*)) ) )

S12 MH PLACEBOS

S13 MH META ANALYSIS

S14 MH SYSTEMATIC REVIEW

S15 TI ("meta analys\*" OR metaanalys\* OR "systematic review" OR "systematic overview" OR "systematic search\*") OR AB ("meta analys\*" OR metaanalys\* OR "systematic review" OR "systematic overview" OR "systematic search\*")

S16 TI ("literature review" OR "literature overview" OR "literature search\*") OR AB ("literature review" OR "literature overview" OR "literature search\*")

17 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit)

S18 TI placebo\* OR AB placebo\*

S19 MH QUANTITATIVE STUDIES

S20 S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19

S21 S3 AND S20

#### **TRANSFUSION EVIDENCE LIBRARY**

Clinical Specialty: Surgery

Search: desmopressin OR deamino OR desamino OR adiuretin OR stimate OR desmotabs OR D-void OR octim OR octostim OR minurin OR minirin OR minrin OR desurin OR desmospray OR defirin OR concentraid OR desmotab OR desmogalen OR presinex OR nocutil OR noctisson OR DDAVP or DDVAP

#### **WEB OF SCIENCE CPCI-S**

**TOPIC:** (desmopressin OR deamino OR desamino OR adiuretin OR stimate OR desmotabs OR D-void OR octim OR octostim OR minurin OR minirin OR minrin OR desurin OR desmospray OR defirin OR concentraid OR desmotab OR desmogalen OR presinex OR nocutil OR noctisson OR DDAVP or DDVAP)

AND

**TOPIC:** ((randomi\* OR rando mLy OR "random assignment" OR "random allocation" OR blind\* OR "control group\*" OR "controlled trial" OR "controlled study"))

#### **LILACS**

tw:((desmopressin\* OR deamino\* OR desamino\* OR adiuretin\* OR stimate OR desmotabs OR “D-void” OR octim OR octostim OR minurin\* OR minirin\* OR minrin OR desurin OR desmospray OR defirin OR concentraid OR desmotab\* OR desmogalen OR presinex OR nocutil OR noctisson OR ddavp OR ddvap) ) AND (instance:“regional”) AND ( db: (“LILACS”) AND type` of study: (“clinical` trials”))

#### **IndMed**

(desmopressin OR deamino OR desamino OR adiuretin OR stimate OR desmotabs OR octim OR octostim OR minurin OR minirin OR minrin OR desurin OR desmospray OR defirin OR concentraid OR desmotab OR desmogalen OR presinex OR nocutil OR noctisson OR DDAVP) AND (randomized OR randomised OR rando mLy OR random allocation OR random assignment OR blinded OR controlled trial OR controlled study OR control group)

#### **KoreaMed**

“Deamino Arginine Vasopressin” [MH] “Randomized Controlled Trial” [PT]

OR

desmopressin [TI] “Randomized Controlled Trial” [PT]

#### **PakMediNet**

Desmopressin OR DDAVP

#### **ClinicalTrials.gov**

desmopressin OR DDAVP

#### **WHO ICTRP**

Condition/Title: surgery OR surgical OR bleeding OR haemorrhage OR perioperative OR operation

AND

Interventions/Title: desmopressin OR deamino OR desamino OR adiuretin OR stimate OR desmotabs OR DDAVP

#### **HKU Clinical Trials Registry**

Search Terms: Desmopressin

Study Type: Interventional

## **WHAT’S NEW**

Last assessed as up-to-date: 3 April 2017.

| Date        | Event  | Description   |
|-------------|--|---|
| 6 July 2017 | New search has been performed                      | The review has been updated to include evidence published to 3 April 2017. The authors of the review have changed                             |
| 6 July 2017 | New citation required and conclusions have changed | The review has been updated with data from 46 new studies. The review now includes data from 65 trials involving a total of 3874 participants |

## **HISTORY**

Protocol first published: Issue 1, 2000

Review first published: Issue 2, 2001

| Date             | Event                         | Description  |
|------------------|-------------------------------|--|
| 20 November 2015 | Amended                       | Published note added that explains changes to be made during the next update |
| 13 June 2008     | Amended                       | Converted to new review format.  |
| 21 April 2008    | New search has been performed | New studies found and included or excluded.                                  |

## CONTRIBUTIONS OF AUTHORS

- Michael Desborough: content expert
- Kathryn Oakland: content expert
- Charlotte Brierley: content expert
- Sean Bennett: content expert
- Carolyn Doree: creator and author of the new search strategy
- Marialena Trivella: statistical expert
- Sally Hopewell: methodological expert
- Simon J Stanworth: content expert
- Lise J Estcourt: content expert

## DECLARATIONS OF INTEREST

- Michael Desborough: investigator for a trial of DDAVP for treatment of thrombocytopenia
- Kathryn Oakland: none known
- Charlotte Brierley: none known
- Sean Bennett: none known
- Carolyn Doree: none known
- Marialena Trivella: none known
- Sally Hopewell: none known
- Simon J Stanworth: investigator for a trial of DDAVP for treatment of thrombocytopenia
- Lise J Estcourt: none known

## SOURCES OF SUPPORT

### Internal sources

- National Institute for Health Research Oxford Biomedical Research Centre Programme, UK.

### External sources

- National Institute for Health Research (NIHR) Cochrane Programme Grant - Safe and Effective Use of Blood Components, UK.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title has changed from 'Desmopressin use for minimising perioperative allogeneic blood transfusion', to 'Desmopressin use for minimising perioperative blood transfusion', as we felt that the latter encapsulated the scope of the review more accurately.

We have included a copy of amendments to the original protocol in [Published notes](#). We updated the original review in accordance with current Cochrane MECIR standards ([Carless 2004](#); [Henry 1998](#)). The original review was published in 1998 ([Henry 1998](#)). Methods have changed considerably since that time, as has clinical management of perioperative blood loss. Consequently, we published an updated protocol before commencing this review ([Desborough 2016](#)).

### Differences between prespecified changes to the protocol and the published review due to lack of data

#### Participants

For types of participants, we have added the following text: "We excluded trials in participants with inherited bleeding disorders such as haemophilia A or von Willebrand disease. DDAVP is already part of standard of care in mild-to-moderate haemophilia A, von Willebrand disease, and inherited platelet function disorders ([Estcourt 2017](#); [Keeling 2008](#); [Laffan 2014](#)).“ These participants were also excluded in original iterations of this review ([Carless 2004](#); [Henry 1998](#)).

#### Outcomes

In the protocol, we intended to report the primary outcomes at three separate time points: intraoperatively, at 24 hours, and total blood loss. We removed the 24-hour time point for clarity because in most cases, this was the same as total blood loss.

#### Subgroup analysis

Data were insufficient for assessment of subgroups of participants with liver disease and uraemia, so we did not perform this analysis. Future updates of this review will include analysis of these subgroups if published data are sufficient. We added platelet dysfunction as a subgroup because publication of recent guidelines has suggested that this is of greatest interest to clinicians ([American Society of Anesthesiologists 2015](#); [Kozek-Langenecker 2013](#); [Rossaint 2016](#); [Society of Thoracic Surgeons 2011](#)). We included subgroups of trials that performed cell salvage or used a transfusion protocol as sensitivity analyses rather than full subgroups. In the previous iteration of this review ([Carless 2004](#)), participants in these subgroups were not found to be different from those not in the subgroups. Consequently, although we believed it was not appropriate to include them as full subgroups in this iteration, we have monitored their effect on the overall effect estimate by including them in sensitivity analyses.

## **Sensitivity analysis**

In addition to changes outlined in the subgroup section above, we made changes to the definition of 'low-risk trials'. We did not provide a precise description of a trial at low risk of bias in the protocol, which included the following text: "for example, RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation". We adjusted the definition of trials at low risk of bias to: "trials with no high risk of bias assessments and at least half low risk of bias assessments". This yielded a global assessment of risk of bias.

## **Timing of outcome assessments**

In the protocol, we intended to assess transfusion and blood loss intraoperatively, at 24 hours, and at 30 days. Most trials reported outcome data up to 24 to 48 hours. Consequently, we did not include the 24-hour time point and reported total blood loss, volume of red cells transfused, and participants receiving a red cell transfusion. In most cases, timing for these outcomes was 24 to 48 hours.

## **Serious adverse events**

Most included trials did not report serious adverse events, with the exception of clinically important hypotension and thrombotic events (which are already included as separate outcomes). For clarity, we reported clinically important hypotension as an outcome rather than as a serious adverse event.

# **NOTES**

## **Revised protocol for this review**

We updated this review in accordance with current Cochrane MECIR standards ([Carless 2004](#); [Higgins 2016](#)). The original review was published in 1998 ([Henry 1998](#)). Methods have changed considerably since that time, as has clinical management of perioperative bleeding. We published the protocol below before updating the review in 2017 to accommodate the MECIR 2016 standards ([Desborough 2016](#); [Higgins 2016](#)).

## **Criteria for considering studies for this review**

### **Types of studies**

We will include randomised controlled trials (RCTs). There will be no restrictions on language or publication status.

### **Types of participants**

Adults or children undergoing any type of surgery or interventional procedure.

### **Types of interventions**

Subcutaneous or intravenous DDAVP.

We will consider:

- trials comparing subcutaneous or intravenous DDAVP versus placebo or no active comparator; and
- trials comparing subcutaneous or intravenous DDAVP versus active comparator (e.g. tranexamic acid).

### **Types of outcome measures**

We have added time frames to the primary and secondary outcomes and added the number of participants with any bleeding, quality of life, and serious adverse events as outcomes.

### Primary outcomes

- Number of participants transfused with blood (during the procedure, up to 24 hours post procedure, and within 30 days of the procedure)
- Volume of blood transfused (expressed as total units of blood or millilitres per kilogram for children; during the procedure, up to 24 hours post procedure, and within 30 days of the procedure)
- Blood loss in millilitres per adult participant, or blood loss in millilitres per kilogram for children (total blood loss, intraoperative blood loss, and postoperative blood loss up to 24 hours post procedure)

### Secondary outcomes

- Reoperation due to bleeding
- Number of participants with any bleeding - low-risk procedures only (intraoperative blood loss, and postoperative blood loss up to 24 hours post procedure)
- All-cause mortality within 30 days from the procedure
- Risk of thrombotic events (arterial or venous):
  - myocardial infarction up to 30 days post infusion
  - stroke up to 30 days post infusion
  - venous thromboembolism up to 30 days post infusion
- Serious adverse events within 30 days of the procedure
- Quality of life

### Search methods for identification of studies

We will create a new search strategy. We will search for RCTs in the following databases:

- CENTRAL (Cochrane Library, latest issue)
- MEDLINE (OvidSP, 1946 to present);
- PubMed (epublications only, to present);
- Embase (OvidSP, 1974 to present);
- CINAHL (EBSCOhost, 1937 to present);
- UKBTS/SRI Transfusion Evidence Library ([www.transfusionevidencelibrary.com](http://www.transfusionevidencelibrary.com)) (1950 to present);
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to present);
- LILACS (BIREME/PAHO/WHO, 1982 to present);
- IndMed (ICMR-NIC, 1985 to present);
- KoreaMed (KAMJE, 1997 to present);
- PakMediNet (2001 to present).

We will combine searches in MEDLINE, Embase, and CINAHL with adaptations of the Cochrane RCT search filters, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

We will also search ClinicalTrials.gov ([clinicaltrials.gov](http://clinicaltrials.gov)), the WHO International Clinical Trials Registry (ICTRP - [apps.who.int/trialsearch](http://apps.who.int/trialsearch)), and the Hong Kong University Clinical Trials Register ([www.hkuctr.com](http://www.hkuctr.com)) to identify ongoing trials. We have included the new search strategy in [Appendix 2](#).

## Data collection and analysis

### Data extraction

We will collect data on trial registration and the new outcomes in this review: number of participants with any bleeding; quality of life; and serious adverse events.

### Risk of bias

We will perform an assessment of all RCTs using the Cochrane 'Risk of bias' tool according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors will work independently to assess each element of potential bias listed below as 'high', 'low', or 'unclear risk of bias'. We will report a brief description of the judgement statements upon which review authors have assessed potential bias in the 'Characteristics of included studies' table. We will ensure that a consensus on the degree of risk of bias is met through comparison of review authors' statements and, when necessary, through consultation with a third review author. We will use the Cochrane tool for assessing risk of bias, which includes the following domains:

- selection bias: random sequence generation and allocation concealment;
- performance bias: blinding of participants and personnel;
- detection bias: blinding of outcome assessment;
- attrition bias: incomplete outcome data;
- reporting bias: selective reporting;
- other bias.

### Measures of treatment effect

For continuous outcomes, we will record means, standard deviations, and total numbers of participants for both treatment and control groups. For dichotomous outcomes, we will record numbers of events and total numbers of participants for both treatment and control groups.

For continuous outcomes using the same scale, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured on different scales, we will present the standard mean difference (SMD). If available, we will extract and report hazard ratios (HRs) for mortality data. If HRs are not available, we will make every effort to estimate the HR as accurately as possible using available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007).

For dichotomous outcomes, we will report the pooled risk ratio (RR) with 95% CIs. When the number of observed events is small (< 5% of sample per group), and when trials include balanced treatment groups, we will report the Peto odds ratio (OR) with 95% CIs (Deeks 2011).

If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

When appropriate, we will report the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) with CIs.

If we cannot report available data in any of the formats described above, we will prepare a narrative report, and, if appropriate, we will present the data in tables.

### Unit of analysis issues

We do not expect to encounter unit of analysis issues, as we are unlikely to include cluster-randomised trials, cross-over studies, and multiple observations for the same outcome in this review. Should we identify any studies of these designs, we will treat them in accordance with advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). If participants are randomised more than once we will contact the authors of the study to request data on the procedure associated with the initial randomisation. For studies with multiple treatment groups, two review authors will exclude subgroups that are considered irrelevant to the analysis. We will tabulate all subgroups in the 'Characteristics of included studies' section. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and will exclude the others (Higgins 2011c).

## Dealing with missing data

When we identify data as missing or unclear in published literature, we will contact study authors directly. We will record the number of participants lost to follow-up for each study. When possible, we will analyse data on an intention-to-treat (ITT) basis, but if insufficient data are available, we will present per-protocol analyses (Higgins 2011c).

## Assessment of heterogeneity

If clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will assess statistical heterogeneity of treatment effects between studies using a  $\text{Chi}^2$  test with a significance level of  $P < 0.1$ . We will use the  $I^2$  statistic to quantify the degree of potential heterogeneity and will classify it as moderate if  $I^2$  is less than 50%, or considerable if  $I^2$  is between 50% and 80%. We will assess potential causes of heterogeneity by conducting sensitivity and subgroup analyses (Deeks 2011).

## Assessment of reporting biases

When we identify at least 10 studies for inclusion in a meta-analysis, we will explore potential publication bias (small-trial bias) by generating a funnel plot and performing a linear regression test. We will consider a  $P$  value of less than 0.1 as statistically significant for this test (Sterne 2011).

## Data synthesis

We will perform analyses according to recommendations provided in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using aggregated data for analysis (Deeks 2011). For statistical analysis, we will enter data into Review Manager 5 software (RevMan 2014). One review author will enter the data, and a second review author will check the data for accuracy.

When meta-analysis is feasible, we will use the fixed-effect model for pooling data. We will use the Mantel-Haenszel method for dichotomous outcomes, and the inverse variance method (or standardised mean differences as necessary) for continuous outcomes. When events are rare, and appropriate conditions are satisfied, we will use the Peto odds method. We will use the generic inverse variance method for time-to-event outcomes.

## Trial sequential analysis

We will provide a sample size estimate showing how many participants need to be included in a meta-analysis for reliable results. We will use trial sequential methods to explore all treatment effects attained before the required sample size is reached, using TSA v0.9 software (TSA 2011). We will sequence trials by first publication date of the full articles. This will provide the information size required to detect a statistically significant underlying effect. We will apply trial sequential analysis to the following outcomes:

- mean blood loss up to 24 hours post procedure; and
- number of participants transfused with blood up to 24 hours post procedure.

We will calculate mean blood loss and transfusion requirements for this population by using the mean blood loss and transfusion requirements derived from control group data. We will calculate the information size necessary for a relative risk reduction of bleeding and of receiving a red cell transfusion of 15%, which is equivalent to the effect size proposed for prophylactic use of tranexamic acid before surgery (Ker 2012).

If the calculated cumulative Z-curve crosses trial sequential monitoring boundaries, we will consider statistical significance to be reached while maintaining the overall type I error rate. Futility boundaries will be produced such that if the cumulative Z-curve crosses the futility threshold, evidence shows that the two treatments do not differ more than the anticipated effect size. We will use the O'Brien Fleming alpha-spending function with an overall 5% type I error rate and 80% statistical power to derive two-sided sequential monitoring and futility boundaries.

## 'Summary of findings' table

We will use the GRADE approach to create a 'Summary of findings' table, as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We will use the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low', using the five GRADE considerations:

- risk of bias: serious or very serious;
- inconsistency: serious or very serious;
- indirectness: serious or very serious;
- imprecision: serious or very serious; and
- publication bias: likely or very likely.

We will include the following outcomes:

- mean blood loss up to 24 hours post procedure;
- number of participants transfused with blood up to 24 hours post-procedure;
- overall mortality up to 30 days post infusion;
- risk of thrombotic events (arterial or venous);
- - myocardial infarction up to 30 days post infusion;
  - stroke up to 30 days post infusion;
  - venous thromboembolism up to 30 days post infusion; and
- quality of life.

### **Subgroup analysis and investigation of heterogeneity**

If adequate data are available, we will perform subgroup analyses for each of the following outcomes to assess their effect on heterogeneity:

- type of surgery or procedure;
- type of participant (liver disease and kidney disease with uraemia);
- age of participant (infants, children, adults);
- preoperative exposure of participants to acetylsalicylic acid (ASA) or other antiplatelet agents;
- use of cell-salvage techniques for the two primary outcomes:
  - number of participants transfused with blood, or both (during the procedure, up to 24 hours post procedure, and within 30 days of the procedure);
  - volume of blood transfused (expressed as total units of blood or millilitres per kilogram for children; during the procedure, up to 24 hours post procedure, and within 30 days of the procedure).

If appropriate, we will also investigate heterogeneity between studies according to use of a transfusion protocol.

### **Sensitivity analysis**

We will assess the robustness of our findings by performing the following sensitivity analyses when appropriate.

- Inclusion only of studies with a low risk of bias (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation).
- Inclusion only of studies with a dropout rate of less than 20%.
- Inclusion only of studies published before 2010 plus those registered prospectively and published after 2010.

### **Changes to future updates of this review**

In future updates of this review, review authors will compare only DDAVP versus placebo (or standard of care) and will remove comparisons of DDAVP versus tranexamic acid and DDAVP versus aprotinin.

In addition, review authors will limit the time period for follow-up for primary outcomes to 48 hours, rather than up to 30 days.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Blood Loss, Surgical [\*prevention & control]; Deamino Arginine Vasopressin [\*administration & dosage]; Erythrocyte Transfusion [\*utilization]; Hemostatics [\*administration & dosage]; Randomized Controlled Trials as Topic; Transplantation, Homologous

### MeSH check words

Adult; Humans