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## Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults (Review)

López-Briz E, Ruiz Garcia V, Cabello JB, Bort-Martí S, Carbonell Sanchis R, Burls A

López-Briz E, Ruiz Garcia V, Cabello JB, Bort-Martí S, Carbonell Sanchis R, Burls A.

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# Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

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## ABSTRACT

### Background

Intermittent locking of central venous catheters (CVCs) is undertaken to help maintain their patency. There are systematic variations in care: some practitioners use heparin (at different concentrations), whilst others use 0.9% NaCl (normal saline). This review looks at the effectiveness and safety of intermittent locking with heparin compared to 0.9% NaCl to see if the evidence establishes whether one is better than the other. This work is an update of a review first published in 2014.

### Objectives

To assess the effectiveness and safety of intermittent locking of CVCs with heparin versus normal saline (NS) in adults to prevent occlusion.

### Search methods

The Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (last searched 11 June 2018) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 5). Searches were also carried out in MEDLINE, Embase, CINAHL, and clinical trials databases (11 June 2018).

### Selection criteria

We included randomised controlled trials in adults  $\geq 18$  years of age with a CVC that compared intermittent locking with heparin at any concentration versus NS. We applied no restriction on language.

### Data collection and analysis

Two review authors independently selected trials, assessed quality, and extracted data. We contacted trial authors to retrieve additional information, when necessary. We carried out statistical analysis using Review Manager 5 and assessed the overall quality of the evidence supporting assessed outcomes using GRADE. We carried out prespecified subgroup analysis.

## Main results

We identified five new studies for this update (six prior studies were included in the original review), bringing the number of eligible studies to 11, with a total of 2392 participants. We noted differences in methods used by the included studies and variation in heparin concentrations (10 to 5000 IU/mL), time to follow-up (1 to 251.8 days), and the unit of analysis used (participant, catheter, line access).

Combined results from these studies showed fewer occlusions with heparin than with NS (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.51 to 0.95;  $P = 0.02$ ; 1672 participants; 1025 catheters from 10 studies;  $I^2 = 14\%$ ) and provided very low-quality evidence.

We carried out subgroup analysis by unit of analysis (testing for subgroup differences ( $P = 0.23$ ;  $I^2 = 30.3\%$ ). When the unit of analysis was the participant, results show no clear differences in all occlusions between heparin and NS (RR 0.79, 95% CI 0.58 to 1.08;  $P = 0.15$ ; 1672 participants; seven studies). Subgroup analysis using the catheter as the unit of analysis shows fewer occlusions with heparin use (RR 0.53, 95% CI 0.29 to 0.95;  $P = 0.03$ ; 1025 catheters; three studies). When the unit of analysis was line access, results show no clear differences in occlusions between heparin and NS (RR 1.08, 95% CI 0.84 to 1.40; 770 line accesses; one study).

We found no clear differences in the duration of catheter patency (mean difference (MD) 0.44 days, 95% CI -0.10 to 0.99;  $P = 0.11$ ; 1036 participants; 752 catheters; six studies; low-quality evidence).

We found no clear evidence of a difference in the following: CVC-related sepsis (RR 0.74, 95% CI 0.03 to 19.54;  $P = 0.86$ ; 1097 participants; two studies; low-quality evidence); mortality (RR 0.76, 95% CI 0.44 to 1.31;  $P = 0.33$ ; 1100 participants; three studies; low-quality evidence); haemorrhage at any site (RR 1.32, 95% CI 0.57 to 3.07;  $P = 0.52$ ; 1245 participants; four studies; moderate-quality evidence); or heparin-induced thrombocytopenia (RR 0.21, 95% CI 0.01 to 4.27;  $P = 0.31$ ; 443 participants; three studies; low-quality evidence).

The main reasons for downgrading the quality of evidence were unclear allocation concealment, imprecision, and suspicion of publication bias.

## Authors' conclusions

Given the very low quality of the evidence, we are uncertain whether intermittent locking with heparin results in fewer occlusions than intermittent locking with NS. Low-quality evidence suggests that heparin may have little or no effect on catheter patency. Although we found no evidence of differences in safety (sepsis, mortality, or haemorrhage), the combined trials are not powered to detect rare adverse events such as heparin-induced thrombocytopenia.

## PLAIN LANGUAGE SUMMARY

### Heparin versus normal saline locking for prevention of occlusion in central venous catheters in adults

#### Background

Central venous catheters are tubes (also called 'lines') temporarily implanted into patients when frequent intravenous access is needed. They can be used for monitoring patients in intensive care, for giving drugs or chemotherapy, or for providing intravenous nutrition. A Hickman line is an example of a central venous catheter. Blood clots and other factors can block these catheters. Blood clots in or on a catheter can also become infected or can travel to the lungs (this is known as a 'pulmonary embolism'). Heparin is a drug that helps to prevent blood clotting, so it may help prevent catheters from blocking or from causing pulmonary embolism. However, heparin can also cause bleeding, allergic reactions, and a drop in the number of platelets in the blood. When a catheter is not in use, a fluid is injected into the catheter until it is next used. This is called locking the catheter. Fluid used for locking is often heparin or normal saline (a sterile solution of salt in water at a concentration suitable for the blood). We did this review to find out whether locking catheters with heparin was better than locking them with saline to avoid blockages, and to determine how safe each method is. This work is an update of a review first published in 2014.

#### Study characteristics and main findings

For this update (most recent search performed 11 June 2018), we found five more studies, giving us a total of 11 studies involving 2392 participants. Our updated review found that locking catheters with heparin may or may not prevent blocking better than flushing with normal saline. We saw little or no difference in duration of catheter patency (length of time catheter remained unobstructed), rate of

infection, mortality, bleeding, or heparin-induced fall in platelet count (thrombocytopenia). We detected no effect with increasing concentrations of heparin dose.

### **Quality of the evidence**

The quality of the evidence ranged from very low to moderate for the main outcomes. We downgraded the quality of evidence owing to risk of bias and imprecision, as the pooled result included an effect of both benefit and harm and the suggestion of publication bias. To sum up, we are uncertain on the effects of heparin compared to normal saline and the findings should be interpreted with caution.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

| Heparin versus normal saline solution locking for prevention of occlusion in central venous catheters in adults   |  |                           |                                  |  |  |  |
|---|--|---------------------------|----------------------------------|--|--|--|
| <b>Patient or population:</b> adults with central venous catheters<br><b>Settings:</b> hospital<br><b>Intervention:</b> heparin<br><b>Comparison:</b> normal saline (0.9% NaCl) |  |                           |                                  |  |  |  |
| Outcomes  | Illustrative comparative risks* (95% CI) |                           | Relative effect (95% CI)         | Number of participants (studies)               | Quality of the evidence (GRADE)        | Comments   |
|   | Assumed risk                             | Corresponding risk        |                                  |  |  |  |
|   | Normal saline (NS, 0.9% NaCl)            | Heparin                   |                                  |  |  |  |
| <b>Occlusion of CVC (combining participant and catheter as unit of analysis)</b><br>Blood withdrawing<br>Follow-up:1 to 231 days  | Study population                         |                           | <b>RR 0.70</b><br>(0.51 to 0.95) | 1672 participants, 1025 catheters<br>(10 RCTs) | ⊕○○○<br><b>Very low</b> <sup>a,b</sup> | NNTB 42<br>(32 to 250)<br>Considering only <b>participant as unit of analysis</b><br>(7 studies, 1672 participants):<br>RR 0.79 (95% CI 0.58 to 1.08)<br>Considering only <b>catheter as unit of analysis</b><br>(3 studies, 1025 catheters):<br>RR 0.53 (95% CI 0.29 to 0.95) |
|   | 103 per 1000                             | 77 per 1000<br>(62 to 86) |                                  |  |  |  |



|   |  |                                  |                                   |                                |  |  |
|---|--|----------------------------------|-----------------------------------|--------------------------------|--|--|
| <b>Duration of catheter patency (days; combining participant and catheter as unit of analysis)</b><br>Blood withdrawing<br>Follow-up: 3 to 180 days | <b>Study population</b>  |                                  | 1788<br>(6 RCTs)                  | ⊕⊕○○<br><b>Low<sup>c</sup></b> | No clear difference in catheter patency was shown. This was less than 1 day longer with heparin locking<br>Considering only <b>participant as unit of analysis</b> (4 studies, 1036 participants):<br>MD 0.66 (95% CI -0.66 to 1.97)<br>Considering only <b>catheter as unit of analysis</b> (2 studies, 752 catheters):<br>MD 0.40 (95% CI -0.20 to 0.99) |  |
|   | Mean catheter patency in the heparin group was <b>0.44 days higher (-0.1 lower to 0.99 higher)</b> than in the NS group<br>Mean catheter patency in the saline group was 9 days (8.36 to 9.7 days) |                                  |                                   |                                |  |  |
| <b>CVC-related sepsis (participant as unit of analysis)</b><br>Positive microbiological culture<br>Follow-up: 22 to 180 days                        | <b>Study population</b>  |                                  | <b>RR 0.74</b><br>(0.03 to 19.54) | 1097<br>(2 RCTs)               | ⊕⊕○○<br><b>Low<sup>d</sup></b>   | No clear evidence of a difference in sepsis between locking methods was shown    |
|   | <b>11 per 1000</b>   | <b>8 per 1000</b><br>(0 to 212)  |                                   |                                |  |  |
| <b>Mortality</b><br>Follow-up: 17 to 180 days   | <b>Study population</b>  |                                  | <b>RR 0.76</b><br>(0.44 to 1.31)  | 1100<br>(3 RCTs)               | ⊕⊕○○<br><b>Low<sup>a</sup></b>   | No clear evidence of a difference in mortality between locking methods was shown |
|   | <b>52 per 1000</b>   | <b>40 per 1000</b><br>(23 to 68) |                                   |                                |  |  |

|  |                  |                          |                           |                  |                                     |  |
|--|------------------|--------------------------|---------------------------|------------------|-------------------------------------|--|
| Haemorrhage at any site<br>Follow-up: 1 to 180 days          | Study population |                          | RR 1.32<br>(0.57 to 3.07) | 1245<br>(4 RCTs) | ⊕⊕⊕○<br><b>Moderate<sup>e</sup></b> | No clear evidence of a difference in haemorrhage between locking methods was shown   |
|  | 13 per 1000      | 17 per 1000<br>(7 to 39) |                           |                  |                                     |  |
| Heparin-induced thrombocytopaenia<br>Follow-up: 7 to 22 days | Study population |                          | RR 0.21<br>(0.01 to 4.27) | 443<br>(3 RCTs)  | ⊕⊕○○<br><b>Low<sup>f</sup></b>      | No clear evidence of a difference in HIT between locking methods was shown. Studies are likely to be underpowered to detect low adverse events |
|  | 9 per 1000       | 2 per 1000<br>(0 to 38)  |                           |                  |                                     |  |

\*The **assumed risk** (e.g. median control group risk across studies) was calculated from the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; CVC: central venous catheter; HIT: heparin-induced thrombocytopaenia; MD: mean difference; NNTB: number needed to treat for an additional beneficial outcome; NS: normal saline; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>a</sup>We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one additional level for imprecision because the 95% CI included both no harm and harm.

<sup>b</sup>We downgraded the quality of evidence by one level owing to high risk of suspected publication bias (Figure 1).

<sup>c</sup>We downgraded by one level owing to risk of bias due to uncertain allocation concealment and by one additional level for imprecision because the pooled result included benefit and harm.

<sup>d</sup>We downgraded by two levels owing to the fact that the total number of events was less than 400, the pooled result included benefit and harm, and confidence intervals were very wide.

<sup>e</sup>We downgraded the quality of evidence by one level for imprecision because the 95% CI included both benefit and harm.

<sup>f</sup>We downgraded the quality of evidence by two levels owing to the fact that only one study detected HIT (Schallom 2012), with a finding that is counterintuitive (lower HIT in patients treated with heparin locking). In addition, investigators removed seven participants from the heparin locked catheter group because of concerns over bleeding or HIT. Moreover, the studies are likely to be underpowered to detect low adverse events, the confidence interval is large, and therefore uncertainty is high.

## BACKGROUND

### Description of the condition

Vascular access devices (VADs) are commonly used in health care. They encompass a wide range of devices that include, among others, central venous catheters (CVCs). A CVC is a catheter with a tip that lies within the proximal third of the superior vena cava, the right atrium, or the inferior vena cava. Catheters can be inserted through a peripheral vein or a proximal central vein, most commonly the internal jugular, subclavian, or femoral vein. Four types of CVCs are available: non-tunnelled catheters, tunnelled catheters (e.g. Hickman catheters, tunnelled dialysis catheters), peripherally inserted catheters, and totally implantable ports (port-a-cath) (Smith 2013).

In the United States, more than five million CVCs are inserted every year (Merrer 2001), leading to approximately 15 million central line days per year in intensive care units (ICUs) (Mermel 2000). CVCs allow measurement of haemodynamic variables that cannot be measured accurately by non-invasive methods (although some minimally invasive methods are now available), and they allow delivery of blood, medication, and nutritional support that cannot be given safely through peripheral venous catheters. Unfortunately, use of CVCs is associated with adverse events. Among them, mechanical complications during insertion (arterial puncture, haematoma, and pneumothorax) in 5% to 29% (Eisen 2006; McGee 2003), infectious complications in 5% to 26% (Merrer 2001; Raad 1997; Veenstra 1999), and thrombosis in 2% to 26% (Lee 2007) are the most common.

To some extent, thrombi are formed on CVCs during the first few hours of use in the form of fibrin tail, fibrin sheath, intraluminal occlusion, or mural thrombus (Jonker 2010), and thrombosis of large vessels occurs after long-term catheterisation (Valerio 1981). The incidence of CVC-related thrombosis varies depending on the patient's condition, catheter tip position and diameter, side and technique of insertion, and the chemical structure and nature of the infusate, among other factors (Verso 2003). CVC-related thrombosis represents an important source of morbidity and mortality among affected patients, not only for its inherent risks but also because thrombus creates a medium for bacterial proliferation that promotes infection (Mermel 2000). Pulmonary embolism, a severe medical condition, occurs in approximately 15% of patients with CVC-related upper extremity deep venous thrombosis (Burns 2008).

To avoid thrombus formation in CVCs, clinicians are currently applying several measures with different levels of success. Among others, heparin-locking catheters (Bishop 2009), heparin-bonded catheters (Shah 2008), systemic heparinisation with unfractionated heparin or with low molecular weight heparin (Randolph 1998b), anticoagulation with warfarin (Bern 1990), or administration of alteplase or urokinase, as in Hemmelgarn 2011 and Ray 1999, respectively, may be used. Heparin locking is the most com-

monly used procedure. According to some trial authors, the use of heparin may be justified with some types of VADs when they are not used frequently (Bishop 2009), but the efficacy of this practice remains unproven (López-Briz 2005).

### Description of the intervention

Heparin locking essentially consists of filling the lumens of CVCs with solutions of unfractionated heparin of varying strength.

### How the intervention might work

Use of CVCs predisposes to vascular thrombosis via vessel wall injury (during catheter placement), hypercoagulability, and alterations in normal blood flow. The balance between haemostatic systems producing thrombi and fibrinolytic systems dissolving them regulates blood vessel lumen patency, but placement of a CVC can alter this fine-tuned process, leading to a persistent thrombotic state. Catheter composition also plays a role in this thrombotic situation, allowing adsorption of fibrin and fibrinogen on its surface, thereby worsening the problem (Jacobs 2003). The anticoagulant properties of heparin have led clinicians to use heparin flushes in an attempt to prevent thrombus formation and to prolong the duration of catheter patency between uses. However, this physiopathological rationale may be wrong when applied to peripheral venous catheters, for which no benefit in using heparin locking versus normal saline (NS) locking has been demonstrated, as two published systematic reviews have independently shown (Goode 1991; Randolph 1998a).

### Why it is important to do this review

Bishop and colleagues reported in 2009 that heparin locking of catheters is a standard practice in the maintenance of CVCs (Bishop 2009), but the effectiveness of this practice so far has not been established in a systematic review. Moreover, variation in nursing practice is considerable because current guidelines provide conflicting recommendations about locking frequency and heparin concentration and volume (Mitchell 2009). A recent survey conducted in ICUs in the United States shows that 64.6% of respondents used NS and 31% used heparin (Sona 2012). The concentrations of heparin most commonly used were 100 IU/mL (37.5%) and 10 IU/mL (29.7%), and the most common intervals for locking catheters were every eight hours and after each use (74.4%). No information is available on CVC maintenance practices in other countries, so could clinical expertise be the guiding principle on this topic?

There are reasons to think that heparin locking catheters might be helpful. This makes pathophysiological sense. One systematic review studied the benefits of heparin in central venous and pulmonary artery catheters (Randolph 1998b). This paper showed

that prophylactic systemic heparin decreases catheter-related venous thrombosis (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.23 to 0.78) and bacterial colonisation of CVCs (RR 0.18, 95% CI 0.06 to 0.60) and may decrease catheter-related bacteraemia (RR 0.26, 95% CI 0.07 to 1.03). [Randolph 1998b](#) included combined data from trials using several doses of systemic prophylactic heparin, including unfractionated heparin (treatment regimens of 1 IU/kg, 3 IU/kg, 50 IU q12h, and 5000 IU intermittently), low molecular weight heparin (2500 IU given subcutaneously daily), or heparin-bonded catheters and did not include trials that provided periodic flushing of CVCs with heparin. However, there are also potential harms associated with heparin use. Heparin-induced thrombocytopenia (HIT), a severe immunological drug reaction known to cause arterial and venous thromboembolism without haemorrhage, raises serious concerns regarding the use of heparin ([Warkentin 2007](#)). Exposure of surgical patients to unfractionated heparin for longer than four days implies an overall risk of HIT of 2.6% ([Martel 2005](#)). This adverse effect of heparin treatment is a common late-onset complication that can develop five or more days after initiation of the drug. Another potential harm that may be associated with heparin use is the incidental administration of a heparin bolus through a catheter line intended for heparin locking. From an economic point of view, avoiding heparin locking would represent a very important cost savings ([Sona 2012](#)). Another systematic review estimated yearly savings of USD109 million to USD218 million when peripheral venous lines were flushed with NS instead of heparin ([Goode 1991](#)). In summary, the effectiveness of heparin locking of CVCs has not yet been demonstrated, and wide systematic variations in both guideline recommendations and practice have surrounded its use. Moreover, use of heparin is not free of risk and has a considerable economic impact. We developed a protocol and performed a systematic review about this topic ([López-Briz 2010](#); [López-Briz 2014](#)). This is the first update of our review first published in 2014.

## OBJECTIVES

To assess the effectiveness and safety of intermittent locking of central venous catheters with heparin versus normal saline in adults to prevent occlusion.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included only randomised controlled trials (RCTs) of heparin locking versus NS solution locking of central venous catheters (CVCs) in adults. We excluded studies when researchers used alternative methods of randomisation (quasi-randomised), such as alternate days of the week, odd and even numbers, dates of birth, hospital numbers, or historical controls.

#### Types of participants

We included studies of adults 18 years of age or older with a CVC. We excluded from this review studies on infants and children, as they are the topic of another Cochrane review ([Bradford 2015](#)).

#### Types of interventions

Interventions included intermittent locking with heparin (any dose with or without systemic drugs) compared with NS solution. All locking protocols were acceptable for inclusion.

#### Types of outcome measures

##### Primary outcomes

- Occlusion of CVCs (defined as inability to infuse fluids through the catheter because of blockage)
- Duration (in days) of catheter patency

##### Secondary outcomes

- Episodes of CVC-related sepsis and CVC-related colonisation (CVC-related sepsis is defined as the presence of symptoms and signs suggestive of sepsis, accompanied by positive blood cultures obtained from a normally sterile site different from the CVC or CVC tip, each growing the same micro-organism; CVC-related colonisation is defined as the presence of micro-organisms in the CVC only and not at another sterile site)
  - Mortality
  - Haemorrhage from any site in the body
  - Heparin-induced thrombocytopenia (HIT) (development of thrombocytopenia after heparin locking of a CVC in an adult with a previously normal platelet count after exclusion of all other causes of thrombocytopenia, along with a positive antibody test)
  - CVC-related thrombosis (determined by colour-coded Doppler ultrasonography, venography, computerised tomography, or magnetic resonance venography)
- Number of additional CVC insertions
- Abnormality of coagulation profile
- Allergic reactions to heparin

## Search methods for identification of studies

We applied no restriction on language of publication.

### Electronic searches

The Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (last searched 11 June 2018) and the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 5). See [Appendix 1](#) for the search strategy used for CENTRAL.

The review authors and the CIS also searched MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and clinical trials registries (last searched 11 June 2018).

We have presented in [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), [Appendix 5](#), and [Appendix 6](#) the search strategies used.

### Searching other resources

We searched the reference lists of relevant studies identified through the electronic searches.

## Data collection and analysis

### Selection of studies

Two review authors (ELB and VRG) independently read the abstract and, if necessary, the full text of potentially relevant references, to identify studies that needed to be further examined. We excluded letters, editorials, commentaries, reviews, and lectures that did not contain original research data. We contacted authors of unpublished and ongoing trials to obtain further information. When differences in opinion arose, we consulted a third review author (RCS).

### Data extraction and management

Three review authors (ELB, VRG, and RCS) independently extracted data regarding populations, interventions, and relevant outcomes, using the standard Cochrane Vascular forms for dichotomous data and continuous data. We contacted study authors to obtain additional data, if necessary ([Goosens 2013](#); [Schallom 2012](#)).

### Assessment of risk of bias in included studies

We assessed the risk of bias in included studies by using standardised criteria from Cochrane for the following ([Higgins 2011](#)).

- Adequacy of random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.

- Selective reporting.
- Other bias.

### Measures of treatment effect

We used risk ratio (RR) with 95% confidence interval (CI) and number needed to treat for an additional beneficial outcome (NNTB) to measure any effect on dichotomous variables (i.e. occlusion of CVCs, mortality, adverse events, etc.). We calculated NNTB values from the RR according to the formula  $NNTB = 1/ACR \times (1 - RR)$ , for which ACR is the assumed control risk ([McQuay 1997](#)).

### Unit of analysis issues

In the protocol version, when we planned the present systematic review, we assumed that the unit of analysis would be the participant. Once we performed the literature search, we found that the unit of analysis used by researchers was the participant or the catheter or line access (i.e. each time a line is used to provide drugs, blood, etc.). We performed analysis separately for each different unit of analysis for outcomes that could have been influenced by the unit of analysis (occlusions and patency), if sufficient data were available. The main analyses stratify studies by unit of analysis type, but we also reported the main results irrespective of the unit of analysis.

For secondary outcomes, when considering adverse effects, we used the participant as the denominator for analysis.

### Dealing with missing data

We contacted the principal investigators of two studies to request additional data ([Goosens 2013](#); [Schallom 2012](#)). These study authors provided relevant data that were later published.

### Assessment of heterogeneity

We attempted to explain relevant clinical, methodological, or statistical heterogeneity using forest plots, and we quantified heterogeneity using the  $I^2$  statistic ([Higgins 2003](#)). Thresholds for interpretation of  $I^2$  can be misleading in that the importance of inconsistency depends on several factors. [Higgins 2011](#) prepared the following rough guide to interpretation.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: shows considerable heterogeneity.

### Assessment of reporting biases

We assessed reporting bias using funnel plots, as we identified a sufficient numbers of studies.

## Data synthesis

We summarised data statistically, if possible. We performed statistical analysis according to the statistical guidelines referenced in the current version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used Review Manager 5 for review production and data analysis. We used a random-effects model. We planned to use a fixed-effect model to pool data when statistical heterogeneity was low, as in our previous review (López-Briz 2014). However, we decided to use a random-effects model, even though  $I^2$  values were low, because although the same drug was used across trials (heparin), we noted clear clinical heterogeneity in the study methods applied (i.e. different doses with systemic heparin or not, different follow-up times, different kinds of patients, etc.).

## Subgroup analysis and investigation of heterogeneity

For the primary outcomes, we performed subgroup analyses for each different unit of analysis. The incidence of CVC-related thrombosis varies depending on clinical type of the participant (onco-haematological, critical, on dialysis, etc.), CVC implantation site, CVC type, and infusate-related factors. We planned to perform subgroup analyses to take these factors into account, if sufficient data were available.

## Sensitivity analysis

We carried out sensitivity analyses to explore the robustness of results by investigating the influence of the following factors on effect size.

- Published or unpublished studies.
- Quality of studies.

- Weight of different studies.
- Different measures of effect size (odds ratio (OR) and risk ratio (RR)).

## 'Summary of findings' table

We created [Summary of findings for the main comparison](#) for the comparison heparin versus NS intermittent locking for prevention of occlusion in central venous catheters in adults. We used GRADEpro GDT software to present the main findings of the review (grade.pro.org) (GRADEproGDT 2015). We judged the outcomes of CVC occlusion, duration of catheter patency, CVC-related sepsis, mortality, haemorrhage, and heparin-induced thrombocytopenia to be the most clinically relevant to healthcare professionals and patients. For each outcome, we calculated assumed control intervention risks from the mean number of events reported in the control groups of selected studies. We used the system developed by the GRADE Working Group to grade the quality of evidence as high, moderate, low, or very low, based on within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias (Guyatt 2008).

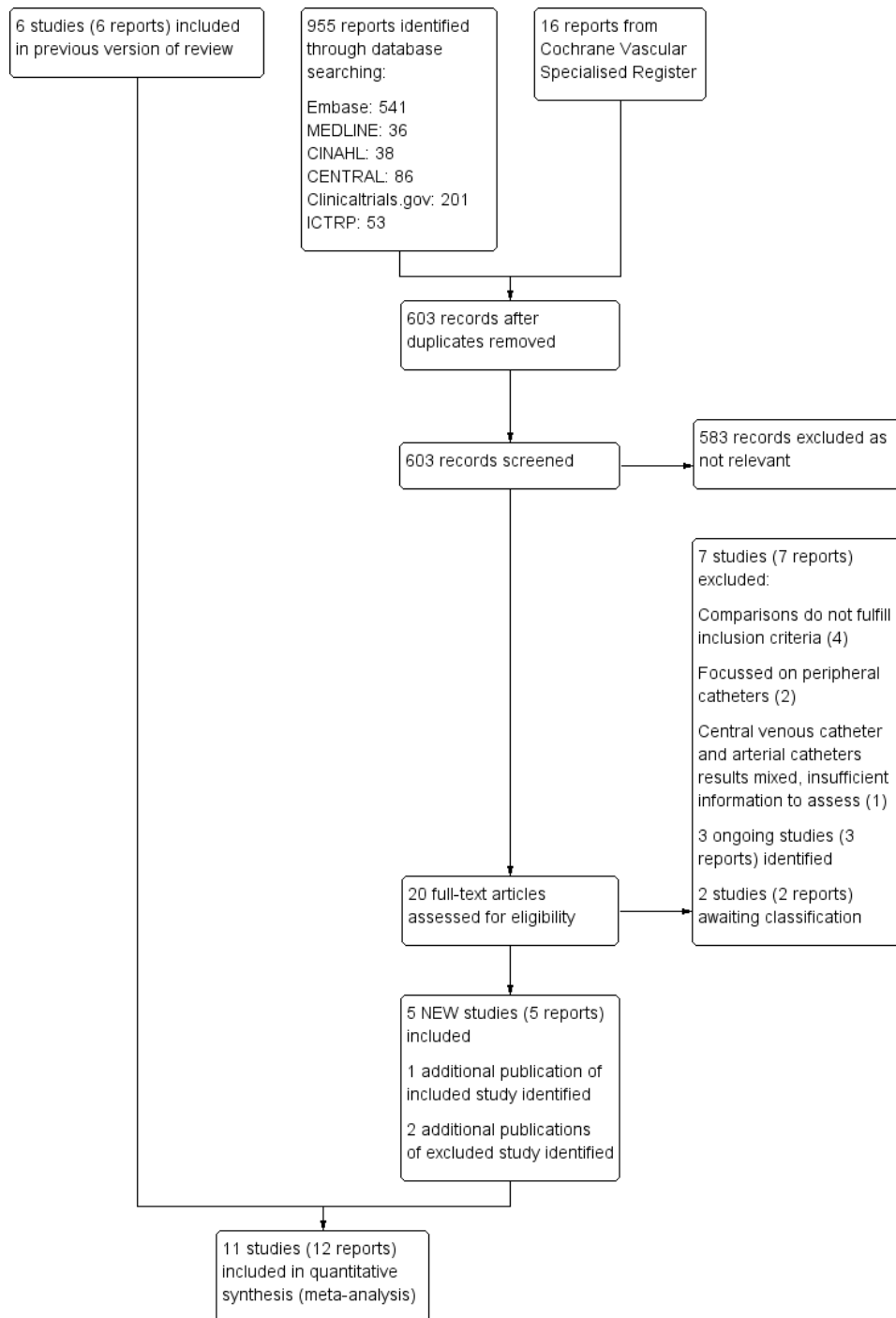
# RESULTS

## Description of studies

### Results of the search

See [Figure 2](#).

**Figure 2. Study flow diagram.**





## Included studies

Five new studies met the inclusion criteria for this update (Beigi 2014; Dal Molin 2015; Heidari 2015; Lyons 2014; Mahesh 2014), bringing the total number of included studies to 11, with a total of 2392 participants (Beigi 2014; Bowers 2008; Dal Molin 2015; Goosens 2013; Heidari 2015; Kaneko 2004; Lyons 2014; Mahesh 2014; Pumarola 2007; Rabe 2002; Schallom 2012). See [Characteristics of included studies](#).

Beigi 2014 was a single-blinded randomised controlled trial with 100 participants with chronic kidney disease. Researchers randomly assigned participants to locking with heparin (1000 IU) versus NS. The unit of analysis was the participant. Only three in the heparin group and one in the NS group withdrew. We sent a letter to study authors to request more information. Length of follow-up was 24 hours.

Bowers 2008 conducted a single-centre randomised study in 102 adult participants with single-lumen peripherally inserted central catheters (PICCs) with luer-activated devices. Trial authors used a random block design with allocation concealment to randomly assign participants to receive NS or heparin lock flush (100 USP U/mL). The main outcome studied was occlusion rate, and the secondary outcome was duration of PICCs (in days). The unit of analysis was the participant for occlusion rate as well as for patency. All participants completed the study (50 in the NS group and 52 in the heparin group).

Dal Molin 2015 was a multi-centre, open-label randomised trial with 430 oncological participants. Investigators randomly assigned participants to locking with heparin 5 mL (50 IU) versus NS 5 mL. Trial authors used the participant as the unit of analysis for occlusion. Study authors reported 5% withdrawals from the NS group and 2.5% from the heparin group without providing details.

Goosens 2013 conducted a randomised controlled open-label non-inferiority trial in 802 participants older than one year scheduled for first insertion of a totally implantable venous access device (TIVAD) through the superior vena cava (SVC) system, with an onco-haematological malignancy and with sufficient life expectancy to complete the planned follow-up of 180 days at the study centre. After randomisation via computerised random number generation, researchers assigned 398 participants to receive an NS lock and 404 to receive a heparin lock in a non-blinded manner. Although participants were randomly assigned, the main unit of analysis was the number of catheters accessed. However, Goosens provided additional information about occlusions per participant. Participants who had difficulties with aspiration through the catheter were registered. Investigators considered outcomes of withdrawal occlusion, catheter-related bacteraemia, and catheter duration within 180 days (unit of analysis - partici-

pant), as well as adverse events. Study authors also provided data on sepsis, thrombosis, and mortality. We requested information on data for adult participants, and Dr Goosens responded: "Only 3.5% of patients were < 18 years old, given that small number we didn't perform any sub analysis. Moreover we don't presume any difference in results between adults and peds" [sic].

Heidari 2015 conducted a double-blinded RCT in 84 participants from the intensive care unit. This study compared a flush of 3 mL of heparin saline solution (10 IU/mL) versus NS locking. The main outcome was CVC patency, and the unit of analysis chosen was the participant. We requested additional information from study authors. Follow-up was 21 days.

Kaneko 2004 performed a single-centre, open-label, randomised controlled clinical trial in adult participants with an inserted double-lumen CVC. This study compared a flush of 20 mL of NS versus a flush of 20 mL of NS followed by locking with 2 mL heparin (1000 IU/mL). Researchers used low molecular weight heparin at 8 IU/kg/h during each haemodialysis session. They randomly allocated 48 participants to the NS (26) or heparin group (22). They studied the outcomes days of catheter survival and thrombotic occlusion (both considered the participant as the unit of analysis), as well as coagulation analytical parameters such as activated coagulation time, activated partial thromboplastin time, and prothrombin time.

Lyons 2014 performed a single RCT on 90 participants from home care and tried to find the most effective locking solution for maintenance of PICCs. This study compared three arms: 10 mL of NS, 5 mL of low-dose heparin (10 IU/mL), and 3 mL of high-dose heparin (100 IU/mL). The main outcome was the development of patency-related complications (sluggishness, occlusions, etc.), and researchers used the participant as the unit of analysis. One participant in the NS group and one in the high-dose heparin group withdrew. We sent a letter to study authors to request more information.

Mahesh 2014 performed an RCT in 100 participants from the Respiratory Intensive Care Unit with CVC with triple lumen. This study compared heparin (3 mL, 10 IU/mL) versus NS (10 mL) flushes every eight hours. The primary outcome of the study was lumen non-patency, defined as inability to both withdraw blood and flush through a lumen, and the unit of analysis was the participant. Researchers reached the conclusion of lumen non-patency after the following interventions: (1) if the lumen could not be flushed, the participant was repositioned and the flush re-attempted; and (2) if the lumen still could not be flushed, the syringe was changed and the flush was re-attempted. Investigators assessed the secondary outcome, HIT, using daily platelet count starting on day 4 from the time of giving heparin flushes to all participants in the heparin group.

Pumarola 2007 carried out a two-phase clinical trial in a polyva-



lent ICU. Participants were adults with multiple pathological processes in whom a three-lumen CVC had been inserted. Researchers used a registered software program (Aleator; Aleator SRL, Buenos Aires, Argentina) for randomisation. However, the study was not blinded. In the first phase, trialists compared two concentrations of heparin (20 IU/mL and 100 IU/mL), establishing patency at 24 hours after catheter implantation and at discharge. In the second phase, they compared heparin at a concentration of 100 IU/mL versus NS and assessed patency at 24 hours, at 72 hours, and at discharge. Only this second phase fulfilled our inclusion criteria. Study authors assessed 95 CVCs during this phase (38 in the heparin group and 57 in the NS group) for occlusion rates and mean days of catheter duration, using the catheter as the unit of analysis for both.

[Rabe 2002](#) studied 99 three-lumen CVCs inserted into 91 adult participants locked with one of the following solutions: NS, heparin (5000 IU/mL), or vitamin C (200 mg/mL). Researchers assigned catheters randomly (using a list of random numbers prepared by the study authors) to one of three groups. They assessed patency every two days to a maximum of 20 days. Study outcomes included thrombotic obstruction and catheter survival, with the catheter used as the unit of analysis.

[Schallom 2012](#) conducted a single-centre study wherein researchers randomly assigned patients in the ICU with a newly placed three- or four-lumen CVC (simple randomisation, sequence concealed) to be flushed with NS or with heparin (10 IU/mL every 8 hours). Among the randomly assigned participants, 295 had at least one lumen with a minimum of two flushes, resulting in 326 catheters (170 allocated to the NS group and 156 to the heparin group) with 709 lumens (395 in the NS group and 314 in the heparin group). The primary outcome was lack of lumen patency (unit of analysis was the catheter). Secondary outcomes included rates of loss of blood return, flush failure, HIT, and catheter-related bloodstream infection.

## Excluded studies

We excluded seven additional studies from this update ([Chen 2014](#); [Han 2016](#); [Liang 2015](#); [NCT03114722](#); [Phulara 2018](#); [Xu 2017](#); [Ziyaeifard 2015](#)). The total number of excluded studies in the current review is 179. We excluded these studies for the following reasons.

- Studies did not meet the criteria established for intervention (heparin) or comparison (0.9% NaCl sterile solution).
- Studies focussed on peripheral catheters.
- Studies focussed on arterial catheters.
- Studies did not provide data stratified by arterial and venous catheters.

We excluded some studies for more than one reason.

See the [Characteristics of excluded studies](#) section for further details.

## Ongoing studies

We identified three new studies as ongoing ([NCT02354118](#); [NCT02923830](#); [RBR-3ht499](#)). See [Characteristics of ongoing studies](#) for further details.

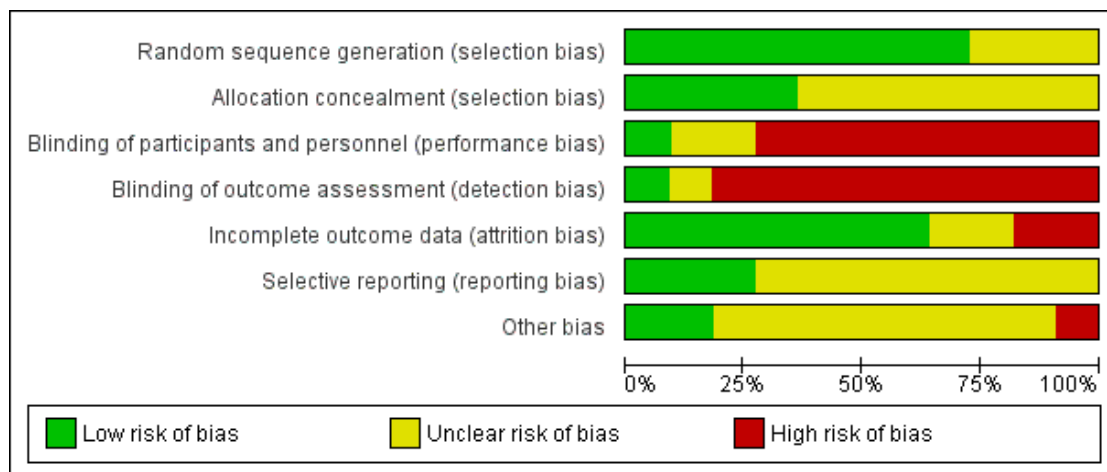
## Studies awaiting classification

We identified two studies as awaiting classification ([Klein 2017](#); [Klein 2018](#)). See [Characteristics of studies awaiting classification](#) for further details.

## Risk of bias in included studies

[Figure 3](#) and [Figure 4](#) show risk of bias according to the quality of included trials.

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



**Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

|                | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------------|---|---|---|---|--|--------------------------------------|------------|
| Beigi 2014     | +   | ?                                       | ?   | -   | +  | ?                                    | ?          |
| Bowers 2008    | +   | ?                                       | -   | -   | +  | ?                                    | +          |
| Dal Molin 2015 | +   | +                                       | -   | -   | +  | +                                    | ?          |
| Goosens 2013   | +   | +                                       | -   | -   | ?  | +                                    | ?          |
| Heidari 2015   | +   | ?                                       | +   | +   | +  | ?                                    | ?          |
| Kaneko 2004    | ?   | ?                                       | -   | -   | -  | ?                                    | ?          |
| Lyons 2014     | ?   | +                                       | ?   | ?   | +  | +                                    | +          |
| Mahesh 2014    | ?   | ?                                       | -   | -   | +  | ?                                    | ?          |
| Pumarola 2007  | +   | ?                                       | -   | -   | -  | ?                                    | -          |
| Rabe 2002      | +   | ?                                       | -   | -   | ?  | ?                                    | ?          |
| Schallom 2012  | +   | +                                       | -   | -   | +  | ?                                    | ?          |

We show summarised results for main outcomes (occlusions and days of patency) and by bias domain.

## Occlusion of CVCs

### Unit of analysis: participant

Seven trials assessed this outcome (Beigi 2014; Bowers 2008; Dal Molin 2015; Goosens 2013; Kaneko 2004; Mahesh 2014; Lyons 2014). We judged the first four to be at low risk for random sequence generation: Beigi 2014 (random allocation numbers); Bowers 2008 (“A random block design with concealment was used”); Dal Molin 2015 (“A random allocation sequence was created using a computerized procedure on-line”); and Goosens 2013 (randomisation computer generated). We assessed the remaining three as having unclear risk.

### Unit of analysis: catheter

Three trials assessed this outcome, and we rated them as having low risk of bias for random sequence generation: Pumarola 2007 (randomisation computer generated); Rabe 2002 (randomisation list prepared by study authors using a “random number generator”); and Schallom 2012 (computerised random number generator in MS Excel used by investigators).

### Unit of analysis: line access

Only Goosens 2013 assessed this outcome. This trial performed computer-generated randomisation, so we rated it as having low risk of bias for random sequence generation.

## Patency

### Unit of analysis: participant

Four studies assessed this outcome (Bowers 2008; Goosens 2013; Heidari 2015; Kaneko 2004). According to random sequence generation, we rated Bowers 2008, Goosens 2013, and Heidari 2015 as having low risk of bias, whereas we rated Kaneko 2004 as having unclear risk of bias because methods were unclear or were not described.

### Unit of analysis: catheter

Two studies assessed patency using the catheter as the unit of analysis (Pumarola 2007; Schallom 2012). We rated both as having low risk of bias according to random sequence generation.

## CVC-related thrombosis

Two trials assessed this outcome. Goosens 2013 used computer-generated randomisation, and Schallom 2012 used a computerised random number generator in MS Excel, so we rated both as having low risk for random sequence generation.

## CVC-related sepsis

Two trials assessed this outcome. Goosens 2013 used computer-generated randomisation, and Schallom 2012 used a computerised random number generator in MS Excel, so we rated both as having low risk for random sequence generation.

## Mortality

Three trials assessed this outcome. Goosens 2013 used computer-generated randomisation; Pumarola 2007 used computer-generated randomisation via the software Aleator. We rated both as having low risk of bias for random sequence generation. Kaneko 2004 provided insufficient information about the sequence generation process, and we judged this study to be at unclear risk of bias.

## Haemorrhage from any site in the body

Four trials assessed this outcome (Beigi 2014; Goosens 2013; Kaneko 2004; Schallom 2012). Beigi 2014 used random allocation number, Goosens 2013 used computer-generated randomisation, and Schallom 2012 used a computerised random number generator in MS Excel, so we rated these studies as having low risk of bias for random sequence generation. We rated Kaneko 2004 as having unclear risk of bias because Information was insufficient to permit judgement.

## Heparin-induced thrombocytopenia

Three studies reported heparin-induced thrombocytopenia: Kaneko 2004, Mahesh 2014, and Schallom 2012. We rated only Schallom 2012 as having low risk of bias, and we judged Kaneko 2004 and Mahesh 2014 to have unclear risk of bias.

## Allocation

Seven studies provided insufficient information about allocation concealment, so we assessed the risk of selection bias for these studies as unclear (Beigi 2014; Bowers 2008; Heidari 2015; Kaneko 2004; Mahesh 2014; Pumarola 2007; Rabe 2002). Pumarola 2007 reported a method of closed envelopes, but it remains unclear

whether the envelopes were opaque or sealed to conceal information. Goosens 2013 concealed the allocation sequence from researchers who enrolled participants by using sequentially numbered participant cards stored in a separate room; Schallom 2012 stated that the allocation sequence was concealed from the researcher enrolling participants; Dal Molin 2015 used a web-based method to conceal allocation; and Lyons 2014 used a sequentially numbered, opaque sealed envelope method, so we assessed these studies as having low risk of selection bias.

## Blinding

Eight studies were open-label or did not blind participants or research staff to the intervention received by participants. We rated these studies as having high risk of performance and detection bias (Bowers 2008; Dal Molin 2015; Goosens 2013; Kaneko 2004; Mahesh 2014; Pumarola 2007; Rabe 2002; Schallom 2012). Beigi 2014 and Lyons 2014 used single-blinding, and we classified their risk of bias as unclear. Heidari 2015 was at low risk of bias as both participants and researchers were unaware of which locking fluid was used (solution was made up by nurses). However, neither occlusion nor patency was likely to be influenced by lack of blinding. We judged that the secondary outcomes, namely, CVC-related thrombosis, episodes of CVC-related sepsis and colonisation, numbers of additional CVC insertions, mortality, coagulation profile, HIT, and allergic reactions to heparin and haemorrhage, were also unlikely to be influenced by lack of blinding.

## Incomplete outcome data

We considered Beigi 2014 (two in heparin groups and one in saline group withdrew), Bowers 2008 (no withdrawals), Dal Molin 2015 (five participants in heparin group and 10 in saline group withdrew), Heidari 2015 (no withdrawals), Mahesh 2014 (no withdrawals), Lyons 2014 (no withdrawals), and Schallom 2012 (no withdrawals) to have low risk of attrition bias because missing outcome data were few and were balanced in numbers across intervention groups, and reasons for missing data were similar across groups.

Researchers in the Rabe 2002 and Goosens 2013 studies insufficiently reported attrition or exclusions to permit judgement, and information about the number of catheters losing patency in each treatment group was lacking in Rabe 2002. So, we rated both of these studies as having unclear risk of attrition bias.

We rated both Kaneko 2004 and Pumarola 2007 as having high risk of bias. Kaneko 2004 reported 40% withdrawals in the heparin group (9/22) and 30% in the NS group (8/26) and provided unclear reasons for withdrawal. Meanwhile, Pumarola 2007 reported a withdrawal rate of 69.6% (87/125) in the heparin group and 54.4% (68/125) in the NS group; the main reason for withdrawal was cancellation of the procedure (74/125 and 52/125, respectively).

## Selective reporting

Dal Molin 2015, Goosens 2013, and Lyons 2014 reported all expected outcomes, so we rated these studies as having low risk of reporting bias. The remaining studies were at unclear risk owing to lack of available protocols or insufficient information retrieved from researchers (Beigi 2014; Bowers 2008; Heidari 2015; Kaneko 2004; Mahesh 2014; Pumarola 2007; Rabe 2002; Schallom 2012).

## Other potential sources of bias

Pumarola 2007 may be underpowered. Researchers analysed only 38 and 57 catheters per group, but the predetermined sample size was 185 catheters per group; trialists stopped the study early for 74 and 52 catheters in the heparin and NS groups, respectively, but did not provide the reason for this. Therefore we rated risk of other bias as high. In Goosens 2013, 3.5% of participants were children and study authors did not perform separate analyses; therefore we rated risk of other bias as unclear. The remaining studies were at low risk of other bias.

## Effects of interventions

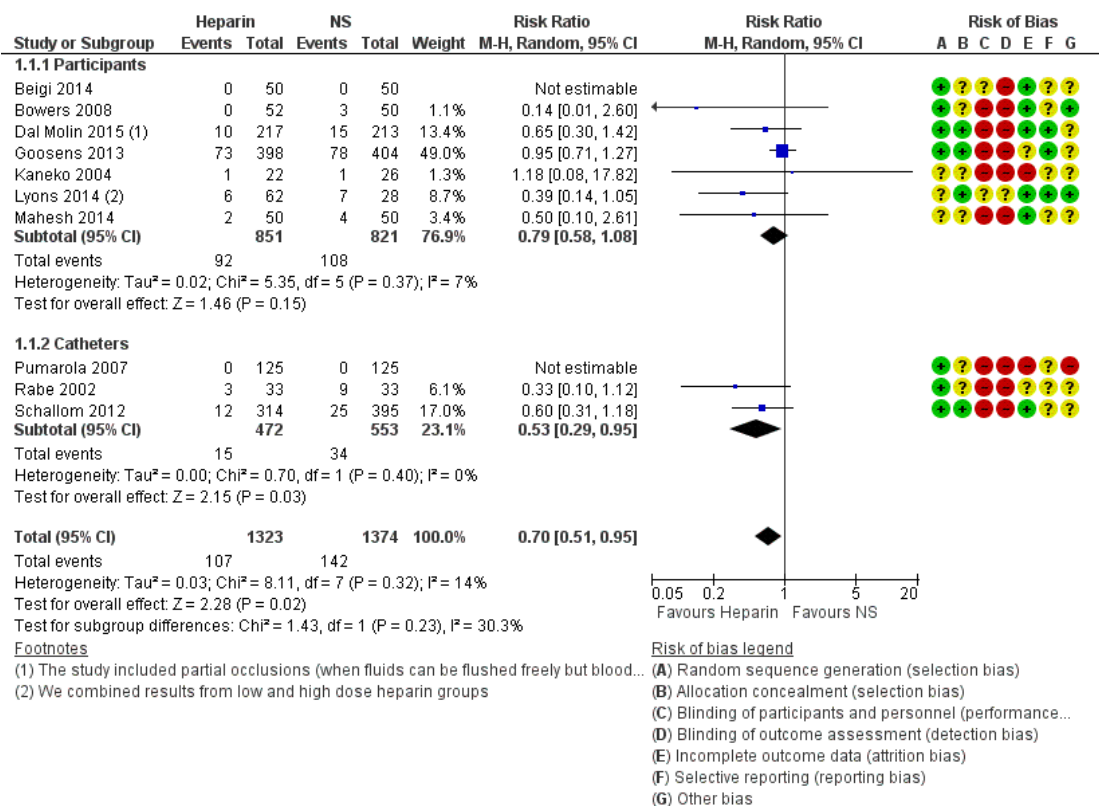
See: [Summary of findings for the main comparison Heparin versus normal saline solution locking for prevention of occlusion in central venous catheters in adults](#)

## Primary outcomes

### Occlusion of CVCs

Ten studies (1672 participants, 1025 catheters) reported on occlusion of CVCs using either the participant or the catheter as the unit of analysis, and we pooled results in the overall meta-analysis (Beigi 2014; Bowers 2008; Dal Molin 2015; Goosens 2013; Kaneko 2004; Lyons 2014; Mahesh 2014; Pumarola 2007; Rabe 2002; Schallom 2012). Results demonstrated a favourable effect of heparin in preventing occlusion (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.51 to 0.95;  $P = 0.02$ ; [Analysis 1.1](#); [Figure 5](#)). Testing for subgroup differences showed little to no difference between subgroups ( $P = 0.23$ ;  $I^2 = 30.3$ ). Using the calculator from Chris Cates' web page ([nntonline.net/visualrx/](http://nntonline.net/visualrx/)), we found that the number needed to treat for an additional beneficial outcome (NNTB) was 42 (95% CI 32 to 250). The funnel plot that we created for this outcome suggested that risk of publication bias was present ([Figure 1](#)). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment, by one more for imprecision because the 95% CI included both benefit and no benefit, and by one more for suspicion of publication bias.

**Figure 5. Forest plot of comparison: I All occlusions, outcome: I.I All studies.**



Seven studies (1672 participants) used the participant as the unit of analysis (Beigi 2014; Bowers 2008; Dal Molin 2015; Goosens 2013; Kaneko 2004; Lyons 2014; Mahesh 2014). We noted no clear evidence of an effect upon pooling this subgroup only (RR 0.79, 95% CI 0.58 to 1.08;  $I^2 = 7\%$ ;  $P = 0.37$ ; Analysis 2.1). We judged the quality of evidence to be low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one more for imprecision because the 95% CI included both benefit and no benefit.

Three studies with 1025 participants used the catheter as the unit of analysis (Pumarola 2007; Rabe 2002; Schallom 2012). Results demonstrated a favourable effect of heparin (RR 0.53, 95% CI 0.29 to 0.95;  $I^2 = 0\%$ ;  $P = 0.03$ ; Analysis 2.2). We used a Mantel-Haenszel (M-H) random-effects model. Using the calculator from Chris Cates' web page (<http://www.nntonline.net/visualrx/>), we found that the NNTB was 71 (95% CI 47 to 667). We judged the quality of evidence to be moderate. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment.

Only one study used line access as the unit of analysis (Goosens 2013). This study included 6137 observations and showed no

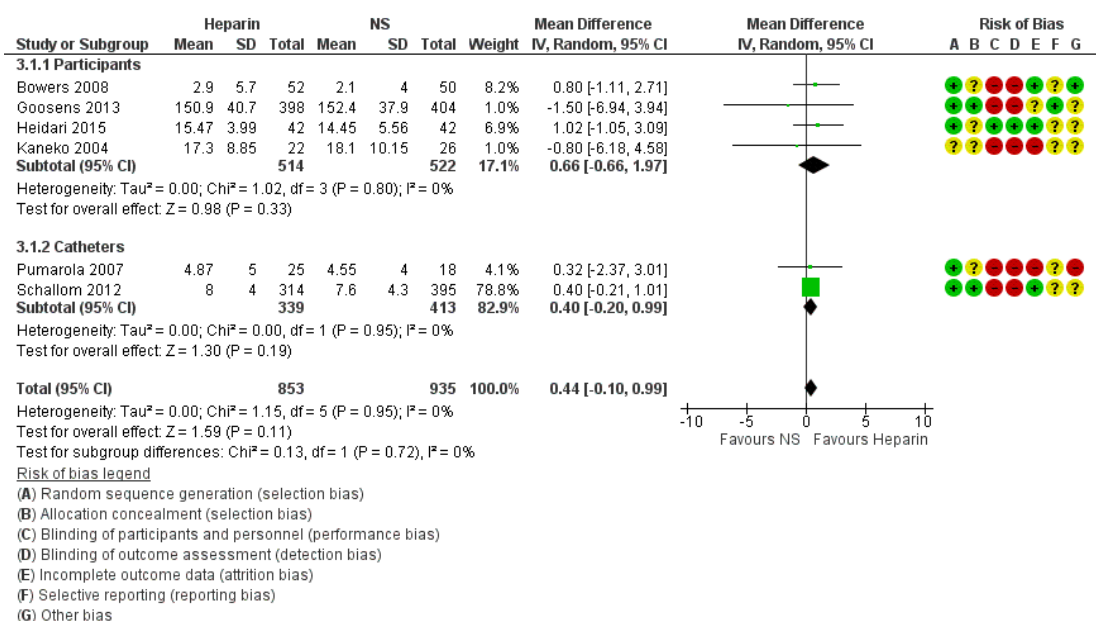
differences in the number of occlusions between heparin and NS locking (RR 1.08, 95% CI 0.84 to 1.40). We judged the quality of evidence to be moderate. We downgraded the quality of evidence by one level for imprecision because the 95% CI included both benefit and no benefit. Despite lack of blinding in this trial, we decided not to downgrade quality because this would not affect the occlusions. Dr Goosens kindly provided data from unit of analysis participants and from unit of analysis lines accessed. To prevent double counting, we decided not to include both types of data in the overall results, and we used data only from unit of analysis participants in the meta-analysis.

#### Duration (in days) of catheter patency

We pooled six studies with 1788 participants (using the participant or the catheter as the unit of analysis) and analysed results for catheter patency duration (Bowers 2008; Goosens 2013; Heidari 2015; Kaneko 2004; Pumarola 2007; Schallom 2012). Data show no difference in this outcome between heparin and NS groups (mean difference (MD) 0.44, 95% CI -0.10 to 0.99;  $P = 0.11$ ; Analysis 3.1). Testing for subgroup differences showed little to no

difference between the subgroups ( $P = 0.72$ ;  $I^2 = 0$ ; Figure 6). We judged the quality of evidence to be low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one more for imprecision because the 95% CI included both benefit and harm.

**Figure 6. Forest plot of comparison: 3 All patency, outcome: 3.1 All studies.**



Four studies with 1036 participants used the participant as the unit of analysis for catheter patency duration (Bowers 2008; Goosens 2013; Heidari 2015; Kaneko 2004). We detected no clear differences between heparin and NS groups (MD 0.66, 95% CI -0.66 to 1.97;  $I^2 = 0\%$ ;  $P = 0.33$ ; Analysis 4.1). We judged the quality of evidence to be low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one more for imprecision because the 95% CI included both benefit and harm.

Two studies with 752 participants used the catheter as the unit of analysis for catheter patency duration (Pumarola 2007; Schallom 2012). We observed no clear differences between heparin and NS groups (MD 0.40, 95% CI -0.20 to 0.99;  $I^2 = 0\%$ ;  $P = 0.19$ ; Analysis 4.2). We judged the quality of evidence to be moderate. We downgraded the quality of evidence by one level for imprecision because the 95% CI included both benefit and harm. No studies reporting on this outcome used line access as the unit of analysis.

## Secondary outcomes

See additional Table 1.

## Episodes of CVC-related sepsis and CVC-related colonisation

Two studies (1097 participants) reported on sepsis (Goosens 2013; Schallom 2012). Analysis showed no clear evidence of an effect with heparin use (RR 0.74, 95% CI 0.03 to 19.54;  $I^2 = 75\%$ ;  $P = 0.86$ ; Analysis 5.1). Heterogeneity among studies was high ( $I^2 = 75\%$ ). In Schallom 2012, four participants in the saline group experienced episodes of CVC-related sepsis compared with none in the heparin group (data received via personal communication with study author). Study authors treated all four participants using non-antibiotic-impregnated catheters. This difference was not statistically significant ( $X^2 = 2.180$ ;  $P = 0.14$ ; Yates correction



applied). [Goosens 2013](#) found catheter-related bacteraemia in two out of 404 cases (0.5%) in the NS group and in six out of 398 cases (1.5%) in the heparin group ( $P = 0.18$ ). We judged the quality of evidence to be low. We downgraded the quality of evidence by two levels for imprecision because the 95% CI was very wide and included both harm and no harm.

### Mortality

Three studies (1100 participants) reported on mortality ([Goosens 2013](#); [Kaneko 2004](#); [Pumarola 2007](#)). Results showed no evidence of an effect (RR 0.76, 95% CI 0.44 to 1.31;  $I^2 = 0\%$ ;  $P = 0.33$ ; [Analysis 5.2](#)). [Kaneko 2004](#) did not report deaths, [Pumarola 2007](#) reported three deaths (two in the heparin group and one in the NS group, without significant differences), and [Goosens 2013](#) reported 48 deaths (28 in the NS group and 20 in the heparin group;  $P = 0.255$ ). No other included studies reported mortality. We judged the quality of evidence to be low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one more for imprecision because the 95% CI included both harm and no harm.

### Haemorrhage from any site in the body

Four studies (1245 participants) reported on bleeding ([Beigi 2014](#); [Goosens 2013](#); [Kaneko 2004](#); [Schallom 2012](#)). We observed no evidence of a difference in bleeding between heparin and NS groups (RR 1.32, 95% CI 0.57 to 3.07;  $I^2 = 0\%$ ;  $P = 0.52$ ; [Analysis 5.3](#)). [Beigi 2014](#) reported four and three bleeding events in heparin and NS groups, respectively. [Goosens 2013](#) reported no haemorrhages in any group. [Kaneko 2004](#) reported oozing from the exit site of the dialysis catheter in five participants in the heparin group and in five in the NS group with no statistically significant differences ( $X^2 = 0.088$ ;  $P = 0.799$ ). In [Schallom 2012](#), one participant in the heparin group presented with bleeding versus none in the NS group ( $X^2 = 0$ ;  $P = 0.984$ ; Yates correction). We judged the quality of evidence to be moderate. We downgraded the quality of evidence by one level for imprecision because the 95% CI included both harm and no harm.

### Heparin-induced thrombocytopenia (HIT)

Only [Kaneko 2004](#), [Mahesh 2014](#), and [Schallom 2012](#) reported on HIT. Neither [Kaneko 2004](#) nor [Mahesh 2014](#) found cases of HIT. [Schallom 2012](#) detected two cases, both in the NS group. Pooling data showed no clear evidence of an effect (RR 0.21, 95% CI 0.01 to 4.27;  $P = 0.31$ ; [Analysis 5.4](#)). We judged the quality of evidence to be low. Only one study detected HIT ([Schallom 2012](#)), with a finding that is counterintuitive (lower HIT in patients treated with heparin locking). Moreover, the confidence interval is large, and therefore uncertainty is high. In addition, investigators removed seven participants from the heparin locked catheter group because of concerns about bleeding or HIT.

### CVC-related thrombosis

Only three studies (1527 participants) reported on the incidence of CVC-related thrombosis ([Dal Molin 2015](#); [Goosens 2013](#); [Schallom 2012](#)). Pooled results show no evidence of a difference in effect between heparin and NS groups (RR 1.24, 95% CI 0.77 to 2.02;  $I^2 = 0\%$ ;  $P = 0.38$ ; [Analysis 5.5](#)).

[Schallom 2012](#) found 10.7% venous thromboembolism in the NS group (16 participants) and 13.1% (19 participants) in the heparin group ( $X^2 = 0.419$ ;  $P = 0.518$ ), with no statistical differences between groups. [Goosens 2013](#) found a confirmed diagnosis of central venous thrombosis in 13 participants (3.3%) in the heparin group and in 11 participants (2.8%) in the NS group ( $X^2 = 0.060$ ;  $P = 0.807$ ), retrospectively. [Dal Molin 2015](#) reported one thrombosis in the heparin group.

We judged the quality of evidence to be moderate. We downgraded the quality of evidence by one level for imprecision because the 95% CI included both benefit and harm.

### Number of additional CVC insertions

None of the included studies provided data on this outcome.

### Abnormality of coagulation profile

Only [Kaneko 2004](#) reported alterations in coagulation parameters. These investigators studied activated coagulation time (ACT), activated partial thromboplastin time (APTT), and prothrombin time (PT). [Kaneko 2004](#) found differences between groups for both ACT ( $P < 0.001$ ) and APTT ( $P = 0.001$ ). In particular, said parameters, except PT ( $P = 0.187$ ), were higher in the heparin group. Differences observed in the PT parameter, which was elevated in the heparin group, did not reach statistical significance. We judged the quality of evidence to be low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one more for imprecision because the 95% CI included both harm and no harm.

### Allergic reactions to heparin

None of the included studies provided data on this outcome.

### Sensitivity analysis

We planned to carry out sensitivity analyses affecting main outcomes (occlusions) for published versus unpublished studies, for quality of studies, and for weight of studies, as well as for odds ratio versus risk ratio.

The only study initially identified as an unpublished study was [Goosens 2013](#), but this study was later published, and we identified no other unpublished studies. So, we cannot perform this kind of predefined sensitivity analysis.

We found that results for occlusion in studies having poor or unclear allocation concealment favoured heparin locking versus



NS (RR 0.39, 95% CI 0.16 to 0.95), but this effect was lost when studies with good allocation concealment were considered (RR 0.74, 95% CI 0.51 to 1.05; [Analysis 6.1](#)).

We explored the influence of studies contributing most to the effect estimate to assess whether a single study could reverse the direction of the effect. When we considered the outcome occlusions, the study with the greatest weight was [Goosens 2013](#) (49.0%). We performed a sensitivity analysis by removing this study from the analysis and found that the direction of effect changed, now favouring heparin locking (RR 0.52, 95% CI 0.30 to 0.91; [Analysis 6.2](#)).

We explored and calculated differences between odds ratio and risk ratio but found them to be not significant.

We also explored effect size in occlusions and patency. Here we standardised the results, so they were independent of the unit of analysis. We did this because there was discussion in the review author group about whether it was appropriate to combine studies for which the unit of analysis was the participant with studies for which the unit of analysis was the catheter. Overall the team concluded that it was reasonable to do so because most participants only ever have one catheter, and therefore the two approximated to each other. However we also treated each unit of analysis as a subgroup ([Analysis 1.1](#)). A different strategy for meta-analysing results that are addressing the same underlying construct but measuring this construct in different ways is to standardise the results by converting them to an effect size, that is, a 'z-score' of a standard normal distribution. We did this in the sensitivity analysis in case readers of the review disagreed with our pragmatic approach in [Analysis 1.1](#).

We calculated the effect size for occlusions when the unit of analysis of the participant was considered (RR 0.84, 95% CI 0.65 to 1.08) versus effect size when the unit of analysis of the catheter was considered (RR 0.54, 95% CI 0.31 to 0.96). Testing for subgroup differences showed no clear differences between the subgroups ( $P = 0.17$ ; [Analysis 6.3](#)).

In a similar way, we assessed effect on patency when the unit of analysis was the participant (RR 0.66, 95% CI -0.66 to 1.97) and when it was the catheter (RR 0.40, 95% CI -0.20 to 0.99). Testing for subgroup differences showed no statistical differences between the subgroups ( $P = 0.72$ ; [Analysis 6.4](#)).

### Subgroup analysis

We planned to perform subgroup analyses by type of participant, CVC site and CVC type, and infusate-related factors. We carried out subgroup analysis by heparin concentration used, oncology/non-oncology patients, number of CVC lumens, and time to follow-up. Data were insufficient for analysis by CVC implantation site or CVC type subgroup. We carried out subgroup analyses by unit of analysis and reported these results above under the relevant outcomes.

Subgroup analysis to investigate occlusion in oncology and non-oncology patients showed differences between groups. Occlusions

in non-oncological participants were different from those in oncological participants (RR 0.48, 95% CI 0.30 to 0.77;  $P = 0.002$ ; vs RR 0.91, 95% CI 0.69 to 1.19;  $P = 0.48$ ; respectively), favouring heparin use in non-oncological participants (test for subgroup differences  $P = 0.02$ ; [Analysis 7.1](#)).

Subgroup analysis to assess the relationship between occlusion and the number of CVC lumens (unit of analysis - participants) showed no clear differences between groups: occlusions in studies using CVCs with one lumen (RR 0.85, 95% CI 0.57 to 1.26) versus those using CVCs with more than one lumen (RR 0.63, 95% CI 0.15 to 2.59) (test for subgroup differences  $P = 0.69$ ; [Analysis 7.2](#)). Subgroup analysis to investigate the effect of heparin concentration on occlusion showed no clear differences between high ( $\geq 1000$  IU/mL) and low concentrations ( $< 1000$  IU/mL). According to heparin concentration, high concentrations (RR 0.41, 95% CI 0.14 to 1.25) versus low concentrations (RR 0.65, 95% CI 0.31 to 1.34) showed no clear differences (test for subgroup differences  $P = 0.50$ ; [Analysis 7.3](#)).

We performed subgroup analysis to assess whether occlusions were related to time to follow-up. When time to follow-up was less than one month (RR 0.48, 95% CI 0.30 to 0.77), we found differences favouring heparin. When time to follow-up was one month or longer, we noted no clear differences (RR 0.91, 95% CI 0.69 to 1.19). Testing for subgroup differences showed differences between the subgroups ( $P = 0.02$ ; [Analysis 7.4](#)).

## DISCUSSION

### Summary of main results

The aim of the present update was to assess the effectiveness of intermittent locking with heparin versus normal saline (NS) in adults with central venous catheters (CVCs) in terms of prevention of occlusion and overall benefits versus harms. Central venous catheters are frequently used to provide blood derivatives, medication, or nutritional support to patients, as well as for diagnostic monitoring, cardiac pacing, and other procedures. However, their use could result in thrombosis and infection and may prolong hospital stay.

Very low-quality evidence suggests that in adults, intermittent locking of CVCs with heparin may result in fewer occlusions than intermittent locking with NS. Low-quality evidence suggests that heparin has little or no effect on catheter patency. Although we did not detect differences in safety, the trials that were combined are not sufficiently powered to detect rare adverse events, such as heparin-induced thrombocytopenia (HIT). Lack of an effect of heparin concentration and the suggestion of publication bias as demonstrated by the funnel plot mean that these results should be interpreted cautiously. These findings on efficacy (occlusion and patency) could be related to the types of participants included (more benefit for non-oncological patients) and to the quality of

trials. The quality of the evidence ranged from very low to moderate.

## Overall completeness and applicability of evidence

Review authors examined all addressed outcomes. Statistical heterogeneity was low ( $I^2 = 0$ ) for the main outcomes of efficacy (occlusion and patency) and safety (bleeding, thrombosis, and mortality), despite inclusion of participants with very different conditions (critical, with onco-haematological malignancies, or under haemodialysis), treated with a very wide range of heparin concentrations ranging from 30 IU/mL to 2500 IU/mL. Only sepsis showed significant statistical heterogeneity ( $I^2 = 75\%$ ), which could be explained by the different clinical conditions of participants in the two studies reporting sepsis.

Our results are consistent with those of a retrospective cohort study by [Jonker 2010](#), which detected increased use of alteplase to clean catheters flushed with NS compared with catheters locked with heparin. However, these results may be biased by the indirectness of outcomes.

It is interesting to consider also the use of systemic anticoagulants among different studies. In [Pumarola 2007](#) and [Goosens 2013](#), use of any anticoagulation was a criterion of exclusion; although [Bowers 2008](#), [Kaneko 2004](#), [Rabe 2002](#), and [Schallom 2012](#) provided no data on permitted use of systemic anticoagulation in every participant ([Kaneko 2004](#)), or in only some participants ([Rabe 2002](#); [Schallom 2012](#)), differences were found to be not significant. Moreover, [Dal Molin 2015](#) excluded patients with intolerance to heparin, and [Heidari 2015](#) excluded patients with risk of bleeding. However, exclusion of [Pumarola 2007](#) and [Goosens 2013](#) - two studies that used the exclusion criterion of use of anticoagulants - resulted in no change in findings of the sensitivity analysis.

Length of follow-up for safety in this review could be too short to reveal relevant adverse events. Only [Dal Molin 2015](#) (231 days) and [Goosens 2013](#) (180 days) provided long-term follow-up, whereas [Beigi 2014](#), [Lyons 2014](#), [Mahesh 2014](#), [Pumarola 2007](#), [Rabe 2002](#), and [Schallom 2012](#) studied participants for a shorter time; [Heidari 2015](#) had medium-term follow-up (around 20 days); [Bowers 2008](#) and [Kaneko 2004](#) studied participants for a period ranging from 40 to 50 days. Consequently, the potential for higher incidence with long-term follow-up cannot be discarded. Given that CVCs could be placed for several months according to the needs of patients, adverse events may be more relevant than those described in the present systematic review. None of the 11 included trials were planned to study adverse events. In summary, it cannot be ruled out that adverse events may occur with longer exposure or larger numbers of participants.

Despite results suggesting no differences in safety, it is probable that a high proportion of patients could be at increased risk with heparin use. This increased risk of adverse events due to heparin

locking may be especially relevant among patients with liver or kidney failure and those with recent surgery (especially of the brain, eye, or spine), spinal anaesthesia, or recent injury. Also patients who have a history of heart problems, high blood pressure, menstrual problems, bleeding problems, or a history of ulcers or other stomach problems, or who are taking drugs such as non-steroidal anti-inflammatory drugs or antiplatelet agents, may have increased risk of bleeding. Adverse events may be reduced by flushes with NS.

Heparin-induced thrombocytopenia (HIT) is an adverse event that may be life-threatening. It is more common after intraoperative or perioperative administration of heparin. Its incidence is reported at between 0.1% and 5%. Risk factors for HIT include type of heparin used (greater risk with unfractionated heparin), duration of exposure, patient setting, and patient gender (1.5 to 2 times higher among women) ([Battistelli 2010](#)). In general, higher doses of heparin result in greater risk of HIT. However, lower heparin doses used to flush catheters have occasionally been associated with HIT ([McNulty 2005](#)). In the present systematic review, HIT was not reported in the heparin groups, and only two cases were reported in the NS groups ([Schallom 2012](#)), suggesting altogether an undiagnosed adverse event. Nevertheless, routine use of NS instead of heparin may reduce HIT.

## Quality of the evidence

We have presented the main results in [Summary of findings for the main comparison](#). The quality of evidence ranged from very low to moderate.

The quality of evidence for the main outcome (all occlusions of CVC) was very low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment, by another level for imprecision (95% confidence interval (CI) included both no harm and harm), and by an additional level for risk of bias due to suspected publication bias (see funnel plot; [Figure 1](#)). Although the common rule is not to create a funnel plot for fewer than 10 studies, we created a funnel plot because the included studies described different effects and different sizes. Although other possible sources of asymmetry can be addressed (selection bias, poor method, artefacts, or chance), we cannot discard publication bias.

Despite the fact that some trials were not blinded, we judged that lack of blinding was not important for this outcome.

We judged the quality of evidence for duration of overall catheter patency as low. We downgraded by one level for risk of bias due to unclear allocation concealment and by another level for imprecision.

We judged the quality of evidence for CVC-related sepsis/colonisation to be low. We downgraded the quality of evidence by two levels for imprecision because the 95% CI included both no harm and harm, the 95% CI was very wide, and the total number of events was less than 400.

We judged the quality of evidence for mortality and abnormality of coagulation profile to be low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one more level for imprecision because the 95% CI included both no harm and harm.

We judged the quality of evidence for haemorrhage from any site and for heparin-induced thrombocytopenia to be low. We downgraded the quality of evidence by one level for imprecision because the 95% CI included both no harm and harm. Moreover the finding is counterintuitive (lower HIT among patients treated with heparin locking).

We did not include the secondary outcomes CVC-related thrombosis and abnormality of the coagulation profile in [Summary of findings for the main comparison](#). We judged the quality of evidence for CVC-related thrombosis to be moderate. We downgraded the quality of evidence by one level for imprecision because the 95% CI included both no harm and harm. We judged the quality of evidence for abnormality of the coagulation profile to be low. We downgraded the quality of evidence by one level for risk of bias due to unclear allocation concealment and by one more for imprecision because the 95% CI included both no harm and harm.

In summary, risk of bias for unclear allocation concealment and imprecision were the items that downgraded the quality of evidence for most outcomes, and risk of publication bias could be added for the outcome “all occlusions”.

## Potential biases in the review process

Review authors carried out study selection and data extraction in a duplicate manner. We published a protocol for this systematic review ([López-Briz 2010](#)). None of the authors of this review update was involved in any of the included or excluded studies. We selected a priori all outcomes analysed. We contacted trial authors and retrieved additional information. Hence the probability of publication bias among studies included in this systematic review is low. However, we could not discard bias from non-published studies after we assessed the funnel plot for publication bias ([Figure 1](#)).

For the unit of analysis of participant or catheter, heparin showed a small benefit. We concluded that it was reasonable to pool both units of analysis because most participants only ever have one catheter, and therefore the two approximated to each other. This was an “a posteriori” decision, and it must be kept in mind when review results are interpreted.

## Agreements and disagreements with other studies or reviews

Other systematic reviews focussed on heparin use in CVCs have used different inclusion and/or exclusion criteria from those of this

review. [Randolph 1998b](#) reviewed randomised controlled trials in adult and paediatric participants in whom heparin was infused continuously through the catheter, administered subcutaneously (SC), or bonded to the catheter. They found a trend toward a reduction in catheter thrombus and a significant reduction (57%) in venous thrombosis. Statistical heterogeneity was not significant in both cases. Heparin dosage ranged from SC 5000 IU every 12 hours to 1 IU/mL in continuous perfusion added to total parenteral nutrition.

[Klerk 2003](#) also reviewed studies with adult and paediatric participants with CVCs in whom heparin flushes or antithrombotic agents were administered in prophylactic or therapeutic doses. This review concluded that heparin added to parenteral nutrition did not significantly decrease the risk of catheter-related thrombosis. However, this review cannot be compared with the present one because it differs in the design of included studies (randomised controlled trials and prospective cohort studies) and in the intervention provided (systemic heparin).

A previous systematic review conducted by some of the authors of this Cochrane review found and included only two studies, one of which included paediatric participants ([López-Briz 2005](#)). Results show no differences between heparin and NS locking.

[Mitchell 2009](#) conducted a systematic review focussed on adult participants with CVCs or peripherally inserted central catheters (PICCs) comparing heparin locking, continuous heparin perfusion, NS locking, urokinase locking, and heparin-bonded catheter versus any other intervention. The review authors concluded that “there is insufficient evidence on which to find that flushing catheters with heparin are more effective than flushing with saline solution”.

In paediatric participants, [Shah 2008](#) found that continuous heparin infusion reduced the risk of catheter occlusion with no statistically significant differences in the duration of catheter patency. However, the review authors could not provide recommendations for heparin use in neonates with PICCs. These review authors detected high clinical heterogeneity and high heterogeneity in treatment effect.

Guidelines have led to a wide variety of locking protocols, with many different types of locking solutions, volumes, locking frequencies, and heparin concentrations because these guidelines are based mainly on manufacturers’ recommendations - not on published evidence ([Mitchell 2009](#); [Sona 2012](#)). The Infusion Therapy Standards of Practice ([INS 2016](#)) “lists Heparin 10 units per mL or preservative free 0.9% sodium chloride to lock CVADs. This lower strength of heparin is recommended in an effort to reduce the occurrence of heparin-induced thrombocytopenia and thrombosis (HITT)”, and [Sousa 2016](#) stated that “Intermittent flushing with heparin is a standard practice in the maintenance of CVC patency. However, when compared with 0.9% normal saline flushing, no differences in thrombosis rates were found”.

Lately, three systematic reviews stated no differences. [Dal Molin 2014](#) performed a network meta-analysis and concluded: “There

is no evidence of a different effectiveness between heparin flushing and normal saline or other solutions in reducing catheter occlusions". Zhong 2017 concluded that heparin locking is not superior to saline in the maintenance of CVC lumen catheters. In a post hoc analysis, these review authors suggested that heparin could be effective when used with follow-up of less than one month. We found the same data but noted lack of plausibility only about this time-limited effect. Bradford 2015 and Bradford 2016 carried out a similar systematic review in paediatric patients and concluded: "It remains unclear whether heparin is necessary for CVC maintenance". Nevertheless, review authors provided conclusions about occlusions with only two trials, one of which, Goossens 2013, included only 3.5% of patients under 18 years (26 participants). Summarising all these systematic reviews revealed a protective effect for occlusions with heparin, but without statistical significance. Our review update includes more trials and more participants, and our results reached statistical significance.

## AUTHORS' CONCLUSIONS

### Implications for practice

Very low-quality evidence suggests that in adults, central venous catheters that are intermittently locked with heparin result in fewer occlusions than catheters locked with normal saline (NS). Low-quality evidence suggests that heparin may have little or no effect on duration of catheter patency. We found no evidence of an increased effect with increasing concentrations of heparin and no evidence of differences in the relative safety of the two methods of intermittent locking when central venous catheter (CVC)-related sepsis, mortality, or haemorrhage was considered, although the trials combined are not powered to detect rare adverse events

such as heparin-induced thrombocytopenia. To sum up, we are uncertain about the effects of heparin compared to NS, and review findings should be interpreted with caution.

### Implications for research

Better designed large-scale randomised controlled trials are needed to definitively establish or rule out a net benefit of locking with heparin versus 0.9% NaCl (normal saline); these trials should also explore effectiveness in different patient groups, such as patients under haemodialysis or those with onco-haematological malignancies. Trials should report the outcome using both the participant and the catheter as units of analysis to allow evidence to be combined more consistently. Occlusions and adverse events must be the focus of future trials, and we suggest at least one month of follow-up. In addition, assessment by type of line (i.e. dialysis/apheresis vs peripherally inserted central catheter (PICC) or vs other) is important. Addressing the question of harm from rare events requires high-quality prospective cohort studies with sufficient duration of follow-up. Decision analytical modelling incorporating the costs of heparin and saline and the probabilities and costs of alteplase use and catheter replacement may also help establish the thresholds required to make one or another method the most appropriate and efficient choice.

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**Sona 2012**

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**Sousa 2016**

Sousa B, Furlanetto J, Hutka M, Gouveia P, Wuerstlein R, Mariz JM, et al. Central venous access in oncology: ESMO Clinical Practice Guidelines. *Annals of Oncology* 2015; Vol. 26, issue Suppl 5:v152–68.

**Valerio 1981**

Valerio D, Hussey JK, Smith FW. Central vein thrombosis associated with intravenous feeding - a prospective study. *Journal of Parenteral and Enteral Nutrition* 1981;**5**(3):240–2.

**Veenstra 1999**

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**Warkentin 2007**

Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A editor (s). *Heparin-Induced Thrombocytopenia*. 4th Edition. New York: Informa Healthcare, 2007:21–66.

**Zhong 2017**

Zhong L, Wang HL, Xu B, Yuan Y, Wang X, Zhang YY, et al. Normal saline versus heparin for patency of central venous catheters in adult patients - a systematic review and meta-analysis. *Critical Care* 2017;**21**(1):5. [PUBMED: 28063456]

**References to other published versions of this review****López-Briz 2010**

López-Briz E, Ruiz Garcia V, Cabello JB, Bort-Martí S, Carbonell Sanchis R, Burls A. Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. DOI: 10.1002/14651858.CD008462

**López-Briz 2014**

López-Briz E, Ruiz Garcia V, Cabello JB, Bort-Martí S, Carbonell Sanchis R, Burls A. Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 10. DOI: 10.1002/14651858.CD008462.pub2

\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

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

#### Beigi 2014

|   |  |   |
|---|--|---|
| Methods   | RCT  |   |
| Participants  | 100 adult patients from Iran with chronic kidney disease   |   |
| Interventions   | Locking with heparin (1000 IU) vs with 0.9% saline   |   |
| Outcomes  | Manoeuvre needed to maintain catheter patency; catheter thrombosis; bleeding; PTT  |   |
| Notes   | Follow-up: 24 hours<br>Unit of randomisation: the participant<br>Source of support: Isfahan University of Medical Sciences |   |
| <i><b>Risk of bias</b></i>  |  |   |
| <b>Bias</b>   | <b>Authors' judgement</b>  | <b>Support for judgement</b>  |
| Random sequence generation (selection bias)                               | Low risk   | Random allocation numbers   |
| Allocation concealment (selection bias)                                   | Unclear risk   | Not stated  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk   | Single-blinded  |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk  | Not blinded to outcomes but outcome measurement not likely to be influenced by lack of blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk   | Three participants in the heparin group and 1 in the 0.9% NaCl group withdrew                   |
| Selective reporting (reporting bias)                                      | Unclear risk   | We sent a letter to study authors regarding the protocol, but we received no response           |
| Other bias  | Unclear risk   | Only 24 hours of follow-up  |

## Bowers 2008

|   |  |   |
|---|--|---|
| Methods   | RCT open-label   |   |
| Participants  | 102 participants with single-lumen PICCs with luer-activated devices, from USA   |   |
| Interventions   | Locking with: <ul style="list-style-type: none"><li>● Heparin 100 IU/mL locking (3 mL)</li><li>● 0.9% sodium chloride locking (10 mL)</li></ul>  |   |
| Outcomes  | Occlusion of PICCs, average duration of use of catheter (in days)  |   |
| Notes   | Follow-up until the first of the following: event (occlusion) or discharge<br>No data on use of systemic anticoagulation, as stated by study authors<br>Unit of randomisation: the participant<br>Source of support: none declared |   |
| <i><b>Risk of bias</b></i>  |  |   |
| <b>Bias</b>   | <b>Authors' judgement</b>  | <b>Support for judgement</b>  |
| Random sequence generation (selection bias)                               | Low risk   | Quote: "A random block design with concealment was used"  |
| Allocation concealment (selection bias)                                   | Unclear risk   | Information insufficient to permit judgement. Method of concealment not described or not described in sufficient detail to allow a definitive judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk  | Open-label trial, but the outcome is not likely to be influenced by lack of blinding  |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk  | No blinding of outcome assessment but outcome measurement not likely to be influenced by lack of blinding   |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk   | Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups                                |
| Selective reporting (reporting bias)                                      | Unclear risk   | Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified           |
| Other bias  | Low risk   | Study appears to be free of other sources of bias   |

|               |   |
|---------------|---|
| Methods       | Multi-centre open-label RCT conducted in 14 Italian oncology clinics  |
| Participants  | 430 adult patients with cancer with a new TIVAD from Italy  |
| Interventions | 5 mL (50 IU) of normal saline via positive-pressure technique vs “heparin” (the device was flushed as in the normal saline group, then was locked with 5 mL of heparin solution (50 UI/mL) using positive-pressure technique)   |
| Outcomes      | Main outcome: port failure for lumen occlusion<br>Secondary outcomes: catheter-related infections, thrombosis, extravasation  |
| Notes         | Patients with leukaemia or known intolerance to heparin were excluded, as were those whose device had some complications after insertion or who were planning to start parenteral nutrition with lipid. Patients with implanted TIVAD requiring TPN during the course of the study were kept off the study because of increased risk of occlusion due to TPN. Median follow-up was 231.8 days in the saline group and 251.8 day in the heparin group<br>Unit of randomisation: the participant<br>Source of support: Fondo Edo Tempia of Biella |

***Risk of bias***

| Bias  | Authors' judgement | Support for judgement  |
|---|--------------------|--|
| Random sequence generation (selection bias)                               | Low risk           | Quote: “A random allocation sequence was created using a computerized procedure on-line”   |
| Allocation concealment (selection bias)                                   | Low risk           | Allocation was determined after the nurse/doctor entered some patient and device data into the web page of the study. The goal of the procedure was to ensure that the clinician was not informed a priori if patient had been assigned to normal saline group or heparin group. Therefore allocation sequence was concealed |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Open-label, but outcome measurement not likely to be influenced by lack of blinding  |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | Open-label, but outcome measurement not likely to be influenced by lack of blinding  |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | 5% of withdrawals in 0.9% NaCl group and 2.5% in heparin group with no details provided  |

|                                      |              |  |
|--------------------------------------|--------------|--|
| Selective reporting (reporting bias) | Low risk     | Eudract_number: 2009-013620-22. All outcomes reported in the protocol were stated in the paper |
| Other bias                           | Unclear risk | Not enough information to permit judgement of other bias                                       |

### Goosens 2013

|               |  |
|---------------|--|
| Methods       | RCT open-label non-inferiority   |
| Participants  | 802 participants older than 1 year with an onco-haematological malignancy, from Belgium  |
| Interventions | Locking with: <ul style="list-style-type: none"> <li>• 10 mL 0.9% NaCl and after 3 mL heparin (100 IU/mL)</li> <li>• 10 mL 0.9% NaCl</li> </ul>  |
| Outcomes      | Primary outcome: withdrawal occlusion at access (i.e. inability to aspirate blood while injection is easy)<br>Secondary outcomes: catheter-related bacteraemia within 180 days, duration of catheter   |
| Notes         | Follow-up: 180 days<br>Following contact with trialists, we obtained additional raw data, which we used in the analysis<br>Use of heparin IV was an exclusion criterion<br>Main unit of randomisation was the number of catheters accessed, but Goosens provided additional information about occlusions per participant<br>Source of support: partially funded by Leuven Kankerinstituut and by B Braun Belgium |

### *Risk of bias*

| Bias  | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Low risk           | Computerised random number generation   |
| Allocation concealment (selection bias)                                   | Low risk           | Allocation concealment by means of sequentially numbered participant cards, stored in a separate room                                 |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Not blinded, but the outcome is categorical (blood aspiration possible or not) and is not likely to be influenced by lack of blinding |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | Not blinded, but the outcome is categorical (blood aspiration possible or not) and is not likely to be influenced by lack of blinding |

**Goosens 2013** (Continued)

|  |              |  |
|--|--------------|--|
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Reporting of attrition/exclusions insufficient to permit judgement: no information on number of catheters losing patency in each group |
| Selective reporting (reporting bias)                     | Low risk     | NCT00994136: all outcomes available  |
| Other bias   | Unclear risk | No separate analyses for children (3.5%) and adults. Not enough information to permit judgement of other bias                          |

**Heidari 2015**

|               |   |
|---------------|---|
| Methods       | RCT double-blinded  |
| Participants  | 84 patients from Iran in ICU  |
| Interventions | 3 mL heparin saline solution (10 IU/mL) locking vs 0.9% NaCl locking  |
| Outcomes      | CVC patency   |
| Notes         | Follow-up: 21 days<br>Exclusion criteria: risk of bleeding, receiving blood products and TPN during study, increase in body temperature greater than 37.7°C<br>Unit of randomisation: the participant<br>Source of support: Mazandaran University of Medical Sciences |

***Risk of bias***

| Bias  | Authors' judgement | Support for judgement  |
|---|--------------------|--|
| Random sequence generation (selection bias)                               | Low risk           | Random numbers generated by Excel software's Rand Between Function   |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not stated   |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants were unaware of the method used   |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Low risk           | In this study, the ward nurse prepared heparin and normal saline solutions, and the researcher was unaware of the content of serum |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | All participants were followed up  |
| Selective reporting (reporting bias)                                      | Unclear risk       | We sent a letter to study authors regarding the protocol, but we received no response  |

|            |              |  |
|------------|--------------|--|
| Other bias | Unclear risk | Not enough information to permit judgement of other bias |
|------------|--------------|--|

# Kaneko 2004

|               |  |
|---------------|--|
| Methods       | RCT open-label   |
| Participants  | 48 participants under haemodialysis with double-lumen CVC, from Japan  |
| Interventions | Locking with: <ul style="list-style-type: none"> <li>• 20 mL 0.9% NaCl + 2 mL heparin 1000 IU/mL lock</li> <li>• 20 mL 0.9% NaCl</li> </ul>  |
| Outcomes      | Thrombotic occlusion, catheter survival, catheter patency time, haematological and coagulation markers, safety   |
| Notes         | LMWH (dalteparin, parnaparin, or reviparin) at 8 IU/kg was used during each haemodialysis session<br>Follow-up was not clearly reported, but average period of catheter patency until removal or occlusion was almost the same mean 17.3 days in the saline group and 18.1 days in the heparin group<br>Unit of randomisation: the participant<br>Source of support: provided in part by Fresenius Medical Care Dialysis Foundation and by Unitika Ltd |

## Risk of bias

| Bias  | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Information about sequence generation process insufficient to permit judgement  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Information insufficient to permit judgement  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Outcome not likely to be influenced by lack of blinding   |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | No blinding of outcome assessment, but outcome measurement not likely to be influenced by lack of blinding                                    |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | High risk          | Withdrawals (9/22 = 40%) in heparin group and saline group (8/26 = 30%). No data regarding reasons for withdrawals                            |
| Selective reporting (reporting bias)                                      | Unclear risk       | Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified |

**Kaneko 2004** (Continued)

|            |              |  |
|------------|--------------|--|
| Other bias | Unclear risk | Not enough information to permit judgement of other bias |
|------------|--------------|--|

**Lyons 2014**

|               |   |
|---------------|---|
| Methods       | RCT single-blinded  |
| Participants  | 90 home care patients, from USA. Participants were recruited from the home infusion service's affiliated university medical centre at the time of their discharge to home with PICCs placed   |
| Interventions | 0.9% NaCl 10 mL vs low doses of heparin (10 IU/mL) 5 mL vs high doses of heparin (300 IU/mL) 3 mL   |
| Outcomes      | Quote: "Development of patency-related complications and other significant issues such as sluggishness, occlusion, missed medication doses, catheter replacement, additional nursing visits, and the use of alteplase"  |
| Notes         | Follow-up according to "Subjects' length of time in the study was determined by their prescribed therapy length and/or the study's end date"<br>Mean follow-up: 23 days per participant<br>Unit of randomisation: the participant<br>Source of support: Gardner Foundation of the INS and Alpha Nu Chapter of Sigma Theta Tau International |

***Risk of bias***

| Bias  | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Quote: "were randomly assigned"   |
| Allocation concealment (selection bias)                                   | Low risk           | Sequentially numbered, opaque, sealed envelope method. Principal investigator was blind to which study group a participant was assigned |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk       | Single-blinded without more details   |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Single-blinded without more details   |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | Without withdrawals   |
| Selective reporting (reporting bias)                                      | Low risk           | We contacted the study author, who sent the study protocol to us  |

|            |          |   |
|------------|----------|---|
| Other bias | Low risk | Study appears to be free of other sources of bias |
|------------|----------|---|

## Mahesh 2014

|               |   |
|---------------|---|
| Methods       | RCT   |
| Participants  | 100 participants from the Respiratory Intensive Care Unit with CVC with triple lumen, from India  |
| Interventions | Heparin (3 mL, 10 IU/mL) or 0.9% NaCl (10 mL) flushes every 8 hours   |
| Outcomes      | <p>Primary outcome: lumen non-patency, defined as inability to both withdraw blood and flush through a lumen. The conclusion of lumen non-patency was arrived at only after the following interventions:</p> <ul style="list-style-type: none"> <li>• If the lumen could not be flushed, the participant was repositioned and the flush re-attempted</li> <li>• If still unable to flush, the syringe was changed and the flush re-attempted</li> </ul> <p>Secondary outcome: heparin-induced thrombocytopenia (HIT), assessed by daily platelet count, starting on day 4 from the time of giving heparin flushes for all participants in Group H</p> |
| Notes         | <p>Exclusion criteria: known heparin allergy, diagnosis of HIT, bleeding risk identified by attending physician, age &lt; 18 years or &gt; 58 years, requiring prolonged ICU stay with ailments such as terminal illness, severe septicemia, MODS, etc</p> <p>Follow-up: average 1 week</p> <p>Unit of randomisation: the participant</p> <p>Source of support: none declared</p>   |

## Risk of bias

| Bias  | Authors' judgement | Support for judgement  |
|---|--------------------|--|
| Random sequence generation (selection bias)                               | Unclear risk       | Without details  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Without details  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Trial is not blinded, but outcome measurement is not likely to be influenced by lack of blinding |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | Trial is not blinded, but outcome measurement is not likely to be influenced by lack of blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | Without withdrawals  |



|                                      |              |  |
|--------------------------------------|--------------|--|
| Selective reporting (reporting bias) | Unclear risk | The protocol is not available. Moreover this is not indexed in PubMed or CENTRAL |
| Other bias                           | Unclear risk | Not detected   |

**Pumarola 2007**

|               |  |
|---------------|--|
| Methods       | RCT blinded  |
| Participants  | 250 patients in ICU with 3-lumen CVC, from Spain   |
| Interventions | Locking with: <ul style="list-style-type: none"> <li>• 5 mL 0.9% NaCl</li> <li>• 5 mL heparin 100 IU/mL</li> </ul>   |
| Outcomes      | Catheter patency at 24 hours, at 72 hours, and at discharge from ICU (mean 4.74, SD 5)   |
| Notes         | Two-phase trial: in the first phase, 2 different dosages of heparin were compared; in the second phase, heparin was compared with 0.9% NaCl in 95 CVCs<br>Follow-up until first of the following: event (occlusion) or discharge<br>Exclusion criterion: systemic anticoagulant use<br>Unit of randomisation: the catheter<br>Source of support: none declared |

***Risk of bias***

| Bias  | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Low risk           | Randomisation computer generated (software Aleator)   |
| Allocation concealment (selection bias)                                   | Unclear risk       | Information was insufficient to permit judgement. Method of concealment is not described or is not described in sufficient detail to allow a definitive judgement                               |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Open-label trial, but the outcome is not likely to be influenced by lack of blinding  |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | No blinding of outcome assessment, but outcome measurement not likely to be influenced by lack of blinding  |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | High risk          | Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups, but a very high rate of withdrawals: heparin 87/125 and saline 68/125 |

**Pumarola 2007** (Continued)

|                                      |              |   |
|--------------------------------------|--------------|---|
| Selective reporting (reporting bias) | Unclear risk | Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified   |
| Other bias                           | High risk    | Study may be underpowered: only 38 and 57 participants per group were analysed, but predetermined sample size was 125 participants per group. Study was stopped early for 74 participants in the heparin group and for 52 participants in the 0.9% NaCl group |

**Rabe 2002**

|               |  |
|---------------|--|
| Methods       | RCT open-label   |
| Participants  | 91 ICU patients with 99 implanted 3-lumen CVCs, from Germany   |
| Interventions | Catheter lock with 0.5 mL of: <ul style="list-style-type: none"> <li>• Heparin 5000 IU/mL</li> <li>• 0.9% NaCl</li> <li>• Vitamin C 200 mg/mL</li> </ul>   |
| Outcomes      | Catheter patency (tested every 2 days)   |
| Notes         | Follow-up: 20 days<br>Prophylactic or therapeutic anticoagulation used in the 3 groups but with non-significant differences<br>Unit of randomisation: the catheter<br>Source of support: none declared |

***Risk of bias***

| Bias  | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Low risk           | Randomisation list prepared by study authors using a random number generator                                  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Information insufficient to permit judgement  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Open-label trial, but the outcome is not likely to be influenced by lack of blinding                          |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | No blinding of outcome assessment, but outcome measurement is not likely to be influenced by lack of blinding |

**Rabe 2002** (Continued)

|  |              |   |
|--|--------------|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Reporting of attrition/exclusions insufficient to permit judgement: no information about number of catheters losing patency in each group     |
| Selective reporting (reporting bias)                     | Unclear risk | Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified |
| Other bias   | Unclear risk | Not enough information to permit judgement of other bias  |

**Schallom 2012**

|               |  |
|---------------|--|
| Methods       | RCT open-label   |
| Participants  | 295 patients (326 catheters, 709 lumens) from medical or surgical ICU in whom a 3- or 4-lumen CVC was inserted, from USA   |
| Interventions | Flushes every 8 hours with: <ul style="list-style-type: none"> <li>• 3 mL heparin 10 IU/mL</li> <li>• 10 mL 0.9% NaCl</li> </ul>   |
| Outcomes      | Rate of lumen non-patency, blood loss return, flush failure, rate of catheter-related blood-stream infection, HIT  |
| Notes         | Follow-up: 22 days<br>Prophylactic or therapeutic anticoagulation was used in both groups with non-significant differences<br>Unit of randomisation: the catheter<br>Source of support: no financial support |

***Risk of bias***

| Bias  | Authors' judgement | Support for judgement  |
|---|--------------------|--|
| Random sequence generation (selection bias)                               | Low risk           | Investigators used a computerised random number generator in MS Excel  |
| Allocation concealment (selection bias)                                   | Low risk           | Quote: "The allocation sequence was concealed until the card was retrieved upon obtaining patient consent"<br>Follow-up: 1-27 days |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Outcome not likely to be influenced by lack of blinding  |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | No blinding of outcome assessment, but outcome measurement not likely to be influenced by lack of blinding                         |

**Schallom 2012** (Continued)

|  |              |   |
|--|--------------|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk     | Only 1/165 in saline group and 7/162 in heparin group withdrew  |
| Selective reporting (reporting bias)                     | Unclear risk | Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified |
| Other bias   | Unclear risk | Not enough information to permit judgement of other bias  |

CVC: central venous catheter.

HIT: heparin-induced thrombocytopenia.

ICU: intensive care unit.

LMWH: low molecular weight heparin.

MODS: multi-organ dysfunction syndrome.

PICCs: peripherally inserted central catheters.

PTT: partial thromboplastin time.

RCT: randomised controlled trial.

SD: standard deviation.

TIVAD: totally implantable vascular access device.

TPN: total parenteral nutrition.

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

| Study                           | Reason for exclusion  |
|---------------------------------|---|
| <a href="#">AACCN 1993</a>      | Arterial catheters were used  |
| <a href="#">Abdelkefi 2004</a>  | Interventions do not fulfil inclusion criteria (continuous infusion)  |
| <a href="#">Abdelkefi 2005</a>  | Interventions do not fulfil inclusion criteria (continuous infusion)  |
| <a href="#">Abdelkefi 2005a</a> | Interventions do not fulfil inclusion criteria (heparin-coated catheters)   |
| <a href="#">Abdelkefi 2007</a>  | Interventions do not fulfil inclusion criteria (heparin-bonded catheter + normal saline vs non-coated catheter + continuous infusion heparin) |
| <a href="#">Abdelkefi 2008</a>  | Interventions do not fulfil inclusion criteria (impregnated catheters)  |
| <a href="#">Agnelli 2009</a>    | Interventions do not fulfil inclusion criteria (systemic nadroparin)  |
| <a href="#">Akyuz 2010</a>      | Comparison does not fulfil inclusion criteria (heparin vs taurolidine + citrate)  |
| <a href="#">Alexander 2010</a>  | Peripheral catheters were used  |

(Continued)

|                |   |
|----------------|---|
| Ankola 1993    | Arterial catheters were used; interventions do not fulfil inclusion criteria                                  |
| Anton 2009     | Intervention and participants do not fulfil inclusion criteria (children, heparin-bonded catheters)           |
| Appelgren 1996 | Interventions do not fulfil inclusion criteria (heparin-bonded catheters)                                     |
| Aquino 2002    | Interventions do not fulfil inclusion criteria (urokinase flushes)  |
| Araujo 2008    | Interventions do not fulfil inclusion criteria (catheter comparison)  |
| Arnts 2011     | Peripheral catheters were used. Participants do not fulfil inclusion criteria (neonates)                      |
| Arrants 1999   | Interventions do not fulfil inclusion criteria (saline lock only)   |
| Ashton 1990    | Peripheral catheters were used  |
| Aslam 2011     | Comparisons do not fulfil inclusion criteria (heparin or citrate vs heparin + tigecycline + N-acetylcysteine) |
| Bailey 1979    | Interventions do not fulfil inclusion criteria (continuous perfusion of heparin)                              |
| Balduini 2010  | Peripheral catheters were used  |
| Barrett 1990   | Interventions do not fulfil inclusion criteria (peripheral catheters)   |
| Barriga 1997   | Interventions do not fulfil inclusion criteria (heparin with or without vancomycin)                           |
| Bennegard 1982 | Interventions do not fulfil inclusion criteria (heparin-coated vs non-coated catheters)                       |
| Bertolino 2012 | Peripheral catheters were used  |
| Bejtes 2004    | Comparison does not fulfil inclusion criteria (heparin vs citrate-taurolidine)                                |
| Bisseling 2010 | Comparison does not fulfil inclusion criteria (heparin vs taurolidine)  |
| Bleyer 2005    | Comparison interventions do not fulfil inclusion criteria (heparin vs minocycline + EDTA)                     |
| Bolgiano 1990  | Arterial catheters were used  |
| Branger 2011   | Interventions do not fulfil inclusion criteria (arteriovenous fistula vs tunnelled jugular vein catheter)     |
| Branson 1993   | Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate)                         |
| Brismar 1982   | Interventions do not fulfil inclusion criteria (systemic heparin)   |
| Broom 2009     | Comparison interventions do not fulfil inclusion criteria (heparin vs ethanol)                                |

(Continued)

|                  |  |
|------------------|--|
| Broom 2012       | Comparison interventions do not fulfil inclusion criteria (heparin vs ethanol)               |
| Butt 1987        | Arterial catheters were used   |
| Buturovic 1998   | Comparison interventions do not fulfil inclusion criteria (heparin vs citrate vs polygeline) |
| Campos 2011      | Comparison interventions do not fulfil inclusion criteria (heparin vs ethanol)               |
| Cardinal 2000    | Comparisons do not fulfil inclusion criteria (heparin vs sodium citrate)                     |
| Carrasco 2004    | Interventions do not fulfil inclusion criteria (heparin-coated catheter)                     |
| Carratala 1999   | Interventions do not fulfil inclusion criteria (heparin vs heparin + vancomycin)             |
| Casale 2009      | Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)        |
| Catorze 2011     | Arterial catheters were used   |
| Catton 2006      | Peripheral catheters were used   |
| Chen 2014        | Comparisons do not fulfil inclusion criteria (heparin vs NaCl 10%)                           |
| Cheronis 2013    | Comparisons do not fulfil inclusion criteria (heparin vs trimethoprim + EDTA + ethanol)      |
| Chu 2009         | Comparisons do not fulfil inclusion criteria (heparin vs heparin + gentamicin)               |
| Clifton 1991     | Interventions do not fulfil inclusion criteria (heparin continuous flush)                    |
| Coli 2006        | Interventions do not fulfil inclusion criteria (oral anticoagulant drugs)                    |
| Conte 2003       | Interventions do not fulfil inclusion criteria (systemic low molecular weight heparin)       |
| Coplon 2007      | Comparisons do not fulfil inclusion criteria (heparin vs gentamicin + citrate)               |
| Corbett 2013     | Comparisons do not fulfil inclusion criteria (heparin vs taurolidine + heparin + citrate)    |
| Cortes 2006      | Comparisons do not fulfil inclusion criteria (heparin vs minocycline + EDTA)                 |
| Daniell 1973     | Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)    |
| Davanipur 2011   | Comparison does not fulfil inclusion criteria (heparin vs cloxacillin + heparin)             |
| De Cicco 2009    | Interventions do not fulfil inclusion criteria (acenocoumarin vs dalteparin vs no treatment) |
| de la Torre 2012 | Peripheral catheters were used   |
| del Cotillo 2008 | Interventions do not fulfil inclusion criteria (arterial catheters)                          |

(Continued)

|                                  |   |
|----------------------------------|---|
| <a href="#">del Pozo 2012</a>    | Interventions do not fulfil inclusion criteria (comparison of antibiotic concentrations)    |
| <a href="#">Dogra 2002</a>       | Comparison interventions do not fulfil inclusion criteria (heparin vs gentamicin + citrate) |
| <a href="#">Donham 1987</a>      | Peripheral catheters were used  |
| <a href="#">Duncan 2005</a>      | Comparison interventions do not fulfil inclusion criteria (heparin vs citrate)              |
| <a href="#">Duncan 2010</a>      | Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)                       |
| <a href="#">Dunser 2005</a>      | Interventions do not fulfil inclusion criteria (coated vs non-coated catheters)             |
| <a href="#">Eloy 1987</a>        | Interventions do not fulfil inclusion criteria (catheter comparison)                        |
| <a href="#">Epperson 1984</a>    | Interventions do not fulfil inclusion criteria (peripheral catheters)                       |
| <a href="#">Garay Rubio 2011</a> | Peripheral catheters were used  |
| <a href="#">Garrelts 1989</a>    | Peripheral catheters were used  |
| <a href="#">Glaspy 2000</a>      | Interventions do not fulfil inclusion criteria (systemic dalteparin)                        |
| <a href="#">Goh 2011</a>         | Interventions do not fulfil inclusion criteria (IV continuous heparin administration)       |
| <a href="#">Goode 1993</a>       | Peripheral catheters were used  |
| <a href="#">Griffin 2005</a>     | Interventions do not fulfil inclusion criteria (papaverine)                                 |
| <a href="#">Grosso 1989</a>      | Interventions do not fulfil inclusion criteria (calcium heparin)                            |
| <a href="#">Gyr 1995</a>         | Interventions do not fulfil inclusion criteria (peripheral catheters)                       |
| <a href="#">Hall 2006</a>        | Interventions do not fulfil inclusion criteria (continuous flush)                           |
| <a href="#">Hamilton 1988</a>    | Peripheral catheters were used  |
| <a href="#">Han 2016</a>         | Interventions do not fulfil inclusion criteria (low vs high doses of heparin)               |
| <a href="#">Harter 2002</a>      | Interventions do not fulfil inclusion criteria (coated vs non-coated catheters)             |
| <a href="#">Haynes 2002</a>      | Interventions do not fulfil inclusion criteria (SC device)                                  |
| <a href="#">Hemmelgarn 2011</a>  | Comparison interventions do not fulfil inclusion criteria (heparin vs alteplase)            |
| <a href="#">Hendrickx 2001</a>   | Comparison interventions do not fulfil inclusion criteria (citrate vs heparin)              |
| <a href="#">Heng 2011</a>        | Interventions do not fulfil inclusion criteria (ethanol lock)                               |

(Continued)

|   |   |
|---|---|
| <a href="#">HGU Gregorio Marañón 2010</a> | Comparisons do not fulfil inclusion criteria (heparin vs ethanol)                             |
| <a href="#">Hoffer 1999</a>               | Interventions do not fulfil inclusion criteria (valved vs non-valved catheters)               |
| <a href="#">Horne 1995</a>                | Comparison interventions do not fulfil inclusion criteria (heparin vs lepirudin)              |
| <a href="#">Hryszko 2013</a>              | Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)         |
| <a href="#">Hu 2011</a>                   | Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)         |
| <a href="#">Imamovic 2009</a>             | Comparisons do not fulfil inclusion criteria (heparin vs citrate)                             |
| <a href="#">Ishii 2013</a>                | Interventions do not fulfil inclusion criteria (heparin continuous administration)            |
| <a href="#">Israel Ministry of Health</a> | Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)                         |
| <a href="#">Jasinsky 2007</a>             | Interventions do not fulfil inclusion criteria (antireflux device)                            |
| <a href="#">Jeppesen 2013</a>             | Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)                         |
| <a href="#">Johnson 2002</a>              | Interventions do not fulfil inclusion criteria (mupirocin)                                    |
| <a href="#">Jonkers 2012</a>              | Comparison interventions do not fulfil inclusion criteria (heparin vs taurolidine)            |
| <a href="#">Jowett 1986</a>               | Peripheral catheters were used  |
| <a href="#">Kankanala 2012</a>            | Comparison does not fulfil inclusion criteria (heparin vs citrate)                            |
| <a href="#">Karthus 2006</a>              | Interventions do not fulfil inclusion criteria (systemic dalteparin)                          |
| <a href="#">Kokenge 2010</a>              | Comparison does not fulfil inclusion criteria (heparin vs citrate)                            |
| <a href="#">Kovacs 2005</a>               | Interventions do not fulfil inclusion criteria (systemic dalteparin)                          |
| <a href="#">Kudsk 1985</a>                | Interventions do not fulfil inclusion criteria (heparin administered in continuous perfusion) |
| <a href="#">Kulkarni 1994</a>             | Interventions do not fulfil inclusion criteria (continuous flush)                             |
| <a href="#">Lacasaña Bellmunt 2006</a>    | Peripheral catheters were used  |
| <a href="#">Lavau-Denes 2013</a>          | Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)     |
| <a href="#">Le 2003</a>                   | Interventions do not fulfil inclusion criteria (dressings)                                    |
| <a href="#">Leslie 1996</a>               | Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)         |
| <a href="#">Liang 1998</a>                | Peripheral catheters were used  |



(Continued)

|                      |  |
|----------------------|--|
| Liang 2015           | Interventions do not fulfil inclusion criteria (2 heparin doses were compared)   |
| Liao 2002            | Peripheral catheters were used   |
| Lindblad 1994        | Interventions do not fulfil inclusion criteria (systemic heparin)  |
| Lok 2007             | Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate)  |
| Long 2006            | Interventions do not fulfil inclusion criteria (heparin-bonded catheters)  |
| Lustig 2011          | Comparisons do not fulfil inclusion criteria (heparin vs citrate + ethanol + methylene blue)   |
| Macrae 2008          | Comparison does not fulfil inclusion criteria (heparin vs citrate)   |
| Maki 2011            | Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate + methylene blue + methylparaben + propylparaben) |
| Malo 2010            | Comparison interventions do not fulfil inclusion criteria (heparin vs tinzaparin)  |
| Marin 2000           | Interventions do not fulfil inclusion criteria (heparin-bonded catheters)  |
| McIntyre 2004        | Comparison interventions do not fulfil inclusion criteria (heparin vs heparin + gentamicin)  |
| Meier 2011           | Interventions do not fulfil inclusion criteria (catheter comparison)   |
| Meyer 1995           | Interventions do not fulfil inclusion criteria (peripheral catheters)  |
| Mismetti 2003        | Interventions do not fulfil inclusion criteria (systemic dalteparin)   |
| Monreal 1996         | Interventions do not fulfil inclusion criteria (systemic nadroparin)   |
| Moran 2012           | Comparison interventions do not fulfil inclusion criteria (gentamicin + citrate vs heparin)  |
| Mortazavi 2011       | Comparison interventions do not fulfil inclusion criteria (heparin vs heparin + cefotaxime)  |
| Mudge 1998           | Interventions do not fulfil inclusion criteria (peripheral catheters)  |
| Na 2012              | Arterial catheters were used   |
| NCT03114722          | Comparison does not fulfil inclusion criteria (heparin vs citrate)   |
| Niers 2007           | Interventions do not fulfil inclusion criteria (systemic nadroparin)   |
| Niesen 2003          | Interventions do not fulfil inclusion criteria (peripheral catheters)  |
| Nieto-Rodriguez 1992 | Peripheral catheters were used   |

(Continued)

|                           |  |
|---------------------------|--|
| NIH Clinical Centers 2002 | Comparisons do not fulfil inclusion criteria (heparin vs lepirudin)  |
| Nori 2006                 | Comparison does not fulfil inclusion criteria (gentamicin vs minocycline)  |
| Oguzhan 2012              | Interventions do not fulfil inclusion criteria (heparin + NaCl 26% vs heparin)   |
| Oran 2008                 | Comparison interventions do not fulfil inclusion criteria (heparin lock 3 times a week vs heparin lock 6 times a week) |
| Periard 2008              | Interventions do not fulfil inclusion criteria (catheter comparison)   |
| Pervez 2002               | Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate + gentamicin)                     |
| Phulara 2018              | Peripheral catheters were used   |
| Pouw 1995                 | Interventions do not fulfil inclusion criteria (systemic heparin)  |
| Power 2009                | Comparison interventions do not fulfil inclusion criteria (heparin vs citrate)   |
| Quenot 2013               | Comparisons do not fulfil inclusion criteria (heparin vs citrate)  |
| Rajani 1979               | Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)                              |
| Randon 2006               | Comparisons do not fulfil inclusion criteria (heparin vs non-needle system)  |
| Ray 1999                  | Comparison interventions do not fulfil inclusion criteria (heparin vs urokinase)                                       |
| Reichardt 2002            | Interventions do not fulfil inclusion criteria (systemic heparin)  |
| Rijnders 2005             | Interventions do not fulfil inclusion criteria (antibiotics vs placebo)  |
| Roberts 1994              | Peripheral catheters were used   |
| Ruggiero 1983             | Interventions do not fulfil inclusion criteria (heparin continuous)  |
| Sanders 2008              | Comparison interventions do not fulfil inclusion criteria (heparin vs ethanol)   |
| Sang Sook 2012            | Arterial catheters were used   |
| Saxena 2006               | Comparison does not fulfil inclusion criteria (heparin vs cefotaxime + heparin)  |
| Saxena 2006a              | Comparison does not fulfil inclusion criteria (heparin vs cefotaxime + heparin)  |
| Scherr 2002               | Arterial catheters were used   |
| Schouten 2013             | Comparisons do not fulfil inclusion criteria (heparin vs citrate)  |

(Continued)

|                  |  |
|------------------|--|
| Schroder 2008    | Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)  |
| Shirzad 2013     | Comparisons do not fulfil inclusion criteria (heparin vs heparin + cefazolin)  |
| Silva 2008       | Interventions do not fulfil inclusion criteria (antibiotic ointment vs antibiotic lock)  |
| Silva 2013       | Comparison does not fulfil inclusion criteria (heparin vs heparin + cefazolin + gentamicin)  |
| Smith 1990       | Interventions do not fulfil inclusion criteria (heparin lock left in place)  |
| Sofroniadou 2012 | Comparison does not fulfil inclusion criteria (heparin vs heparin + vancomycin vs heparin + linezolid)   |
| Solomon 2001     | Comparison does not fulfil inclusion criteria (heparin vs urokinase)   |
| Solomon 2010     | Comparison does not fulfil inclusion criteria (heparin vs taurolidine + citrate)   |
| Stas 2001        | Comparison does not fulfil inclusion criteria (heparin vs citrate)   |
| Thomson 2011     | Comparison interventions do not fulfil inclusion criteria (different concentrations of heparin)  |
| Thurlimann 1992  | Interventions do not fulfil inclusion criteria (peripheral catheters)  |
| Tolar 1996       | Interventions do not fulfil inclusion criteria (no heparin use)  |
| Trottier 1995    | Interventions do not fulfil inclusion criteria (different catheterisation sites)   |
| Tuncali 2005     | Interventions do not fulfil inclusion criteria (arterial catheters, continuous flushing)   |
| Tuten 1991       | Peripheral catheters were used   |
| Venditto 2010    | Comparison interventions do not fulfil inclusion criteria (heparin vs citrate vs heparin + gentamicin)   |
| Vercaigne 2011   | Comparisons do not fulfil inclusion criteria (heparin vs citrate + ethanol)  |
| Verso 2005       | Interventions do not fulfil inclusion criteria (systemic enoxaparin)   |
| Wang 2012        | Peripheral catheters were used   |
| Warkentin 1998   | Although designed as an RCT, we contacted study authors as insufficient information was provided and the study has never been published; we received no response |
| Weijmer 2005     | Comparison does not fulfil inclusion criteria (heparin vs citrate)   |
| Whitta 2006      | Interventions do not fulfil inclusion criteria (continuous heparin flushing)   |
| Witkowski 2010   | Arterial catheters were used   |

(Continued)

|                 |  |
|-----------------|--|
| Wolf 2011       | Comparisons do not fulfil inclusion criteria (heparin vs ethanol)  |
| Wong 2009       | Interventions do not fulfil inclusion criteria (heparin 2500 IU/mL vs heparin 500 IU/mL vs sodium citrate + glucose)   |
| Xu 2017         | Peripheral catheters were used   |
| Young 2009      | Interventions do not fulfil inclusion criteria (warfarin)  |
| Zacharski 2005  | Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)  |
| Zhang 2009      | Interventions do not fulfil inclusion criteria (heparin vs gentamicin + heparin)   |
| Ziyaeifard 2015 | Data were not stratified by arterial and central venous catheters. We received no response to request for additional data, so we were unable to use the published data |

EDTA: ethylenediaminetetraacetic acid.

RCT: randomised controlled trial.

SC: subcutaneous.

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

#### Klein 2017

|               |   |
|---------------|---|
| Methods       |   |
| Participants  |   |
| Interventions |   |
| Outcomes      |   |
| Notes         | Publication is abstract only, does not contain data, further information is required from study authors |

#### Klein 2018

|               |  |
|---------------|--|
| Methods       |  |
| Participants  |  |
| Interventions |  |
| Outcomes      |  |

|       |   |
|-------|---|
| Notes | Awaiting full copy of publication, abstract does not contain data, further information is required from study authors |
|-------|---|

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

#### NCT02354118

|                     |   |
|---------------------|---|
| Trial name or title | Maintaining Patency in Implanted Port Catheters   |
| Methods             | RCT   |
| Participants        | Estimated enrolment: 396<br>Inclusion criteria: <ul style="list-style-type: none"> <li>• Able to read and understand English</li> <li>• Has an implanted port in place less than 1 year</li> <li>• Evidence of a patent (unobstructed) port catheter before enrolment in the study</li> <li>• Is receiving active treatment (i.e. is receiving a therapeutic drug through the implanted port)</li> <li>• Current treatment protocol projected to continue for a minimum of 3 months</li> <li>• Anticipates receiving care at identified centres for 12 months following enrolment in the study</li> <li>• Does not receive care for implanted port at any other facility</li> </ul> |
| Interventions       | Control group (active comparator): control group will have port catheters flushed with 20 mL saline and after with 5 mL heparin 100 units/mL each 3 months<br>Intervention group (experimental): saline-only catheter flush. Intervention group will have port catheters flushed with saline only   |
| Outcomes            | Occlusion, days without obstruction, safety   |
| Starting date       | 29 January 2015   |
| Contact information | Partusch S  |
| Notes               | Recruiting participants   |

#### NCT02923830

|                     |   |
|---------------------|---|
| Trial name or title | Maintaining Patency in BioFlo Implanted Port Catheters With Saline Only Flushes   |
| Methods             | RCT open-label phase 4  |
| Participants        | 396 participants<br>Inclusion criteria: <ul style="list-style-type: none"> <li>• Able to read and understand English</li> <li>• Has a BioFlo implanted port in place less than 1 year</li> <li>• Evidence of a patent BioFlo port catheter before enrolment in the study</li> <li>• Is receiving active treatment (i.e. is receiving a therapeutic drug) through the BioFlo implanted port</li> <li>• Current treatment protocol projected to continue for a minimum of 3 months</li> </ul> |

|                     |  |
|---------------------|--|
|                     | <ul style="list-style-type: none"> <li>• Anticipates receiving care at identified centres for 12 months following enrolment in the study</li> <li>• Does not receive care for BioFlo implanted port at any other facility</li> </ul> |
| Interventions       | Active comparator: heparinised saline catheter flush; port catheters flushed with 20 mL saline + 5 mL heparin 100 units/mL<br>Experimental: saline-only catheter flush: port catheters flushed with saline only                      |
| Outcomes            | Occlusion, days without obstruction, safety  |
| Starting date       | 30 September 2016  |
| Contact information | Partusch S   |
| Notes               | Recruiting participants  |

**RBR-3ht499**

|                     |   |
|---------------------|---|
| Trial name or title | Efetividade da Solução de Heparina na Prevenção de Oclusão do Cateter de Hickman®: Ensaio Clínico [Effectiveness of Heparin Solution in Preventing Hickman® Catheter Occlusion: Clinical Trial]   |
| Methods             | RCT triple-blind  |
| Participants        | 100 patients with CVC who need haematopoietic stem cell transplantation   |
| Interventions       | Solutions to be compared will be 0.9% saline solution and heparin solution 50 IU/mL. There will be 50 participants for group A and 50 participants for group B. After insertion of the catheter, each time it is deprecated, it will be blocked with solution A or B, according to randomisation  |
| Outcomes            | “The evaluation will be done when opening the catheter path, where it should be aspirated pre-defined intraluminal content, being 2 mL for adult and 1 mL for child. The reflux should occur in up to four attempts, then: open the clamp and aspirate the contents; Inspect mechanical causes such as fracture, torsion or traction; ask the patient to inhale and hold the air; And hyperextend the patient’s neck and ask to place the corresponding hand on the side of the catheter insert in the occipital region. If there is no reflux after the four attempts described above, the catheter must be rinsed without forcing. If, when injecting saline solution 0.9% into the lumen of the catheter, the flow occurs without resistance, the follow-up is closed by occlusion without reflux. Or, if after the four attempts of reflux, the lavage with 0.9% saline is not performed in the lumen of the catheter, that if resistance / pressure is present for the washing, the follow-up of the route by complete occlusion. In the cases of complete occlusion or occlusion without reflux, the follow-up is completed, the standardized clearing maneuver is performed in the service and afterwards the standard locking solution of the service is used. The procedure will be the same for both groups.” |
| Starting date       | <ul style="list-style-type: none"> <li>• Planned date of first enrolment: 22-03-2017</li> <li>• Planned date of last enrolment: 20-10-2017</li> </ul>   |
| Contact information | Sandra Regina da Silva<br>Address: Rua Congo, 271<br>Pinhais<br>Brazil 8320-320   |

|       |  |
|-------|--|
|       | Phone: +55 (41) 99199.2470<br>E-mail: sandra_silvah@yahoo.com.br<br>Universidade Federal do Paraná |
| Notes |  |

CVC: central venous catheter.

RCT: randomised controlled trial.

## DATA AND ANALYSES

### Comparison 1. All occlusions

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method               | Effect size       |
|---------------------------|----------------|---------------------|----------------------------------|-------------------|
| 1 All studies             | 10             | 2697                | Risk Ratio (M-H, Random, 95% CI) | 0.70 [0.51, 0.95] |
| 1.1 Participants          | 7              | 1672                | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.58, 1.08] |
| 1.2 Catheters             | 3              | 1025                | Risk Ratio (M-H, Random, 95% CI) | 0.53 [0.29, 0.95] |

### Comparison 2. Occlusion of CVCs

| Outcome or subgroup title                          | No. of studies | No. of participants | Statistical method               | Effect size         |
|--|----------------|---------------------|----------------------------------|---------------------|
| 1 Occlusion of CVCs (unit of analysis participant) | 7              | 1672                | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.58, 1.08]   |
| 2 Occlusion of CVCs (unit of analysis catheter)    | 3              | 1025                | Risk Ratio (M-H, Random, 95% CI) | 0.53 [0.29, 0.95]   |
| 3 Occlusion of CVCs (unit of analysis line access) | 1              |                     | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Comparison 3. All patency

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method                   | Effect size        |
|---------------------------|----------------|---------------------|--------------------------------------|--------------------|
| 1 All studies             | 6              | 1788                | Mean Difference (IV, Random, 95% CI) | 0.44 [-0.10, 0.99] |
| 1.1 Participants          | 4              | 1036                | Mean Difference (IV, Random, 95% CI) | 0.66 [-0.66, 1.97] |
| 1.2 Catheters             | 2              | 752                 | Mean Difference (IV, Random, 95% CI) | 0.40 [-0.20, 0.99] |

### Comparison 4. Duration of catheter patency

| Outcome or subgroup title                                     | No. of studies | No. of participants | Statistical method                   | Effect size        |
|---|----------------|---------------------|--------------------------------------|--------------------|
| 1 Duration of catheter patency (unit of analysis participant) | 4              | 1036                | Mean Difference (IV, Random, 95% CI) | 0.66 [-0.66, 1.97] |
| 2 Duration of catheter patency (unit of analysis catheter)    | 2              | 752                 | Mean Difference (IV, Random, 95% CI) | 0.40 [-0.20, 0.99] |



### Comparison 5. Safety

| Outcome or subgroup title          | No. of studies | No. of participants | Statistical method               | Effect size        |
|------------------------------------|----------------|---------------------|----------------------------------|--------------------|
| 1 CVC-related sepsis               | 2              | 1097                | Risk Ratio (M-H, Random, 95% CI) | 0.74 [0.03, 19.54] |
| 2 Mortality                        | 3              | 1100                | Risk Ratio (M-H, Random, 95% CI) | 0.76 [0.44, 1.31]  |
| 3 Haemorrhage from any site        | 4              | 1245                | Risk Ratio (M-H, Random, 95% CI) | 1.32 [0.57, 3.07]  |
| 4 Heparin-induced thrombocytopenia | 3              | 443                 | Risk Ratio (M-H, Random, 95% CI) | 0.21 [0.01, 4.27]  |
| 5 CVC-related thrombosis           | 3              | 1527                | Risk Ratio (M-H, Random, 95% CI) | 1.24 [0.77, 2.02]  |

### Comparison 6. Sensitivity analysis

| Outcome or subgroup title                        | No. of studies | No. of participants | Statistical method               | Effect size        |
|--|----------------|---------------------|----------------------------------|--------------------|
| 1 Occlusion of CVCs related to quality           | 10             | 2697                | Risk Ratio (M-H, Random, 95% CI) | 0.70 [0.51, 0.95]  |
| 1.1 Poor or unclear allocation concealment       | 6              | 666                 | Risk Ratio (M-H, Random, 95% CI) | 0.39 [0.16, 0.95]  |
| 1.2 Good allocation concealment                  | 4              | 2031                | Risk Ratio (M-H, Random, 95% CI) | 0.74 [0.51, 1.05]  |
| 2 Occlusion of CVCs related to weight of studies | 6              | 870                 | Risk Ratio (M-H, Random, 95% CI) | 0.52 [0.30, 0.91]  |
| 2.1 Without most weighted study (Goosens)        | 6              | 870                 | Risk Ratio (M-H, Random, 95% CI) | 0.52 [0.30, 0.91]  |
| 3 All occlusions effect size                     | 10             |                     | Risk Ratio (Random, 95% CI)      | 0.78 [0.62, 0.98]  |
| 3.1 Participants                                 | 7              |                     | Risk Ratio (Random, 95% CI)      | 0.84 [0.65, 1.08]  |
| 3.2 Catheters                                    | 3              |                     | Risk Ratio (Random, 95% CI)      | 0.54 [0.31, 0.96]  |
| 4 All patency effect size                        | 6              |                     | Mean Difference (Random, 95% CI) | 0.44 [-0.10, 0.99] |
| 4.1 Participants                                 | 4              |                     | Mean Difference (Random, 95% CI) | 0.66 [-0.66, 1.97] |
| 4.2 Catheter                                     | 2              |                     | Mean Difference (Random, 95% CI) | 0.40 [-0.20, 0.99] |

### Comparison 7. Analysis of subgroups

| Outcome or subgroup title                                 | No. of studies | No. of participants | Statistical method               | Effect size       |
|---|----------------|---------------------|----------------------------------|-------------------|
| 1 Occlusion of CVCs oncology vs non-oncology participants | 10             | 2697                | Risk Ratio (M-H, Random, 95% CI) | 0.70 [0.51, 0.95] |
| 1.1 Non-oncological participants                          | 8              | 1465                | Risk Ratio (M-H, Random, 95% CI) | 0.48 [0.30, 0.77] |
| 1.2 Oncological participants                              | 2              | 1232                | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.69, 1.19] |

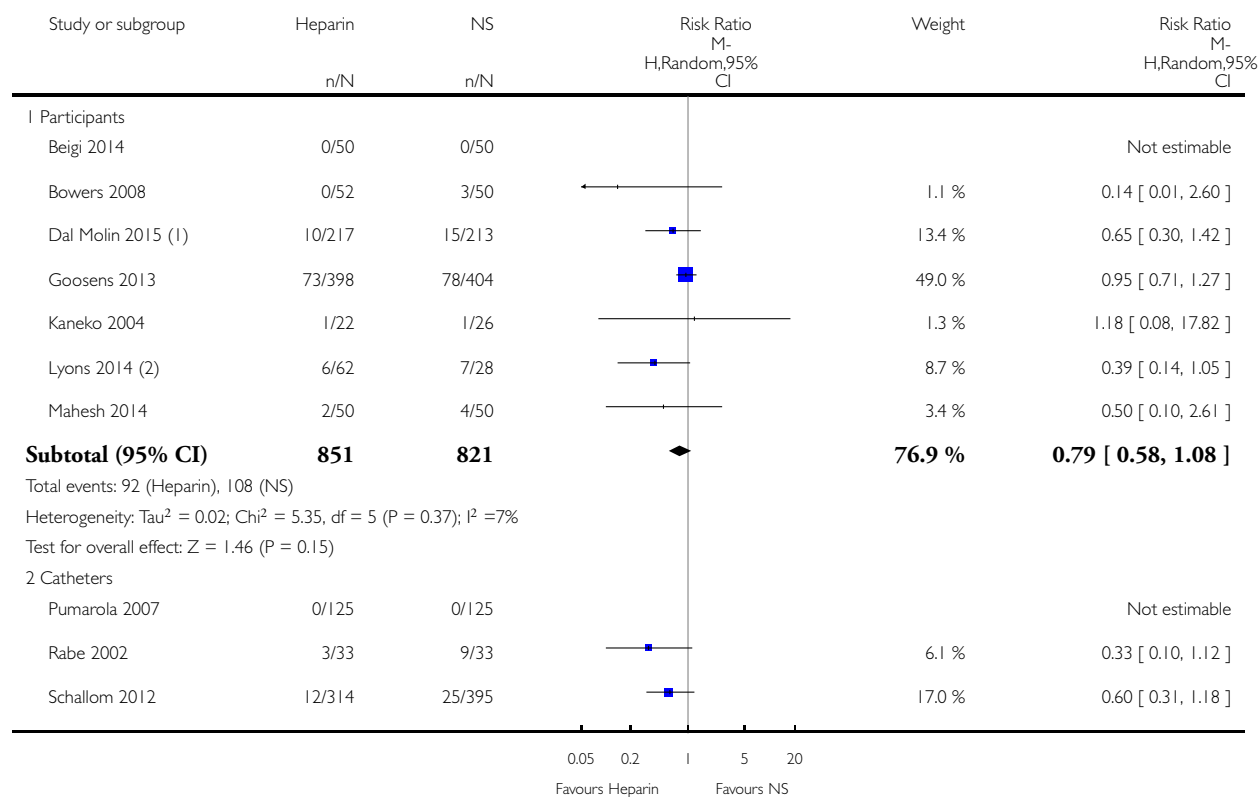
|  |    |      |                                  |                   |
|--|----|------|----------------------------------|-------------------|
| 2 Occlusion of CVCs number of lumens (unit of analysis participants) | 6  | 1582 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.68, 1.15] |
| 2.1 One lumen  | 3  | 1334 | Risk Ratio (M-H, Random, 95% CI) | 0.85 [0.57, 1.26] |
| 2.2 More than one lumen  | 3  | 248  | Risk Ratio (M-H, Random, 95% CI) | 0.63 [0.15, 2.59] |
| 3 All occlusions - heparin concentration                             | 10 | 2497 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.32, 1.20] |
| 3.1 Heparin $\geq$ 1000 IU/mL  | 3  | 214  | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.14, 1.25] |
| 3.2 Heparin < 1000 IU/mL   | 7  | 2283 | Risk Ratio (M-H, Random, 95% CI) | 0.65 [0.31, 1.34] |
| 4 Occlusion of CVCs and time to follow-up                            | 10 |      | Risk Ratio (M-H, Random, 95% CI) | Subtotals only    |
| 4.1 Less than one month  | 8  | 1465 | Risk Ratio (M-H, Random, 95% CI) | 0.48 [0.30, 0.77] |
| 4.2 One month or longer  | 2  | 1232 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.69, 1.19] |

### Analysis 1.1. Comparison 1 All occlusions, Outcome 1 All studies.

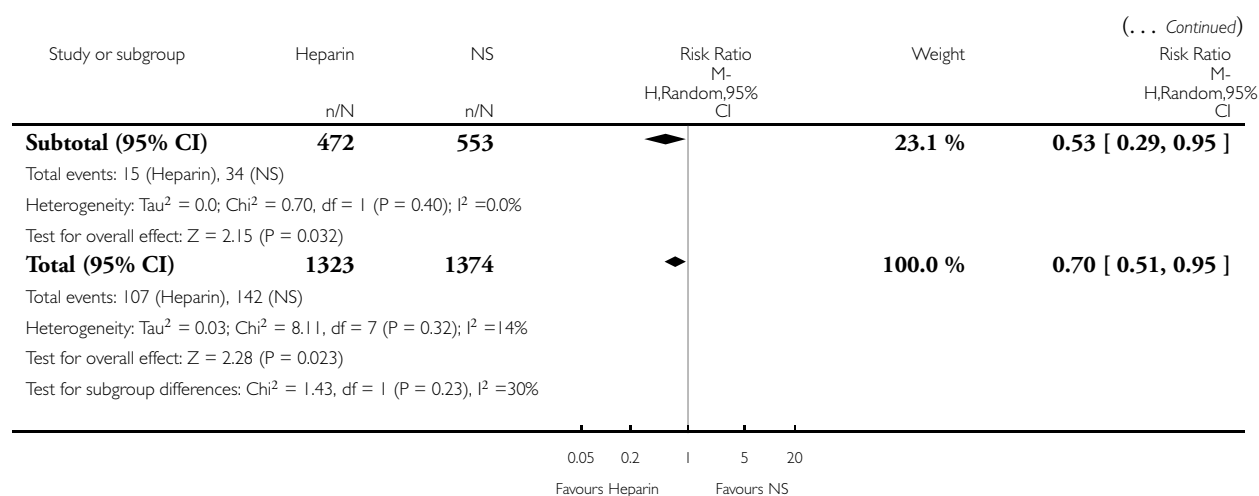
Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 1 All occlusions

Outcome: 1 All studies



(Continued ...)



(1) The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in the saline group

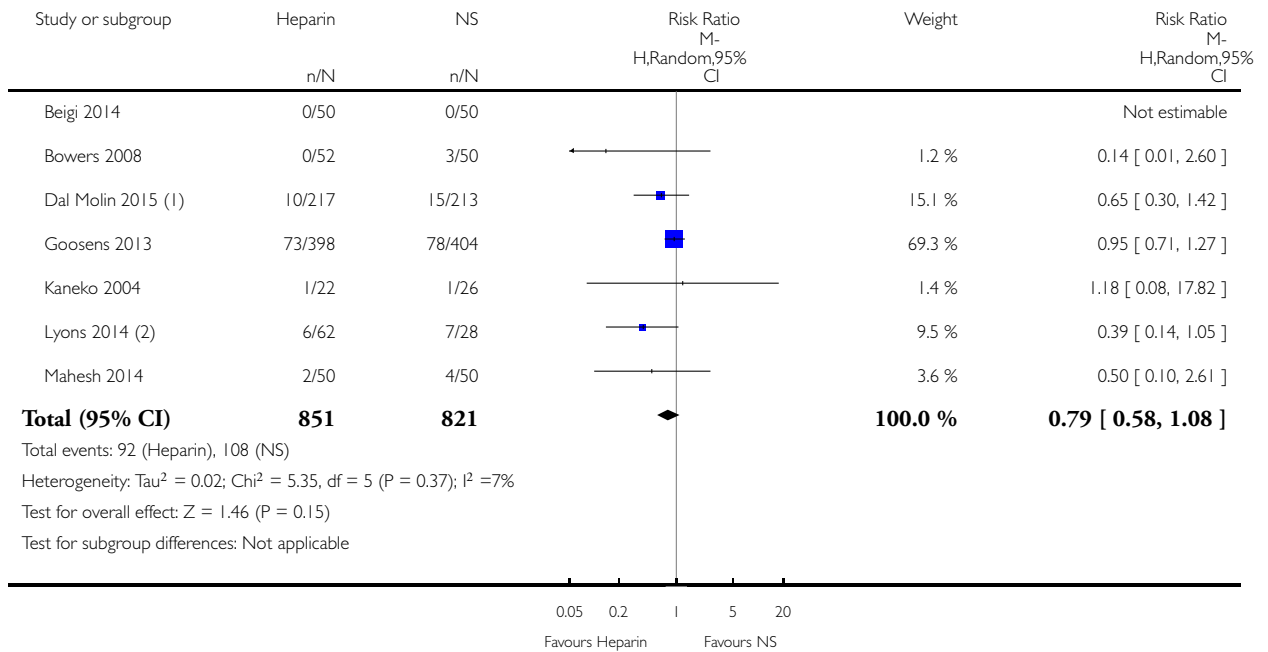
(2) We combined results from low and high dose heparin groups

## Analysis 2.1. Comparison 2 Occlusion of CVCs, Outcome 1 Occlusion of CVCs (unit of analysis participant).

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 2 Occlusion of CVCs

Outcome: 1 Occlusion of CVCs (unit of analysis participant)



(1) The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in the saline group

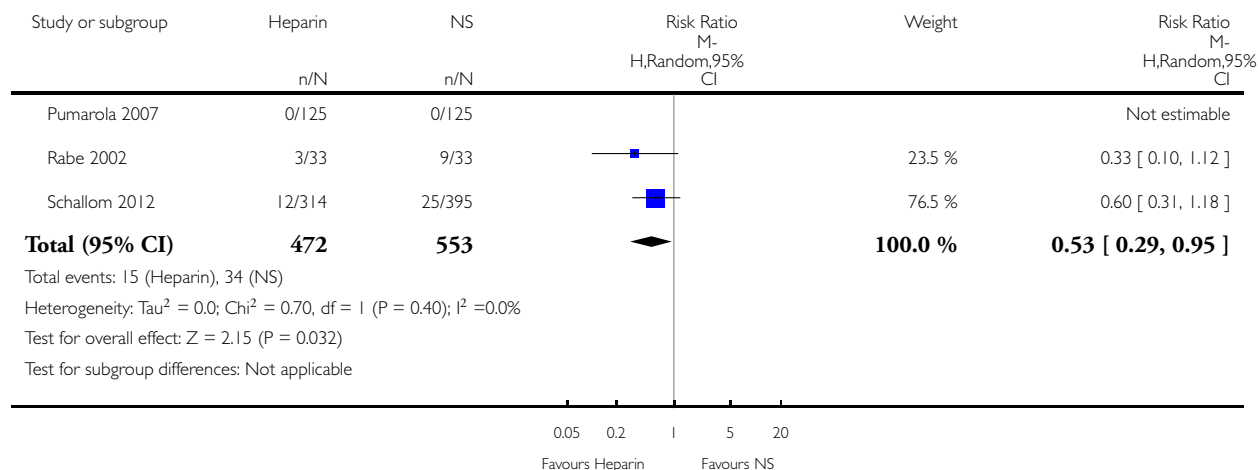
(2) We combined results from low and high dose heparin groups

## Analysis 2.2. Comparison 2 Occlusion of CVCs, Outcome 2 Occlusion of CVCs (unit of analysis catheter).

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 2 Occlusion of CVCs

Outcome: 2 Occlusion of CVCs (unit of analysis catheter)



## Analysis 2.3. Comparison 2 Occlusion of CVCs, Outcome 3 Occlusion of CVCs (unit of analysis line access).

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 2 Occlusion of CVCs

Outcome: 3 Occlusion of CVCs (unit of analysis line access)

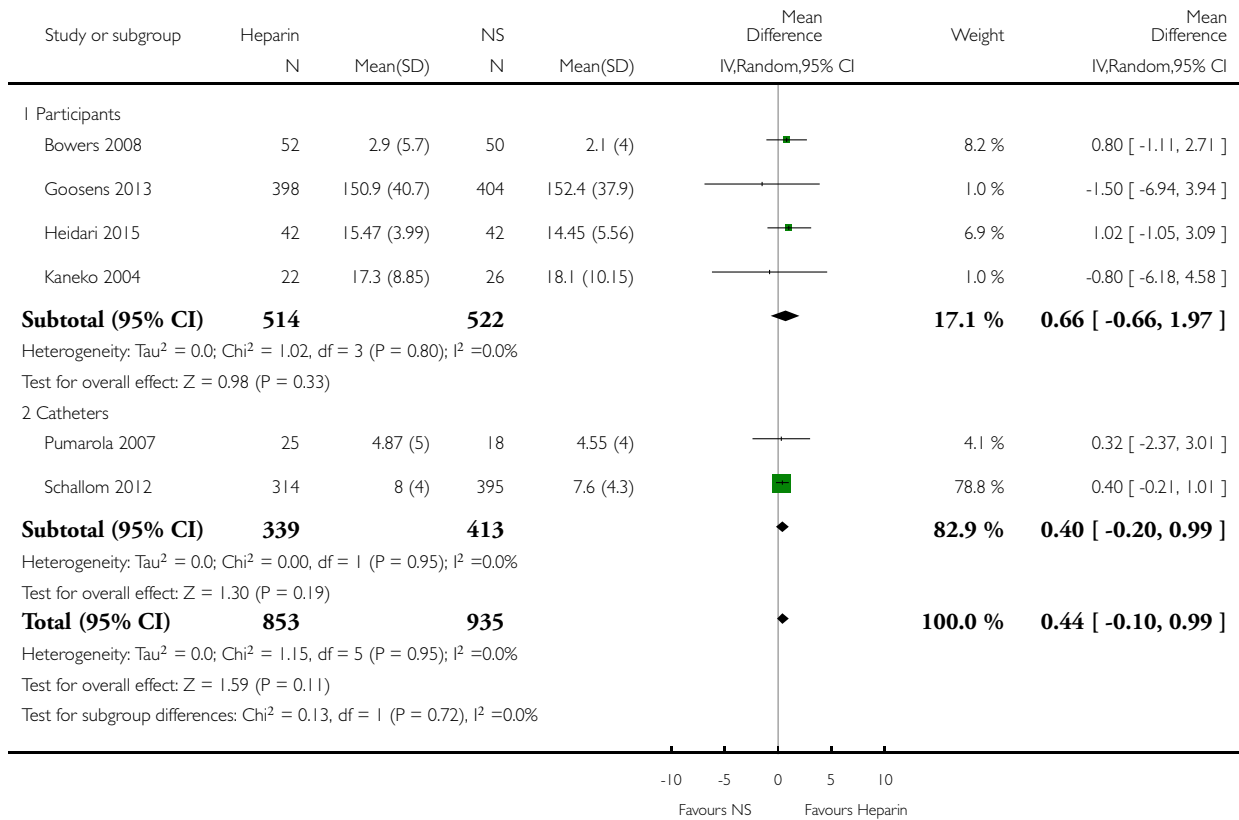


### Analysis 3.1. Comparison 3 All patency, Outcome 1 All studies.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 3 All patency

Outcome: 1 All studies

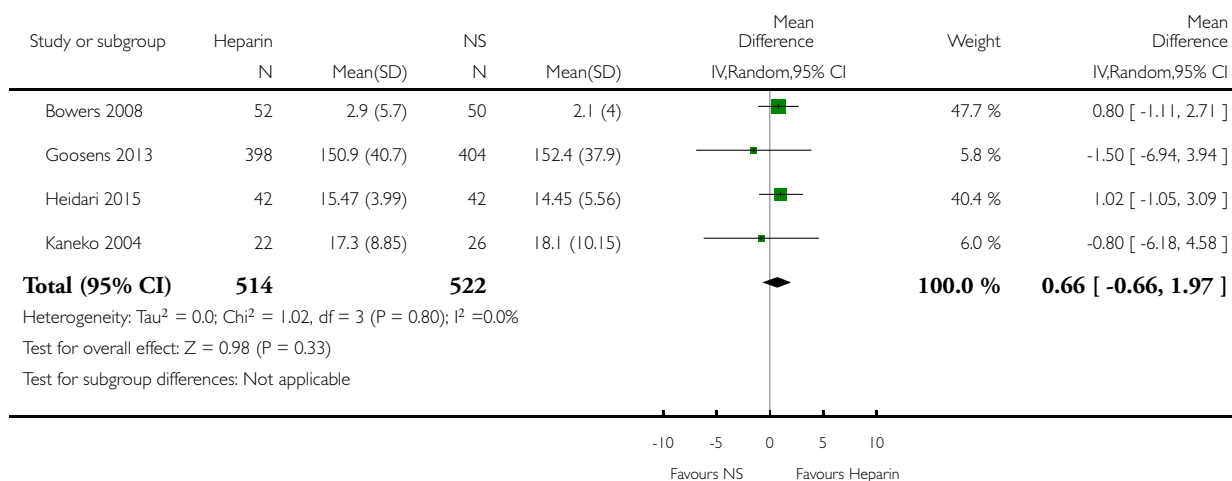


#### Analysis 4.1. Comparison 4 Duration of catheter patency, Outcome 1 Duration of catheter patency (unit of analysis participant).

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 4 Duration of catheter patency

Outcome: 1 Duration of catheter patency (unit of analysis participant)

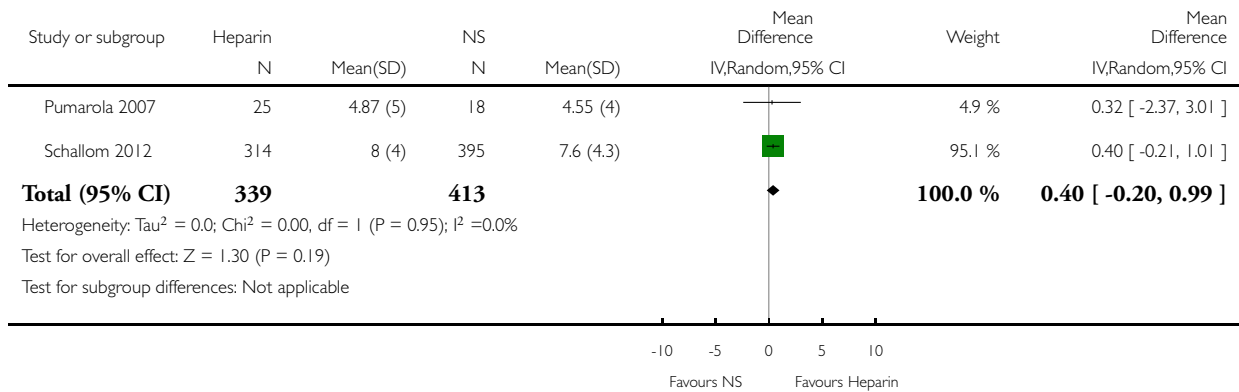


## Analysis 4.2. Comparison 4 Duration of catheter patency, Outcome 2 Duration of catheter patency (unit of analysis catheter).

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 4 Duration of catheter patency

Outcome: 2 Duration of catheter patency (unit of analysis catheter)



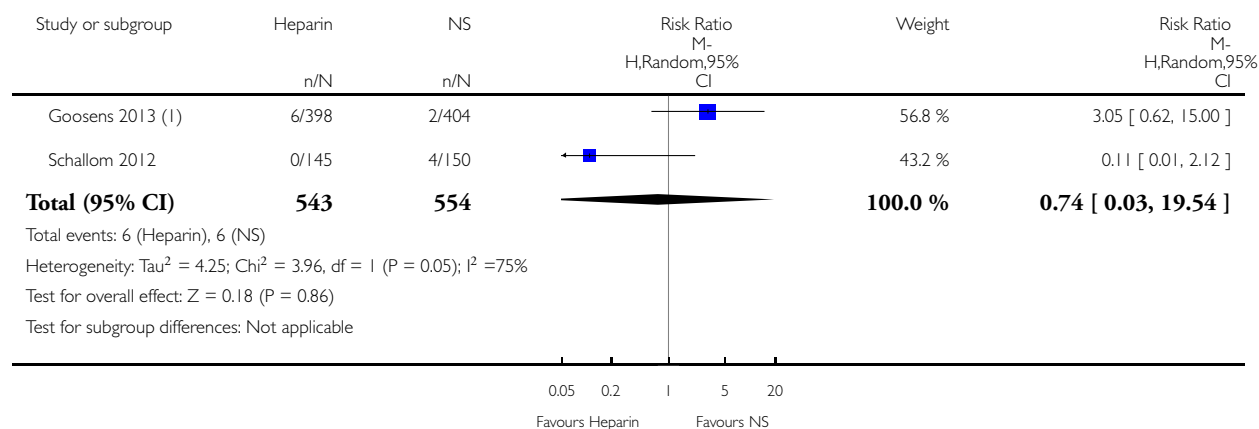


### Analysis 5.1. Comparison 5 Safety, Outcome 1 CVC-related sepsis.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 5 Safety

Outcome: 1 CVC-related sepsis



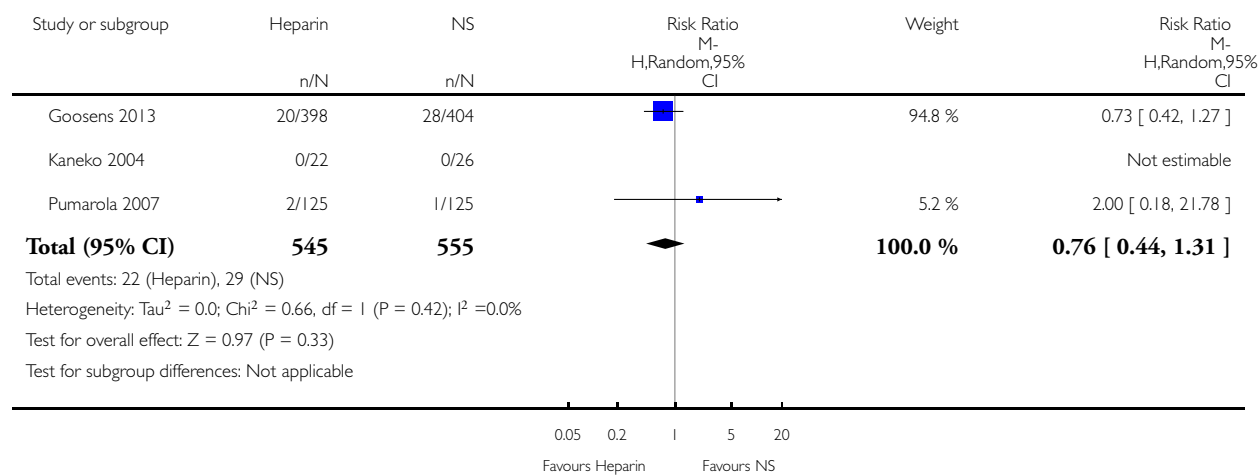
(1) Staphylococcus aureus 2, Staphylococcus epidermidis 3, Candida glabrata 1 in heparin group and Staphylococcus epidermidis 1 and Staphylococcus homini 1 in saline group

## Analysis 5.2. Comparison 5 Safety, Outcome 2 Mortality.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 5 Safety

Outcome: 2 Mortality

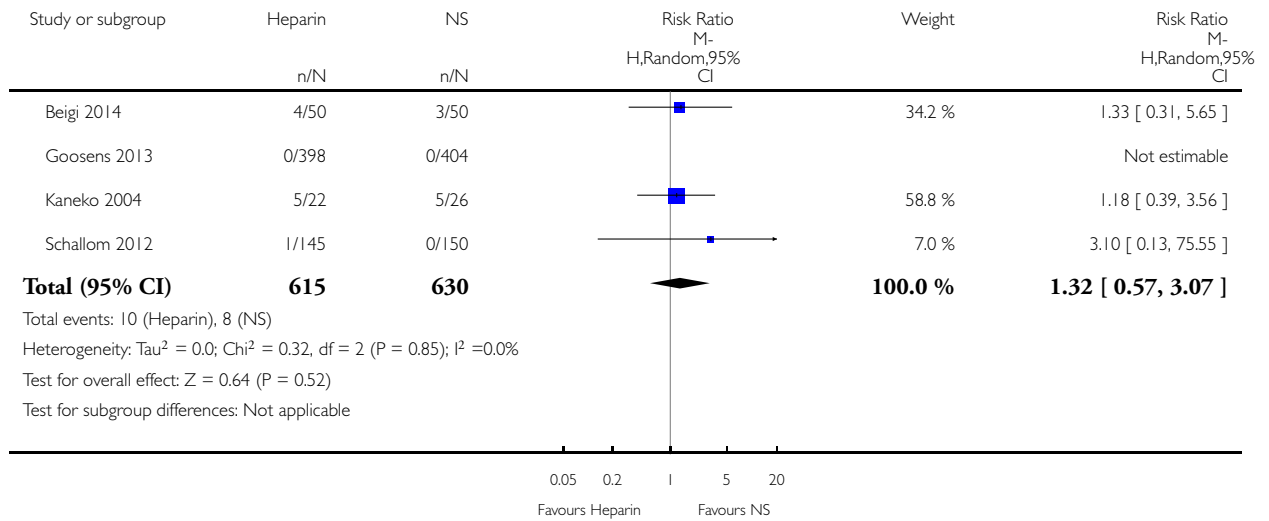


### Analysis 5.3. Comparison 5 Safety, Outcome 3 Haemorrhage from any site.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 5 Safety

Outcome: 3 Haemorrhage from any site

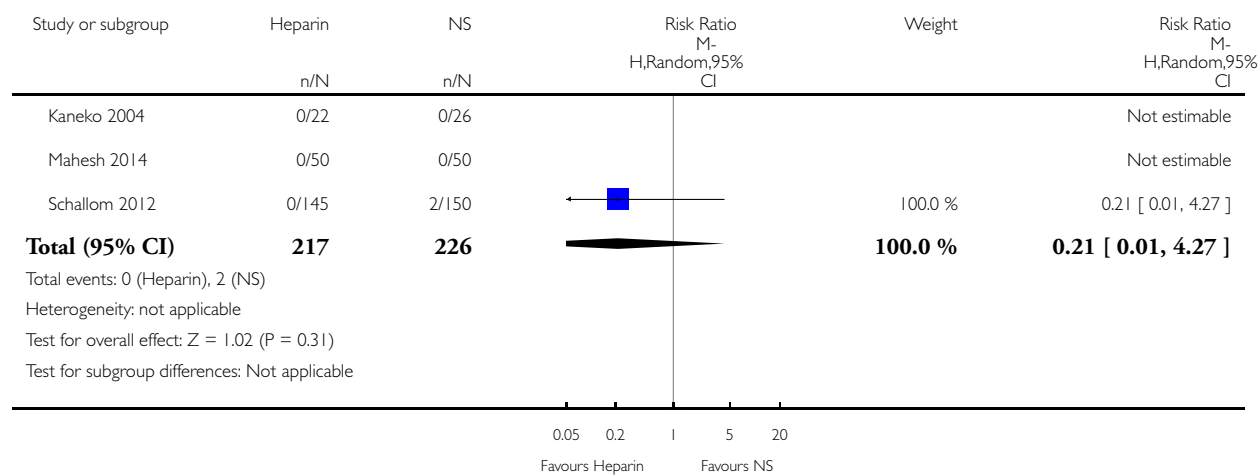


#### Analysis 5.4. Comparison 5 Safety, Outcome 4 Heparin-induced thrombocytopenia.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 5 Safety

Outcome: 4 Heparin-induced thrombocytopenia

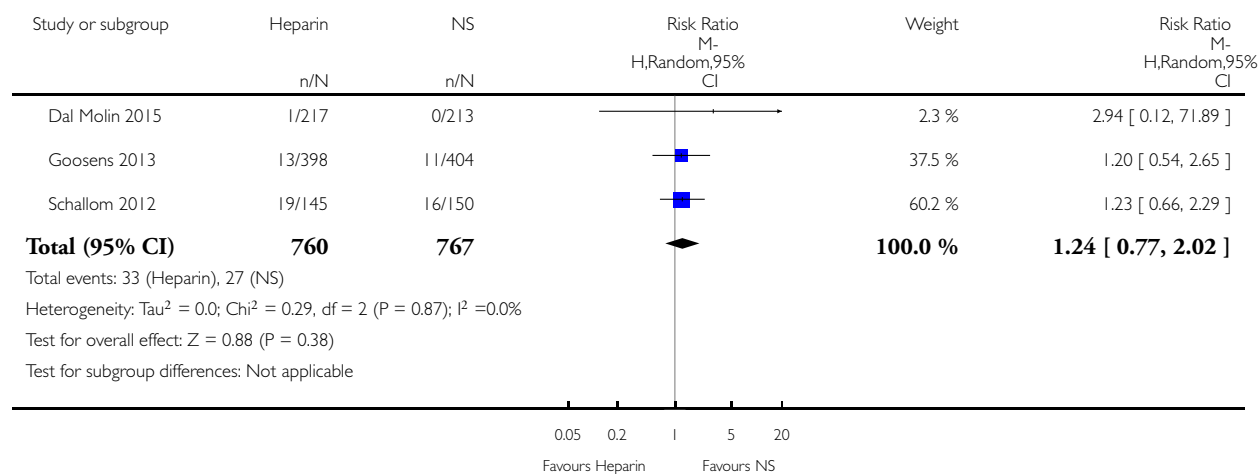


### Analysis 5.5. Comparison 5 Safety, Outcome 5 CVC-related thrombosis.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 5 Safety

Outcome: 5 CVC-related thrombosis

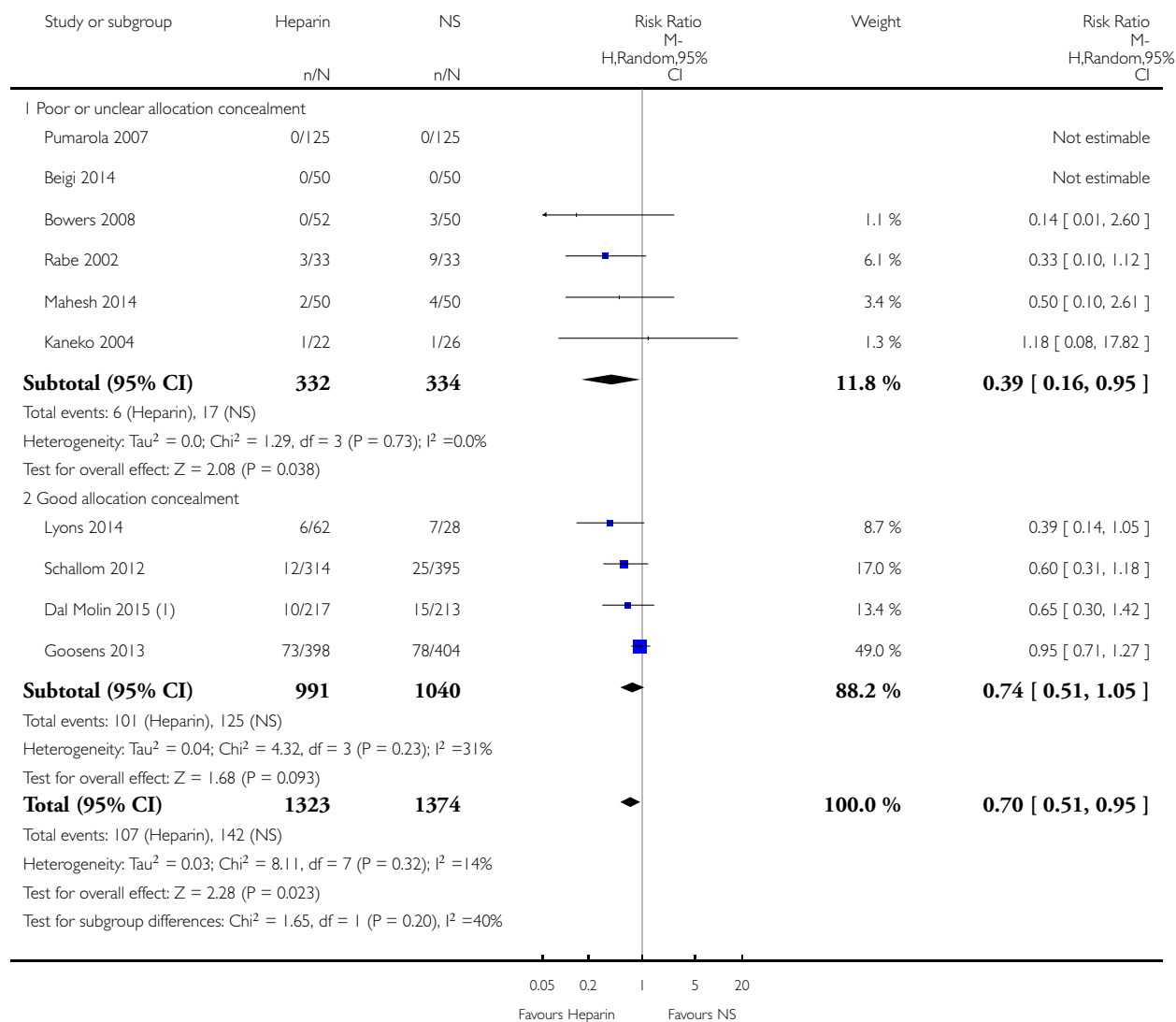


## Analysis 6.1. Comparison 6 Sensitivity analysis, Outcome 1 Occlusion of CVCs related to quality.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 6 Sensitivity analysis

Outcome: 1 Occlusion of CVCs related to quality



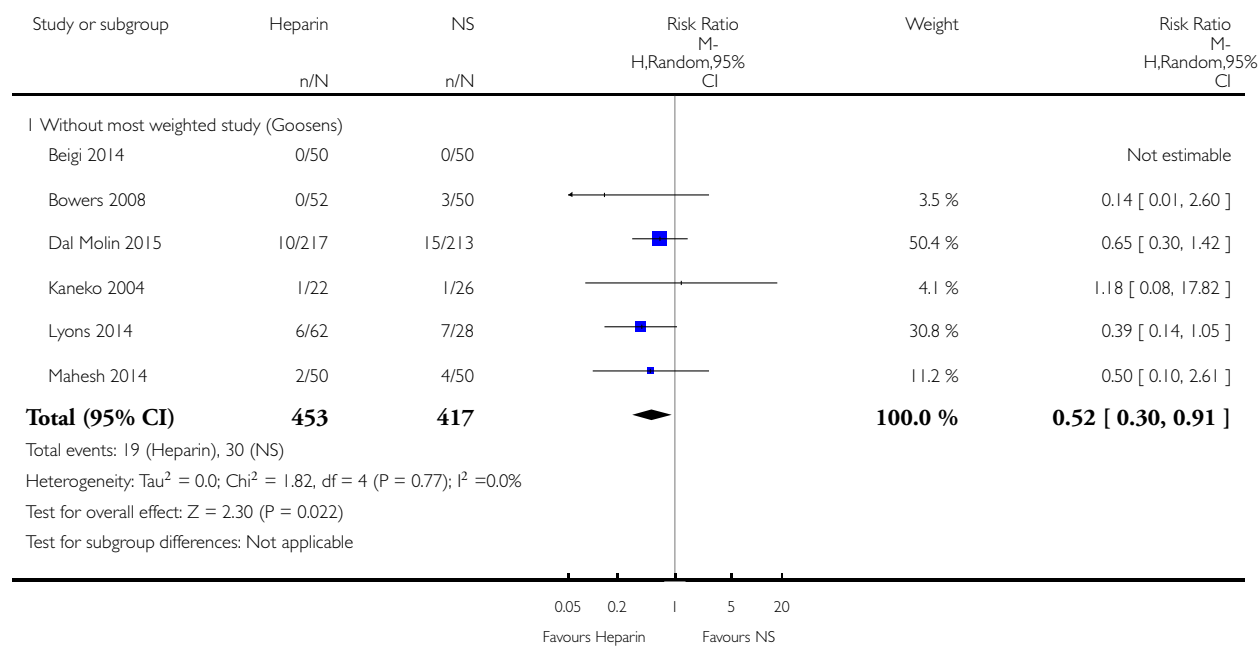
(1) The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in the saline group

## Analysis 6.2. Comparison 6 Sensitivity analysis, Outcome 2 Occlusion of CVCs related to weight of studies.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 6 Sensitivity analysis

Outcome: 2 Occlusion of CVCs related to weight of studies

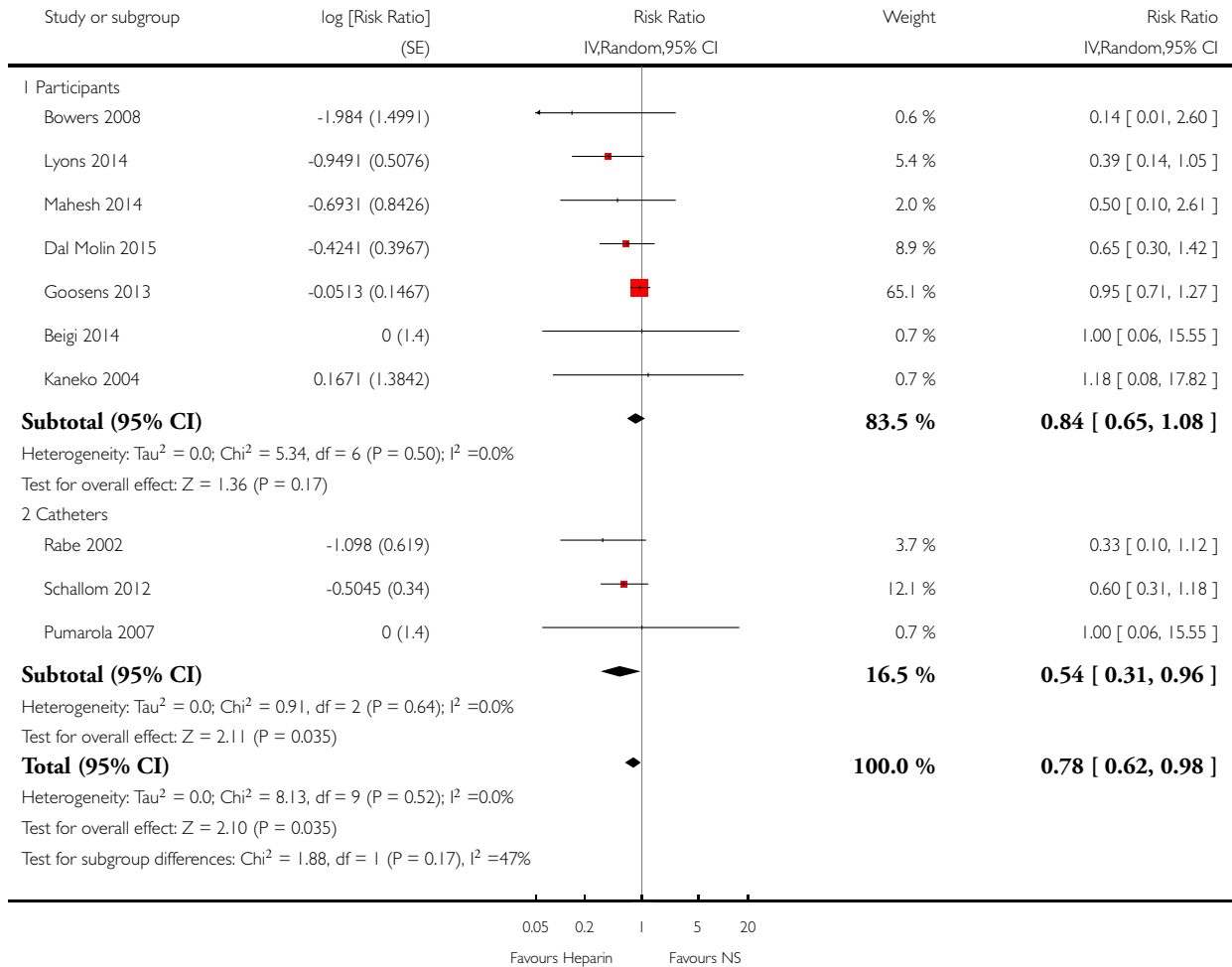


### Analysis 6.3. Comparison 6 Sensitivity analysis, Outcome 3 All occlusions effect size.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 6 Sensitivity analysis

Outcome: 3 All occlusions effect size



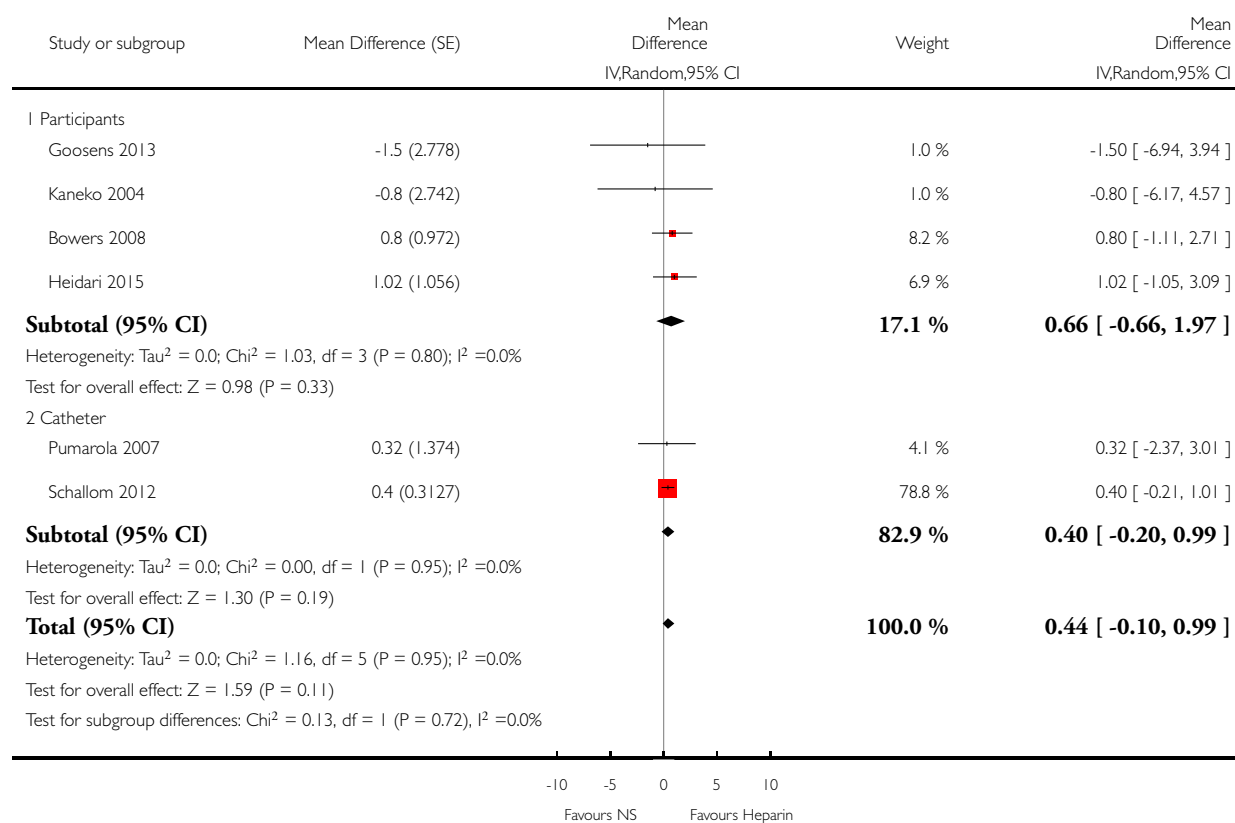


#### Analysis 6.4. Comparison 6 Sensitivity analysis, Outcome 4 All patency effect size.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 6 Sensitivity analysis

Outcome: 4 All patency effect size

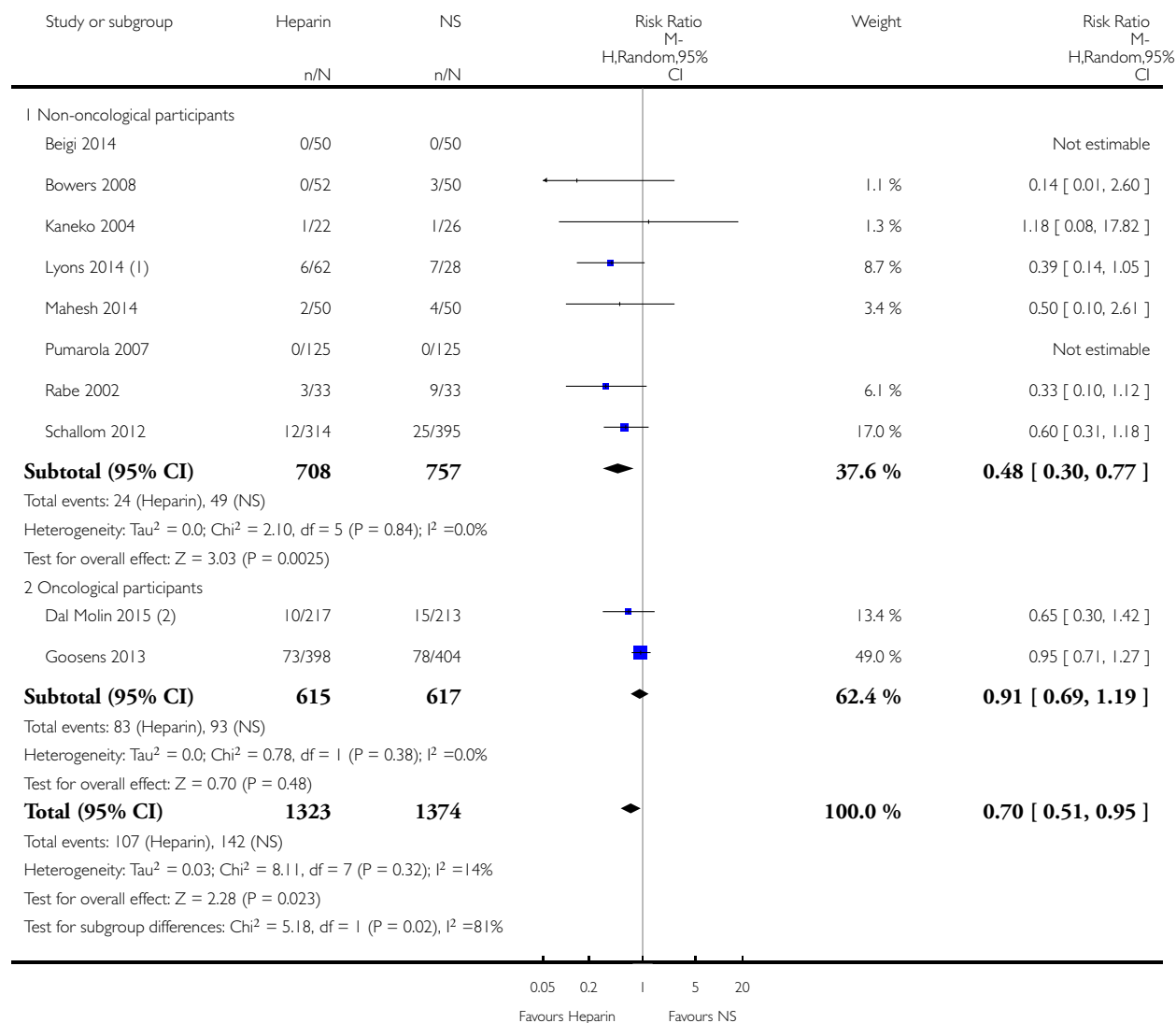


## Analysis 7.1. Comparison 7 Analysis of subgroups, Outcome 1 Occlusion of CVCs oncology vs non-oncology participants.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 7 Analysis of subgroups

Outcome: 1 Occlusion of CVCs oncology vs non-oncology participants



(1) We combined results from low and high dose heparin groups

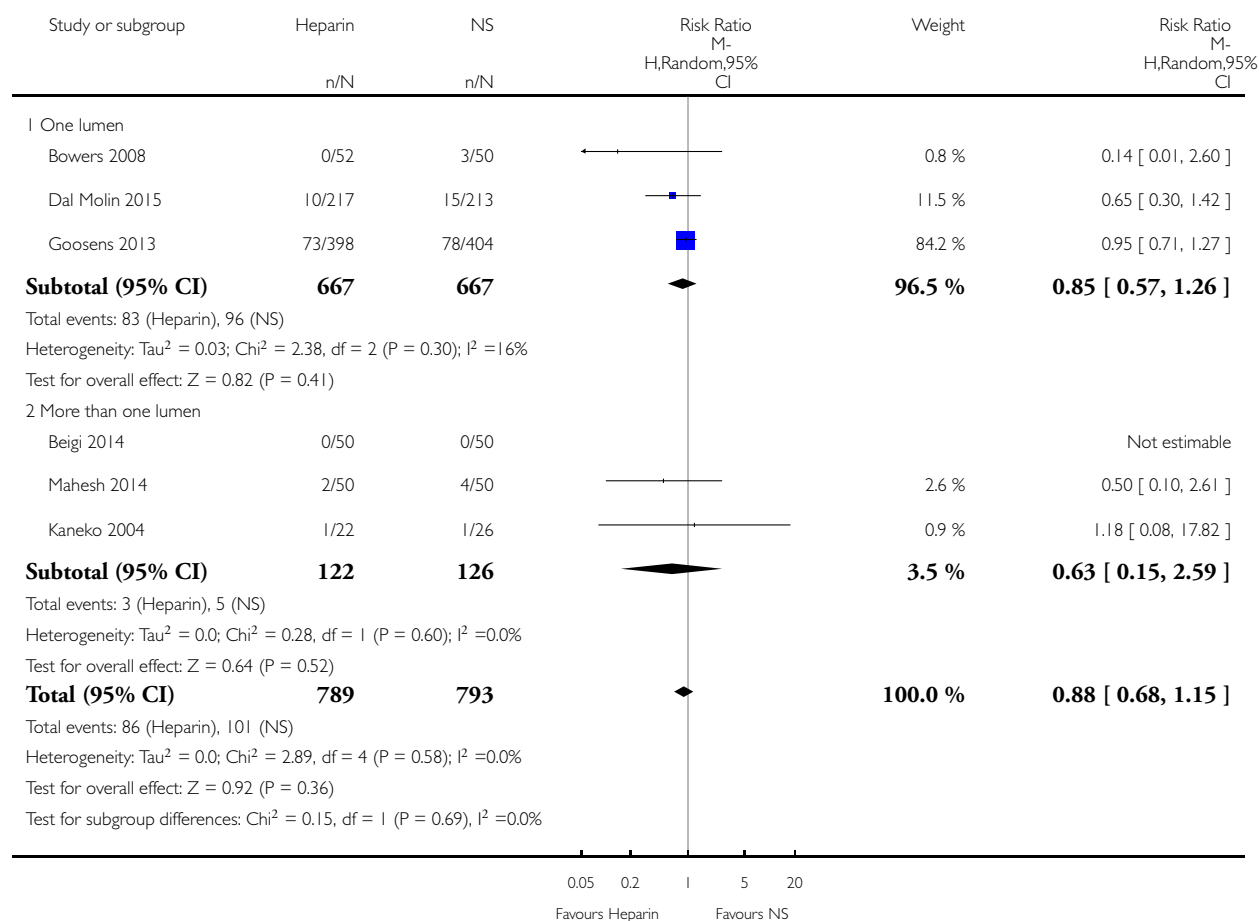
(2) The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in the saline group

## Analysis 7.2. Comparison 7 Analysis of subgroups, Outcome 2 Occlusion of CVCs number of lumens (unit of analysis participants).

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 7 Analysis of subgroups

Outcome: 2 Occlusion of CVCs number of lumens (unit of analysis participants)

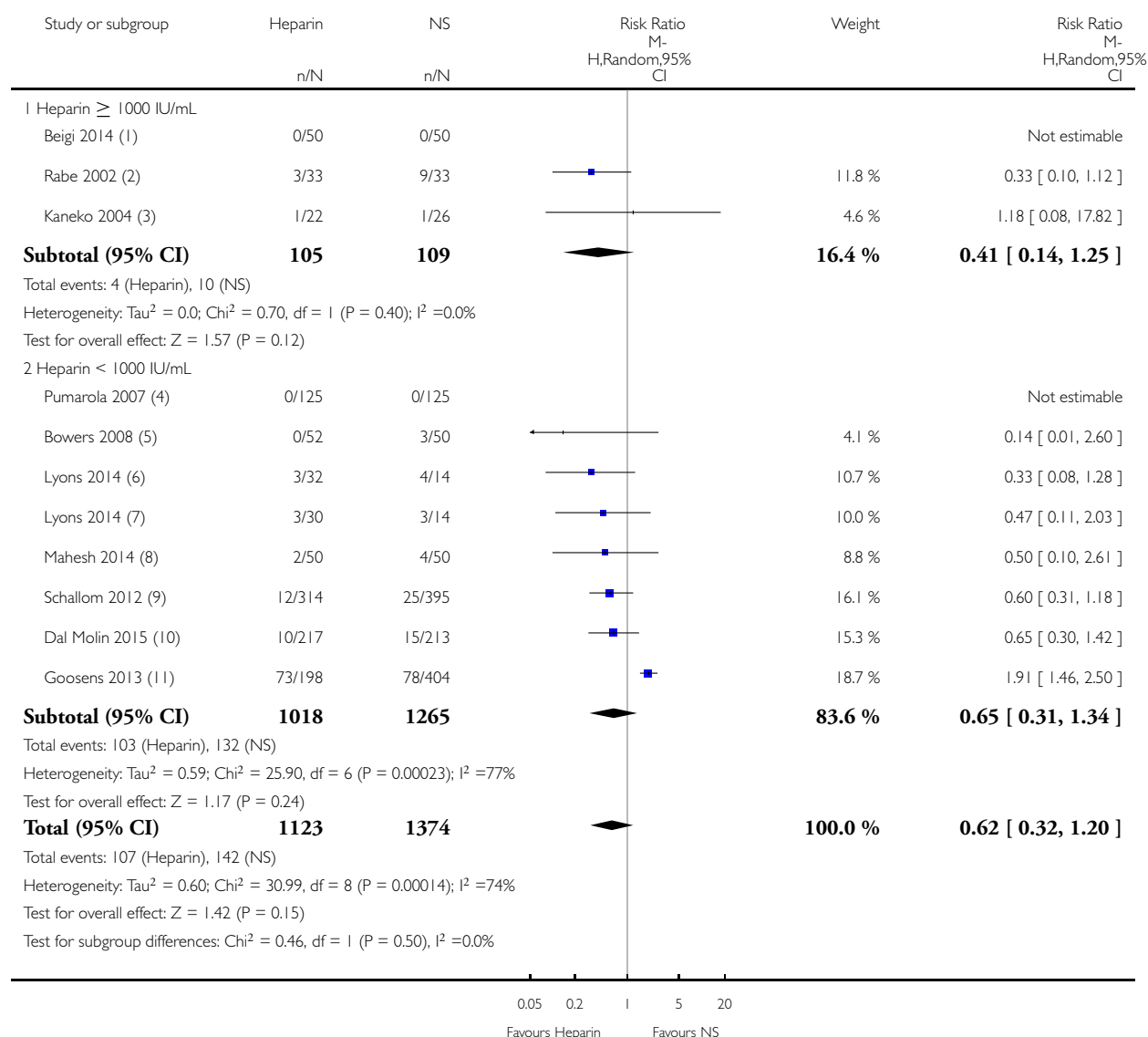


### Analysis 7.3. Comparison 7 Analysis of subgroups, Outcome 3 All occlusions - heparin concentration.

Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 7 Analysis of subgroups

Outcome: 3 All occlusions - heparin concentration



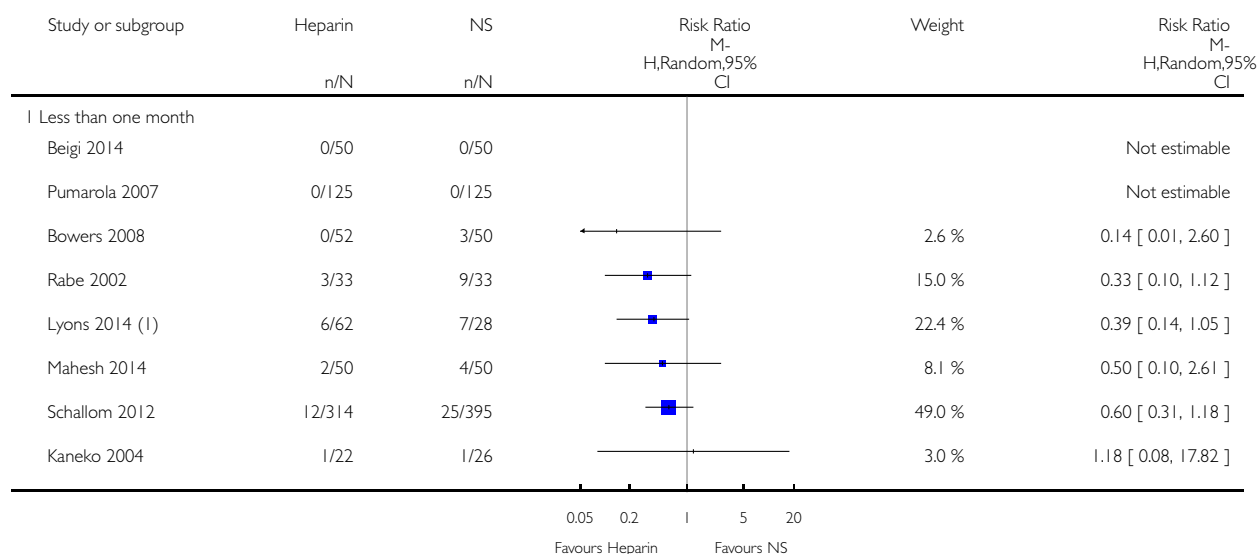
- (1) 1000 IU
- (2) 2500 IU
- (3) 2000 IU
- (4) 100 IU
- (5) 300 IU
- (6) High doses were defined as 300 IU heparin and low doses as 50 IU heparin. We split the events of the saline group
- (7) High doses were defined as 300 IU heparin and low doses as 50 IU heparin. We split the events of the saline group
- (8) 30 IU
- (9) 30 IU
- (10) 250 IU. The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in the saline group
- (11) 300 IU

#### Analysis 7.4. Comparison 7 Analysis of subgroups, Outcome 4 Occlusion of CVCs and time to follow-up.

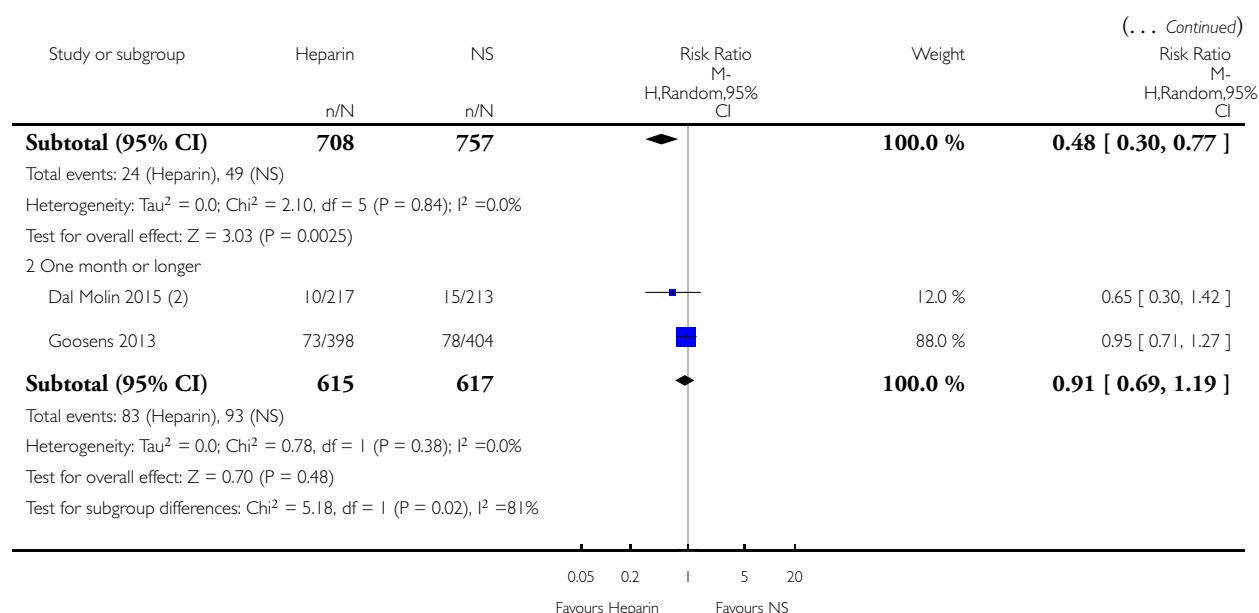
Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 7 Analysis of subgroups

Outcome: 4 Occlusion of CVCs and time to follow-up



(Continued . . .)



(1) We combined results from low and high dose of heparin groups

(2) The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in saline group

## ADDITIONAL TABLES

**Table 1. Secondary outcomes**

| Study         | CVC-related thrombosis |        | CVC-related sepsis |       | Mortality |        | HIT |    |
|---------------|------------------------|--------|--------------------|-------|-----------|--------|-----|----|
|               | H                      | NS     | H                  | NS    | H         | NS     | H   | NS |
| Bowers 2008   | NR                     | NR     | NR                 | NR    | NR        | NR     | NR  | NR |
| Goosens 2013  | 13/398                 | 11/404 | 6/398              | 2/404 | 20/398    | 28/404 | NR  | NR |
| Kaneko 2004   | NR                     | NR     | NR                 | NR    | 0         | 0      | 0   | 0  |
| Mahesh 2014   | NR                     | NR     | NR                 | NR    | NR        | NR     | 0   | 0  |
| Pumarola 2007 | NR                     | NR     | NR                 | NR    | 2/125     | 1/125  | NR  | NR |

**Table 1. Secondary outcomes** (Continued)

|                               |        |        |       |       |    |    |       |       |
|-------------------------------|--------|--------|-------|-------|----|----|-------|-------|
| <a href="#">Rabe 2002</a>     | NR     | NR     | NR    | NR    | NR | NR | NR    | NR    |
| <a href="#">Schallom 2012</a> | 19/145 | 16/150 | 0/145 | 4/150 | NR | NR | 0/145 | 2/150 |

CVC: central venous catheter.

H: heparin.

HIT: heparin-induced thrombocytopenia.

NR: not reported.

NS: normal saline (0.9% NaCl).

## APPENDICES

### Appendix I. CENTRAL search strategy

|     |   |
|-----|---|
| #1  | MESH DESCRIPTOR Heparin EXPLODE ALL TREES       |
| #2  | (hep* or UH or UFH or LMWH):TI,AB,KY            |
| #3  | *parin:TI,AB,KY                                 |
| #4  | *paran:TI,AB,KY                                 |
| #5  | #1 OR #2 OR #3 OR #4                            |
| #6  | MESH DESCRIPTOR Sodium Chloride                 |
| #7  | MESH DESCRIPTOR Saline Solution, Hypertonic     |
| #8  | saline:TI,AB,KY                                 |
| #9  | sodium*:TI,AB,KY                                |
| #10 | NaCl:TI,AB,KY                                   |
| #11 | #6 OR #7 OR #8 OR #9 OR #10                     |
| #12 | #5 AND #11                                      |
| #13 | MESH DESCRIPTOR Catheterization, Central Venous |

(Continued)

|     |   |
|-----|---|
| #14 | MESH DESCRIPTOR Catheterization                             |
| #15 | MESH DESCRIPTOR Catheters, Indwelling                       |
| #16 | MESH DESCRIPTOR Vascular Access Devices                     |
| #17 | MESH DESCRIPTOR Central Venous Catheters                    |
| #18 | catheter*:TI,AB,KY  |
| #19 | cannula*:TI,AB,KY   |
| #20 | (CVC* or PICC):TI,AB,KY                                     |
| #21 | (venous near3 access):TI,AB,KY                              |
| #22 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 |
| #23 | #12 AND #22   |

## Appendix 2. MEDLINE search strategy

1 exp Heparin/  
 2 (hep\$ or UH or UFH or LMWH).ti,ab.  
 3 Sodium Chloride/  
 4 Saline Solution, Hypertonic/  
 5 saline.ti,ab.  
 6 sodium.ti,ab.  
 7 NaCl.ti,ab.  
 8 1 or 2  
 9 or/3-7  
 10 8 and 9  
 11 Catheterization, Central Venous/  
 12 Catheterization/  
 13 Catheters, Indwelling/  
 14 cannul\$.ti,ab.  
 15 catheter\$.ti,ab.  
 16 (CVC or PICC).ti,ab.  
 17 (venous adj3 access).ti,ab.  
 18 or/11-17  
 19 10 and 18  
 20 randomized controlled trial.pt.  
 21 controlled clinical trial.pt.  
 22 randomized.ab.  
 23 placebo.ab.  
 24 clinical trials as topic.sh.  
 25 randomly.ab.  
 26 trial.ti.  
 27 or/20-26



28 exp animals/ not humans.sh.  
 29 27 not 28  
 30 19 and 29

### Appendix 3. Embase search strategy

1 exp heparin/  
 2 (hep\$ or UH or UFH or LMWH).ti,ab.  
 3 1 or 2  
 4 sodium chloride/  
 5 hypertonic solution/  
 6 (saline or sodium or NaCl).ti,ab.  
 7 or/3-6  
 8 3 and 7  
 9 central venous catheterization/  
 10 catheterization/  
 11 catheter thrombosis/pc [Prevention]  
 12 intravenous catheter/ or catheter/ or peripherally inserted central venous catheter/  
 13 (catheter\$ or cannul\$).ti,ab.  
 14 (CVC or PICC).ti,ab.  
 15 (venous adj3 access).ti,ab.  
 16 or/9-15  
 17 8 and 16  
 18 random\$.ti,ab.  
 19 factorial\$.ti,ab.  
 20 (crossover\$ or cross over\$ or cross-over\$).ti,ab.  
 21 placebo\$.ti,ab.  
 22 (doubl\$ adj blind\$).ti,ab.  
 23 (singl\$ adj blind\$).ti,ab.  
 24 assign\$.ti,ab.  
 25 allocat\$.ti,ab.  
 26 volunteer\$.ti,ab.  
 27 CROSSOVER PROCEDURE/  
 28 DOUBLE-BLIND METHOD/  
 29 RANDOMIZED CONTROLLED TRIALS/  
 30 SINGLE-BLIND METHOD/  
 31 or/18-30  
 32 17 and 31

### Appendix 4. CINAHL search strategy

|     |   |
|-----|---|
| S32 | S13 AND S23 AND S31                           |
| S31 | S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 |
| S30 | TX venous N3 access                           |
| S29 | TX (CVC or PICC)                              |

(Continued)

|     |   |
|-----|---|
| S28 | TX catheter*  |
| S27 | TX cannul*  |
| S26 | (MH "Catheters")  |
| S25 | (MH "Catheterization")  |
| S24 | (MH "Catheterization, Central Venous")                                  |
| S23 | S21 AND S22   |
| S22 | S16 OR S17 OR S18 OR S19 OR S20   |
| S21 | S14 OR S15  |
| S20 | TX NaCl   |
| S19 | TX sodium   |
| S18 | TX saline   |
| S17 | (MH "Saline Solution, Hypertonic")                                      |
| S16 | (MH "Sodium Chloride")  |
| S15 | TX (hep* or UH or UFH or LMWH)  |
| S14 | (MH "Heparin+")   |
| S13 | S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 |
| S12 | single blind  |
| S11 | double blind  |
| S10 | triple blind  |
| S9  | latin square  |
| S8  | placebo*  |
| S7  | (MH "Placebos")   |
| S6  | follow-up stud*   |
| S5  | alloca*   |
| S4  | random*   |

(Continued)

|    |                          |
|----|--------------------------|
| S3 | clin* N2 trial*          |
| S2 | (MH "Random Assignment") |
| S1 | (MH "Clinical Trials+")  |

## Appendix 5. Clinicaltrials.gov search

|                      |                   |
|----------------------|-------------------|
| catheter AND heparin | 201 studies found |
|----------------------|-------------------|

## Appendix 6. International Clinical Trials Registry Platform (WHO database)

|                      |                                |
|----------------------|--------------------------------|
| heparin AND catheter | 53 records for 53 trials found |
|----------------------|--------------------------------|

## WHAT'S NEW

Last assessed as up-to-date: 11 June 2018.

| Date         | Event  | Description   |
|--------------|--|---|
| 11 June 2018 | New citation required and conclusions have changed | Search updated. Five new studies included, three new ongoing studies identified, seven additional studies excluded and two studies classed as awaiting classification. Text amended to reflect current Cochrane policy. Conclusions changed |
| 11 June 2018 | New search has been performed                      | Search updated. Five new studies included, three new ongoing studies identified, seven additional studies excluded, and two studies classed as awaiting classification  |

## CONTRIBUTIONS OF AUTHORS

ELB: conception of the review; protocol design; identification, qualification, and analysis of studies; interpretation of analysis; draft of the final review; update of the review.

VRG: conception of the review; protocol design; identification, qualification, and analysis of studies; interpretation of analysis; draft of the final review; update of the review.

JBC: protocol design; identification, qualification, and analysis of studies; interpretation of analysis; draft of the final review.

SBM: identification of trials; analysis of studies; draft of the final review.

RCS: protocol design; third review author in cases of disagreement about study qualifications; interpretation of analysis.

AB: protocol design; interpretation of analysis; draft of the final review.

## DECLARATIONS OF INTEREST

ELB: none known.

VRG: none known.

JBC: none known.

SBM: none known.

RCS: none known.

AB: none known.

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- Chief Scientist Office, Scottish Government Health Directorates, the Scottish Government, UK.

The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

When we planned the present systematic review, and as a result of clinical considerations, we assumed that the unit of analysis would be the participant. When we performed the searches, we found that studies also used the catheter or line access (every time a line was used to provide drugs, blood, etc.) as the unit of analysis. As a result, we analysed separately for each different unit of analysis, in addition to pooling all studies.

Although we used a fixed-effect model in the previous version of this review, we decided to use a random-effects model for this update, even when statistical heterogeneity was low. This decision was based on clinical heterogeneity among trials, such as different lengths of follow-up, different doses for locking heparin, and different co-interventions.

Compared to the previous published version ([López-Briz 2014](#)), in keeping with Cochrane recommendations, we removed references from the list of excluded studies that were systematic reviews, not randomised controlled trials, or trials that included exclusively children or infants.

A distinction must be made between flushing a catheter, which is done for the purpose of washing out the contents of the catheter, and locking a catheter, which is done to inject a fluid that is intended to stay in the catheter until next use. To remove any ambiguity regarding the intention of this review, we have introduced the term 'locking' instead of 'flushing'.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Catheter Obstruction [statistics & numerical data]; \*Catheterization, Central Venous; \*Central Venous Catheters; Anticoagulants [\*administration & dosage]; Heparin [\*administration & dosage]; Sodium Chloride [\*administration & dosage]; Therapeutic Irrigation [methods]

### MeSH check words

Adult; Humans