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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

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[Intervention Review]

# 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 ≥ 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 thrombocytopaenia (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 thrombocytopaenia.

## 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 (thrombocytopaenia). 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**

**Patient or population:** adults with central venous catheters
**Settings:** hospital
**Intervention:** heparin
**Comparison:** 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 | | | | |
| **Occlusion of CVC (combining participant and catheter as unit of analysis)**<br>Blood withdrawing<br>Follow-up:1 to 231 days | **Study population** | | **RR 0.70**<br>(0.51 to 0.95) | 1672 participants, 1025 catheters<br>(10 RCTs) | ⊕◯◯◯<br>**Very low**[a,b] | NNTB 42<br>(32 to 250)<br>Considering only **participant as unit of analysis**<br>(7 studies, 1672 participants):<br>RR 0.79 (95% CI 0.58 to 1.08)<br>Considering only **catheter as unit of analysis**<br>(3 studies, 1025 catheters):<br>RR 0.53 (95% CI 0.29 to 0.95) |
| | **103 per 1000** | **77 per 1000 (62 to 86)** | | | | |

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

[a]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.
[b]We downgraded the quality of evidence by one level owing to high risk of suspected publication bias (Figure 1).
[c]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.
[d]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.
[e]We downgraded the quality of evidence by one level for imprecision because the 95% CI included both benefit and harm.
[f]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 commonly 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 thrombocytopaenia (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 thrombocytopaenia (HIT) (development of thrombocytopaenia after heparin locking of a CVC in an adult with a previously normal platelet count after exclusion of all other causes of thrombocytopaenia, 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 (or number needed to treat for an additional harmful outcome (NNTH)) = 1/ACR*(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 (gradepro.org) (GRADEproGDT 2015). We judged the outcomes of CVC occlusion, duration of catheter patency, CVC-related sepsis, mortality, haemorrhage, and heparin-induced thrombocytopaenia 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).

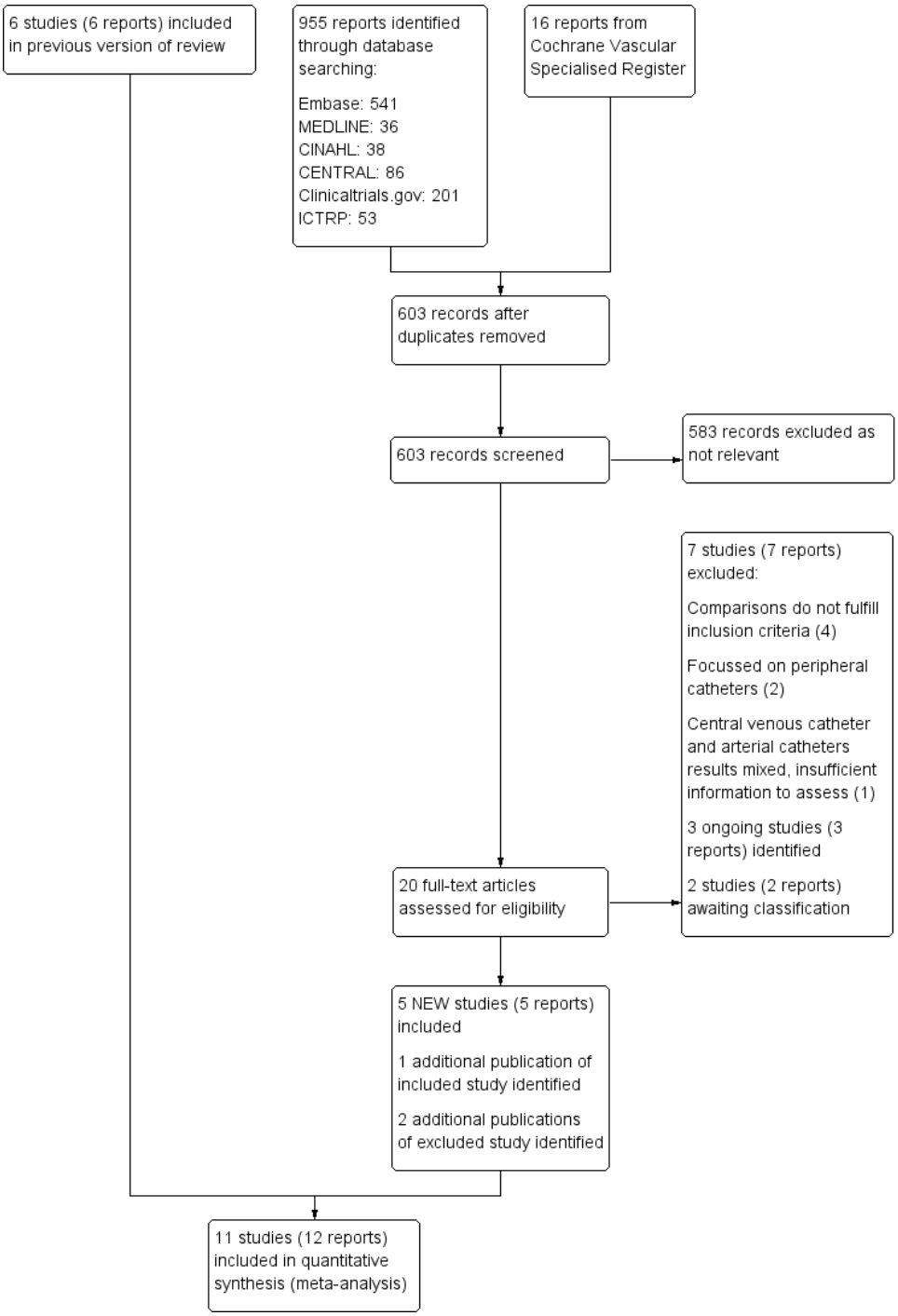
## RESULTS

### 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 - participant), 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.**

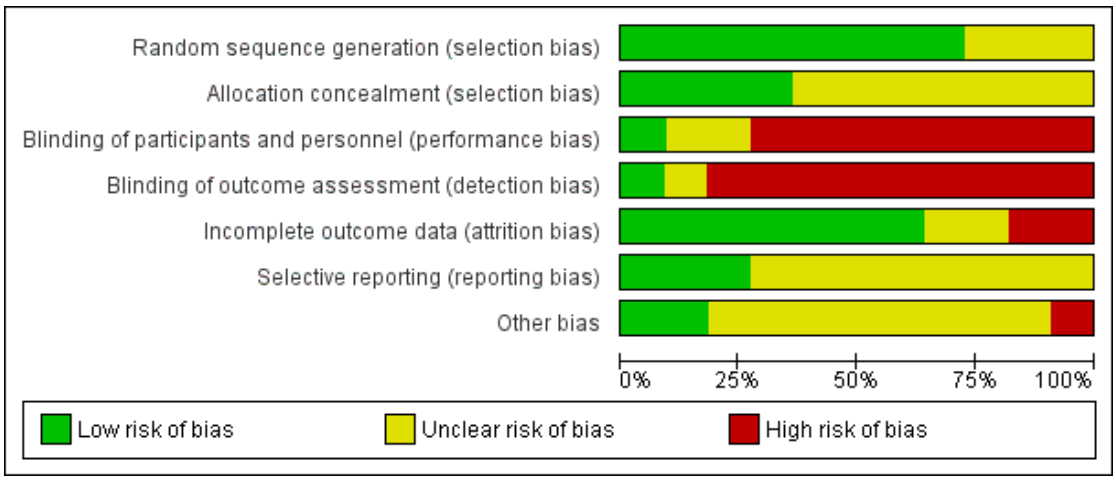
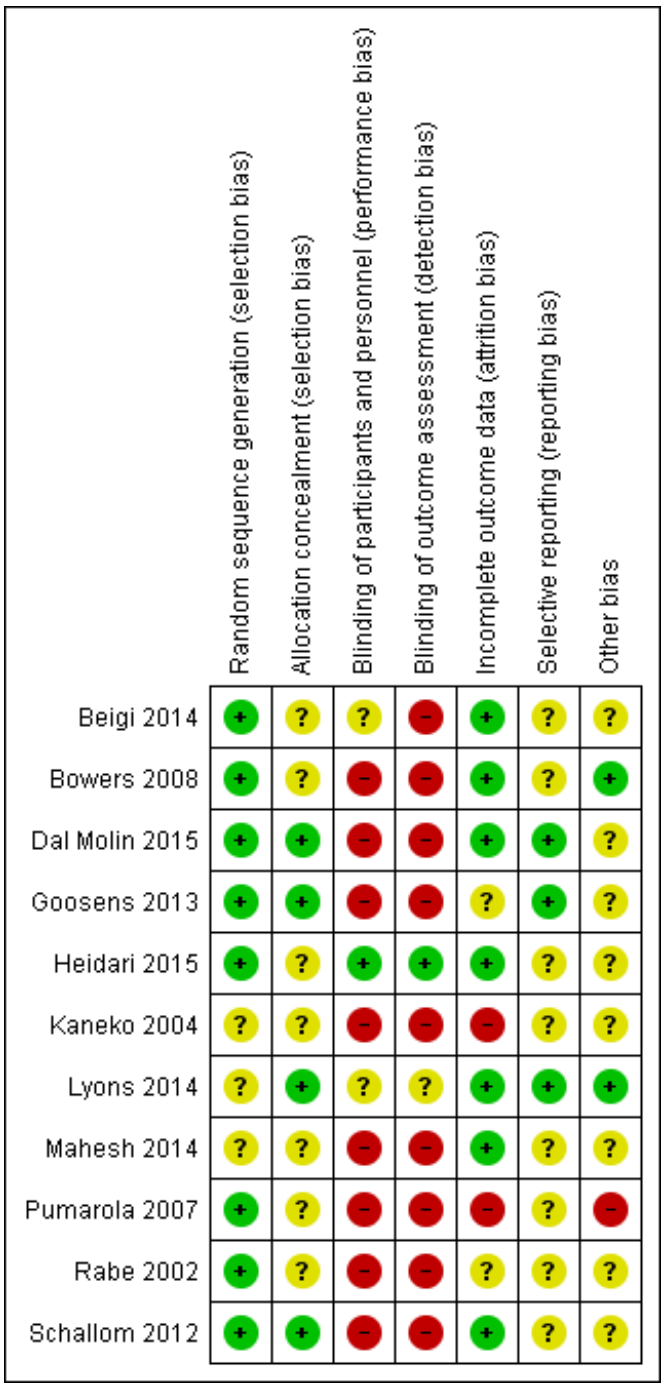


**Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**



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 thrombocytopaenia

Three studies reported heparin-induced thrombocytopaenia: 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

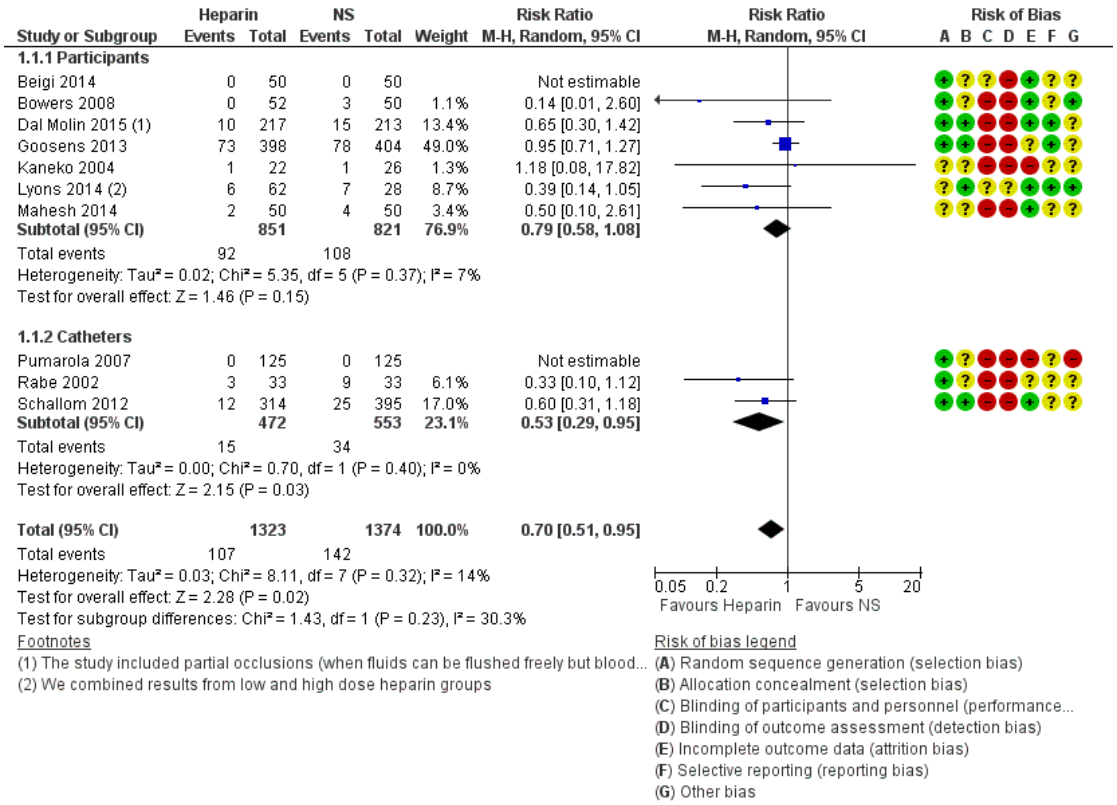
See: **Summary of findings for the main comparison** Heparin versus normal saline solution locking for prevention of occlusion in central venous catheters in adults

### 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/), 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: 1 All occlusions, outcome: 1.1 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.

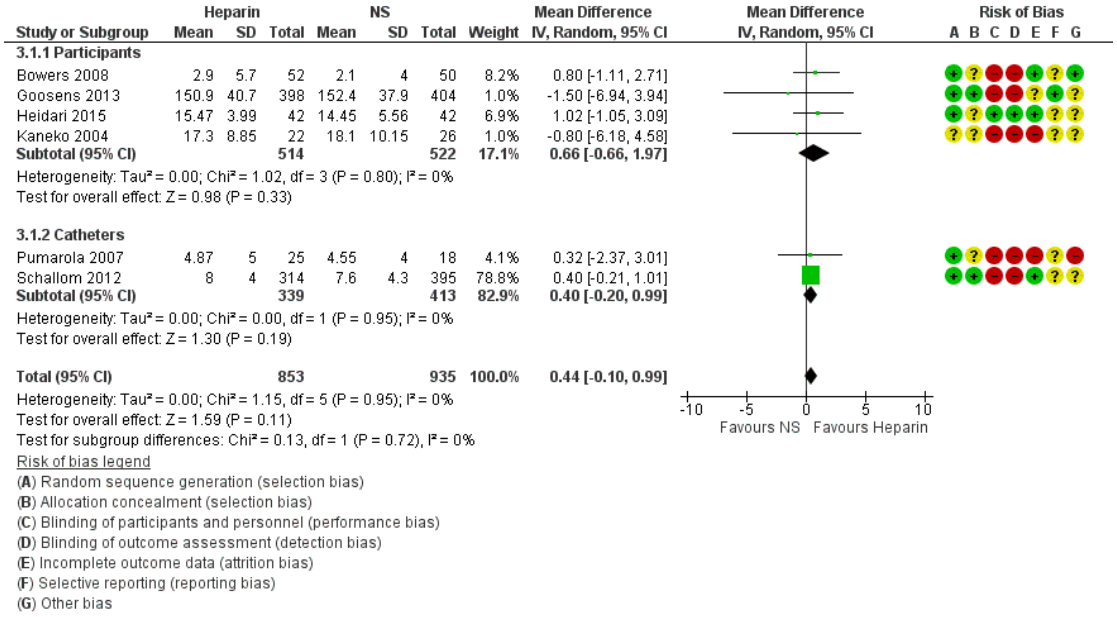
Only one study used line access as the unit of analysis (Goosens 2013). This study included 6137 observations and showed no differences in the number of occlusions between heparin and NS locking (RR 1.08, 95% CI 0.84 to 1.40). We judged the quality of evidence to be moderate. We downgraded the quality 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 thrombocytopaenia (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 (≥ 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 thrombocytopaenia (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 thrombocytopaenia (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 thrombocytopaenia 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, Goosens 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 thrombocytopaenia. 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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# REFERENCES

## References to studies included in this review

**Beigi 2014** *{published data only}*
Beigi AK, HadiZadeh MS, Salimi F, Ghaheri H. Heparin compared with normal saline to maintain patency of permanent double lumen hemodialysis catheters: a randomized controlled trial. Advanced Biomedical Research 2014; Vol. 3:121. DOI: 10.4103/2277-9175.133192

**Bowers 2008** *{published data only}*
Bowers L, Speroni KG, Jones L, Atherton M. Comparison of occlusion rates by flushing solutions for peripherally inserted central catheters with positive pressure Luer-activated devices. *Journal of Infusion Nursing* 2008;**31**(1): 22–7.

**Dal Molin 2015** *{published data only}*
Dal Molin A, Clerico M, Baccini M, Guerretta L, Sartorello B, Rasero L. Normal saline versus heparin solution to lock totally implanted venous access devices: results from a multicenter randomized trial. *European Journal of Oncology Nursing* 2015;**19**(6):638–43.

**Goosens 2013** *{published and unpublished data}*
Goossens GA, Jerome M, Janssens C, Peetermans WE, Fieuws S, Moons P, et al. Heparin versus normal saline as locking solution in totally implantable venous ports: a randomized controlled trial in cancer patients. *Supportive Care in Cancer* 2013;**21**:S28.
* Goossens GA, Jérôme M, Janssens C, Peetermans WE, Fieuws S, Moons P, et al. Comparing normal saline versus diluted heparin to lock non-valved totally implantable venous access devices in cancer patients: a randomised, non-inferiority, open trial. *Annals of Oncology* 2013;**24**(7): 1892–9.

**Heidari 2015** *{published data only}*
Heidari Gorji MA, Rezaei F, Jafari H, Yazdani Cherati J. Comparison of the effects of heparin and 0.9% sodium chloride solutions in maintenance of patency of central venous catheters. *Anesthesiology and Pain Medicine* 2015;**5** (2):e22595.

**Kaneko 2004** *{published data only}*
Kaneko Y, Iwano M, Yoshida H, Kosuge M, Ito S, Narita I, et al. Natural saline-flush is sufficient to maintain patency of immobilized-urokinase double-lumen catheter used to provide temporary blood access for hemodialysis. *Blood Purification* 2004;**22**(5):473–9.

**Lyons 2014** *{published data only}*
Lyons MG, Phalen AG. A randomized controlled comparison of flushing protocols in home care patients with peripherally inserted central catheters. *Journal of Infusion Nursing* 2014;**37**(4):270–81.

**Mahesh 2014** *{published data only}*
Mahesh Babu BV, Kameswara Rao AS, Rajesh K, Harinath Babu V. Heparin or 0.9% sodium chloride to maintain central venous catheter patency: a randomized trial. *Journal of Evolution of Medical and Dental Sciences* 2014;**3**(1): 46–50.

**Pumarola 2007** *{published data only}*
Pumarola CF, Mercader RC, Plana MC, Bueno CC, Casellas SS, Vidal MF, et al. [Comparative study of maintenance of patency of triple lumen central venous catheter] [Estudio comparativo del mantenimiento de la permeabilidad de los cateteres venosos centrales de tres luces]. *Enfermeria Intensiva* 2007;**18**(1):25–35.

**Rabe 2002** *{published data only}*
Rabe C, Gramann T, Sons X, Berna M, Gonzalez-Carmona MA, Klehr HU, et al. Keeping central venous lines open: a prospective comparison of heparin, vitamin C and sodium chloride sealing solutions in medical patients. *Intensive Care Medicine* 2002;**28**(8):1172–6.

**Schallom 2012** *{published and unpublished data}*
Schallom ME, Prentice D, Sona C, Micek ST, Skrupky LP. Heparin or 0.9% sodium chloride flush to maintain central venous catheter patency: a randomized trial. *Critical Care Medicine* 2012;**40**(6):1820–6.

## References to studies excluded from this review

**AACCN 1993** *{published data only}*
American Association of Critical-Care Nurses. Evaluation of the effects of heparinized and nonheparinized flush solutions on the patency of arterial pressure monitoring lines: the AACN Thunder Project. By the American Association of Critical-Care Nurses. *American Journal of Critical Care* 1993;**2**(1):3–15.

**Abdelkefi 2004** *{published data only}*
Abdelkefi A, Othman TB, Kammoun L, Chelli M, Romdhane NB, Kriaa A, et al. Prevention of central venous line-related thrombosis by continuous infusion of low-dose unfractionated heparin, in patients with haemato-oncological disease. A randomized controlled trial. *Thrombosis and Haemostasis* 2004;**92**(3):654–61.

**Abdelkefi 2005** *{published data only}*
Abdelkefi A, Torjman L, Ladeb S, Othman TB, Achour W, Lakhal A, et al. Randomized trial of prevention of catheter-related bloodstream infection by continuous infusion of low-dose unfractionated heparin in patients with hematologic and oncologic disease. *Journal of Clinical Oncology* 2005;**23**(31):7864–70.

**Abdelkefi 2005a** *{published data only}*
Abdelkefi A. Prevention of catheter-related bloodstream infection in patients with haemato-oncological disease. clinicaltrials.gov/ct2/show/NCT00207779 (first received 13 September 2005).

**Abdelkefi 2007** *{published data only}*
Abdelkefi A, Achour W, Othman TB, Ladeb S, Torjman L, Lakhal A, et al. Use of heparin-coated central venous lines to prevent catheter-related bloodstream infection. *Journal of Supportive Oncology* 2007;**5**(6):273–8.

**Abdelkefi 2008** *{published data only}*
Abdelkefi A, Chelli M, Achour W, Ben Romdhane N, Torjman L, Ladeb S, et al. Catheter related bloodstream infection in haematological patients: a prospective, randomized study comparing heparin-coated with chlorhexidine and silver sulfadiazine impregnated central venous catheters. *Blood* 2008;**112**(11):Abstract 1174.

**Agnelli 2009** *{published data only}*
Agnelli G. Prevention of venous and arterial thromboembolism in cancer patients undergoing chemotherapy, with a low molecular weight heparin (nadroparin calcium). A randomized, placebo-controlled, double-blind, multicenter phase III study. clinicaltrials.gov/ct2/show/NCT00951574 (first received 31 July 2009).

**Akyuz 2010** *{published data only}*
Akyuz C, Kupeli S, Yagci-Kupeli B, Buyukpamukcu M. Prophylactic taurolidine use in central venous catheters of pediatric cancer patients: a prospective randomized study from single center. *Pediatric Blood and Cancer* 2010;**55**(5): 949.

**Alexander 2010** *{published data only}*
Alexander H. Heparin versus normal saline as a flush solution. *International Journal for the Advancement of Science and Arts* 2010;**1**(1):63–75.

**Ankola 1993** *{published data only}*
Ankola PA, Atakent YS. Effect of adding heparin in very low concentration to the infusate to prolong the patency of umbilical artery catheters. *American Journal of Perinatology* 1993;**10**(3):229–32.

**Anton 2009** *{published data only}*
Anton N, Cox PN, Massicotte MP, Chait P, Yasui Y, Dinyari PM, et al. Heparin-bonded central venous catheters do not reduce thrombosis in infants with congenital heart disease: a blinded randomized, controlled trial. *Pediatrics* 2009;**123** (3):e453–8.

**Appelgren 1996** *{published data only}*
Appelgren P, Ransjo U, Bindslev L, Espersen F, Larm O. Surface heparinisation of central venous catheters reduces microbial colonization in vitro and in vivo: results from a prospective, randomized trial. *Critical Care Medicine* 1996; **24**(9):1482–9.

**Aquino 2002** *{published data only}*
Aquino VM, Sandler ES, Mustafa MM, Steele JW, Buchanan GR. A prospective double-blind randomized trial of urokinase flushes to prevent bacteremia resulting from luminal colonization of subcutaneous central venous catheters. *Journal of Pediatric Hematology/Oncology* 2002;**24** (9):710–3.

**Araujo 2008** *{published data only}*
Araujo C, Silva JP, Antunes P, Fernandes JM, Dias C, Pereira H, et al. A comparative study between two central veins for the introduction of totally implantable venous access devices in 1201 cancer patients. *European Journal of Surgical Oncology* 2008;**34**(2):222–6.

**Arnts 2011** *{published data only}*
Arnts IJ, Heijnen JA, Wilbers HT, van der Wilt GJ, Groenewoud JMM, Liem KD. Effectiveness of heparin solution versus normal saline in maintaining patency of intravenous locks in neonates: a double blind randomized controlled study. *Journal of Advanced Nursing* 2011;**67**(12): 2677–85.

**Arrants 1999** *{published data only}*
Arrants J, Willis ME, Stevens B, Gripkey L, Herman JA, Hernandez-Brooks L, et al. Reliability of an intravenous intermittent access port (saline lock) for obtaining blood samples for coagulation studies. *American Journal of Critical Care* 1999;**8**(5):344–8.

**Ashton 1990** *{published data only}*
Ashton J, Gibson V, Summers S. Effects of heparin versus saline solution on intermittent infusion device irrigation. *Heart and Lung* 1990;**19**(6):608–12.

**Aslam 2011** *{published data only}*
Aslam S. Phase II trial of a novel catheter lock solution for adjunctive treatment of hemodialysis catheter-associated bacteremia. clinicaltrials.gov/ct2/show/NCT01483872 (first received 26 November 2011).

**Bailey 1979** *{published data only}*
Bailey MJ. Reduction of catheter-associated sepsis in parenteral nutrition using low-dose intravenous heparin. *British Medical Journal* 1979;**1**(6179):1671–3.

**Balduini 2010** *{published data only}*
Balduini C. Heparin in prophylaxis of peripheral venous catheters thrombosis: randomized clinical trial [Studio clinico randomizzato sull'utilizzo di eparina per la profilassi della tromboflebite da catetere venoso periferico]. clinicaltrials.gov/ct2/show/NCT01131754 (first received 26 May 2010).

**Barrett 1990** *{published data only}*
Barrett PJ, Lester RL. Heparin versus saline flushing solutions in a small community hospital. *Hospital Pharmacy* 1990;**25**(2):115–8.

**Barriga 1997** *{published data only}*
Barriga FJ, Varas M, Potin M, Sapunar F, Rojo H, Martinez A, et al. Efficacy of a vancomycin solution to prevent bacteremia associated with an indwelling central venous catheter in neutropenic and non-neutropenic cancer patients. *Medical and Pediatric Oncology* 1997;**28**(3): 196–200.

**Bennegard 1982** *{published data only}*
Bennegard K, Curelaru I, Gustavsson B, Linder LE, Zachrisson BF. Material thrombogenicity in central venous catheterization. I. A comparison between uncoated and heparin-coated, long antebrachial, polyethylene catheters. *Acta Anaesthesiologica Scandinavica* 1982;**26**(2):112–20.

**Bertolino 2012** *{published data only}*
Bertolino G, Pitassi A, Tinelli C, Staniscia A, Guglielmana B, Scudeller L, et al. Intermittent flushing with heparin versus saline for maintenance of peripheral intravenous catheters in a medical department: a pragmatic cluster-randomized controlled study. *Worldviews on Evidence-Based Nursing* 2012;**9**(4):221–6.

**Betjes 2004** *{published data only}*
Betjes MG, van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate-taurolidine-containing lock solution. *Nephrology, Dialysis, Transplantation* 2004;**19**(6): 1546–51.

**Bisseling 2010** *{published data only}*
Bisseling TM, Willems MC, Versleijen MW, Hendriks JC, Vissers RK, Wanten GJ. Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in patients on home parenteral nutrition: a heparin-controlled prospective trial. *Clinical Nutrition* 2010;**29**(4):464–8.

**Bleyer 2005** *{published data only}*
Bleyer AJ, Mason L, Russell G, Raad II, Sherertz RJ. A randomized, controlled trial of a new vascular catheter flush solution (minocycline-EDTA) in temporary hemodialysis access. *Infection Control and Hospital Epidemiology* 2005;**26** (6):520–4.

**Bolgiano 1990** *{published data only}*
Bolgiano CS, Subramaniam PT, Montanari JM, Minick L. The effect of two concentrations of heparin on arterial catheter patency. *Critical Care Nurse* 1990;**10**(5):47–57.

**Branger 2011** *{published data only}*
Branger B, Reboul P, Prelipcean C, Noguera ME, Cariou S, Granolleras C, et al. Tunnelled internal jugular vein catheters with taurolidine lock: an acceptable challenge to arterio-venous fistula in 70 years old haemodialyzed patients: a prospective pilot study. *Nephrologie and Therapeutique* 2011;**7**(4):237–41.

**Branson 1993** *{published data only}*
Branson PK, McCoy RA, Phillips BA, Clifton GD. Efficacy of 1.4 percent sodium citrate in maintaining arterial catheter patency in patients in a medical ICU. *Chest* 1993;**103**(3): 882–5.

**Brismar 1982** *{published data only}*
Brismar B, Hardstedt C, Jacobson S, Kager L, Malmborg AS. Reduction of catheter-associated thrombosis in

parenteral nutrition by intravenous heparin therapy. *Archives of Surgery* 1982;**117**(9):1196–9.

**Broom 2009** ***{published data only}***
Broom JK, O'Shea S, Govindarajulu S, Playford EG, Hawley CM, Isbel NM, et al. Rationale and design of the HEALTHY-CATH trial: a randomised controlled trial of Heparin versus EthAnol Lock THerapY for the prevention of Catheter Associated infecTion in Haemodialysis patients. *BMC Nephrology* 2009;**10**:23.

**Broom 2012** ***{published data only}***
Broom JK, Krishnasamy R, Hawley CM, Playford EG, Johnson DW. A randomised controlled trial of Heparin versus EthAnol Lock THerapy for the prevention of Catheter Associated infecTion in Haemodialysis patients - The HEALTHY-CATH trial. *BMC Nephrology* 2012;**13**: 146.

**Butt 1987** ***{published data only}***
Butt W, Shann F, McDonnell G, Hudson I. Effect of heparin concentration and infusion rate on the patency of arterial catheters. *Critical Care Medicine* 1987;**15**(3):230–2.

**Buturovic 1998** ***{published data only}***
Buturovic J, Ponikvar R, Kandus A, Boh M, Klinkmann J, Ivanovich P. Filling hemodialysis catheters in the interdialytic period: heparin versus citrate versus polygeline: a prospective randomized study. *Artificial Organs* 1998;**22** (11):945–7.

**Campos 2011** ***{published data only}***
Campos RP, do Nascimento MM, Chula DC, Riella MC. Minocycline-EDTA lock solution prevents catheter-related bacteremia in hemodialysis. *Journal of the American Society of Nephrology* 2011;**22**(10):1939–45.

**Cardinal 2000** ***{published data only}***
Cardinal P, Allan J, Pham B, Hindmarsh T, Jones G, Delisle S. The effect of sodium citrate in arterial catheters on acid-base and electrolyte measurements. *Critical Care Medicine* 2000;**28**(5):1388–92.

**Carrasco 2004** ***{published data only}***
Carrasco MN, Bueno A, De Las Cuevas C, Jimenez S, Salinas I, Sartorius A, et al. Evaluation of a triple-lumen central venous heparin-coated catheter versus a catheter coated with chlorhexidine and silver sulphadiazine in critically ill patients. *Intensive Care Medicine* 2004;**30**(4): 633–8.

**Carratala 1999** ***{published data only}***
Carratala J, Niubo J, Fernandez-Sevilla A, Juve E, Castellsague X, Berlanga J, et al. Randomized, double-blind trial of an antibiotic-lock technique for prevention of gram-positive central venous catheter-related infection in neutropenic patients with cancer. *Antimicrobial Agents and Chemotherapy* 1999;**43**(9):2200–4.

**Casale 2009** ***{published data only}***
Casale KE, Horst MA, Anderson AS, Devereux RB. Lower concentration of heparinized flush solution is associated with a higher incidence of femoral sheath clot following diagnostic cardiac catheterization. *Journal of the American College of Cardiology* 2009;**53**(10 Suppl 1):A24.

**Catorze 2011** ***{published data only}***
Catorze N, Teixeira S, Cabrita J, Carreto J, Vieira V, Gonçalves S, et al. Maintenance of arterial catheters with heparin; should we continue?. *Critical Care* 2011;**15**(Suppl 1):P78.

**Catton 2006** ***{published data only}***
Catton JA, Davies J, Dobbins BM, Wood JM, McMahon MJ, Burke D. The effect of heparin in peripheral intravenous nutrition via a fine-bore midline: a randomised double-blind controlled trial. *Clinical Nutrition* 2006;**25**(3):394–9.

**Chen 2014** ***{published data only}***
Chen F-K, Li J-J, Song Y, Zhang Y-Y, Chen P, Zhao C-Z, et al. Concentrated sodium chloride catheter lock solution - a new effective alternative method for hemodialysis patients with high bleeding risk. *Renal Failure* 2014;**36**(1):17–22.

**Cheronis 2013** ***{published data only}***
Cheronis JC. Multi-center, prospective, randomized, open-label, sponsor-blinded, active-control (heparin) clinical investigation to evaluate the safety and effectiveness of B-Lock™ as an antimicrobial catheter lock solution in dialysis patients with a central venous catheter. clinicaltrials.gov/ct2/show/NCT01989091 (first received 30 October 2013).

**Chu 2009** ***{published data only}***
Chu KH, Cheung W, Chan W, Fung KS, Tang HL, Yim KF, et al. A single centre experience of using gentamicin/heparin lock solution in preventing dialysis catheter-related infection. *Hemodialysis International* 2009;**13**(3):372.

**Clifton 1991** ***{published data only}***
Clifton GD, Branson P, Kelly HJ, Dotson LR, Record KE, Phillips BA, et al. Comparison of normal saline and heparin solutions for maintenance of arterial catheter patency. *Heart and Lung* 1991;**20**(2):115–8.

**Coli 2006** ***{published data only}***
Coli L, Donati G, Cianciolo G, Raimondi C, Comai G, Panicali L, et al. Anticoagulation therapy for the prevention of hemodialysis tunneled cuffed catheters (TCC) thrombosis. *Journal of Vascular Access* 2006;**7**(3):118–22.

**Conte 2003** ***{published data only}***
Conte GF, Aravena PC, Fardella PD, Araos DM, Alfaro JI, Flores CA, et al. Prophylaxis of venous thrombosis (VT) associated with central venous catheter (CVC) with low molecular weight heparin (LMWH) in hematologic malignancies [abstract]. Blood 2003; Vol. 102, issue 11: 122b.

**Coplon 2007** ***{published data only}***
Coplon N. Prophylactic antimicrobial catheter lock in hemodialysis patients: a randomized controlled clinical trial. clinicaltrials.gov/ct2/show/NCT00571259 (first received 10 December 2007).

**Corbett 2013** ***{published data only}***
Corbett R, Ashby D, Edwards C, Prout V, Singh S, Bedi R, Duncan N. A randomised control trial of taurolidine-heparin-citrate line locks in prevention of recurrence of catheter related bacteraemia in haemodialysis patients. *Nephrology Dialysis Transplantation* 2013;**28**(Suppl 1):i19.

**Cortes 2006** *{published data only}*
Cortes J. Prospective, randomized trial comparing heparin and minocycline-EDTA flush for the prevention of catheter-related infections and occlusions. clinicaltrials.gov/ct2/show/NCT00378781 (first received 16 September 2006).

**Daniell 1973** *{published data only}*
Daniell HW. Heparin in the prevention of infusion phlebitis. A double-blind controlled study. *JAMA* 1973; **226**(11):12317–21.

**Davanipur 2011** *{published data only}*
Davanipur M, Pakfetrat M, Roozbeh J. Cloxacillin as an antibiotic lock solution for prevention of catheter-associated infection. *Iranian Journal of Kidney Diseases* 2011;**5**(5): 328–31.

**De Cicco 2009** *{published data only}*
De Cicco M, Matovic M, Balestreri L, Steffan A, Pacenzia R, Malafronte M, et al. Early and short-term acenocumarine or dalteparin for the prevention of central vein catheter-related thrombosis in cancer patients: a randomized controlled study based on serial venographies. *Annals of Oncology* 2009;**20**(12):1936–42.

**de la Torre 2012** *{published data only}*
de la Torre Montero JC, Montealegre Sanz M. Heparinization versus salinization in short peripheral catheters for blood draws in clinical trials [Heparinización versus salinización en catéteres periféricos cortos para extracciones de sangre en ensayos clínicos]. *Metas de Enfermeria* 2012;**15**(7):15–8.

**del Cotillo 2008** *{published data only}*
del Cotillo M, Grane N, Llavore M, Quintana S. Heparinized solution vs. saline solution in the maintenance of arterial catheters: a double blind randomized clinical trial. *Intensive Care Medicine* 2008;**34**(2):339–43.

**del Pozo 2012** *{published data only}*
del Pozo JL. Concentration and antibiotic activity in antibiotic lock solutions. clinicaltrials.gov/ct2/show/NCT01592032 (first received 24 April 2012).

**Dogra 2002** *{published data only}*
Dogra GK, Herson H, Hutchison B, Irish AB, Heath CH, Golledge C, et al. Prevention of tunnelled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: a randomized controlled study. *Journal of the American Society of Nephrology* 2002;**13**(8): 2133–9.

**Donham 1987** *{published data only}*
Donham JA, Denning V. Heparin vs. saline in maintaining patency, intermittent infusion devices: pilot study. *Kansas Nurse* 1987;**62**(11):6–7.

**Duncan 2005** *{published data only}*
Duncan N, Singh S, Amao M, Brown W, Dalby E, Edwards C, et al. A single centre randomised control trial of sodium citrate versus heparin line locks for cuffed central venous catheters [abstract no: F-PO539]. Journal of the American Society of Nephrology 2005; Vol. 16:451A.

**Duncan 2010** *{published data only}*
Duncan N. A randomised controlled trial of taurolidine with heparin for prevention of recurrence of catheter related bacteraemia in haemodialysis patients. clinicaltrials.gov/ct2/show/NCT01243710 (accessed 6 October 2014).

**Dunser 2005** *{published data only}*
Dünser MW, Mayr AJ, Hinterberger G, Flörl CL, Ulmer H, Schmid S, et al. Central venous catheter colonization in critically ill patients: a prospective, randomized, controlled study comparing standard with two antiseptic-impregnated catheters. *Anesthesia and Analgesia* 2005;**101**(6):1778–84.

**Eloy 1987** *{published data only}*
Eloy R, Belleville J, Paul J, Pusineri C, Baguet J, Rissoan MC, et al. Thromboresistance of bulk heparinized catheters in human. *Thrombosis Research* 1987;**45**(3):223–33.

**Epperson 1984** *{published data only}*
Epperson EL. Efficacy of 0.9% sodium chloride injection with and without heparin for maintaining indwelling intermittent injection sites. *Clinical Pharmacy* 1984;**3**(6): 626–9.

**Garay Rubio 2011** *{published data only}*
Garay Rubio T, Urruela Oliván M, Hernando Uzkudun A, Asensio Bermejo B, Cossío Díaz C. Effectivity [sic] of saline versus heparinized solution in flushing clogged peripheral catheter [Efectividad en la utilización de suero salino frente a suero salino heparinizado para el lavado de catéteres periféricos obturados]. *Enfermeria Clinica* 2011; **11**(6):283–8.

**Garrelts 1989** *{published data only}*
Garrelts JC, LaRocca J, Ast D, Smith DF Jr, Sweet DE. Comparison of heparin and 0.9% sodium chloride injection in the maintenance of indwelling intermittent i.v. devices. *Clinical Pharmacy* 1989;**8**(1):34–9.

**Glaspy 2000** *{published data only}*
Glaspy JA. A phase III randomized, double-blind, placebo-controlled study to evaluate the effects of fragmin (5, 000 IU subcutaneously) in preventing catheter-related complications when given daily to cancer patients with central venous catheters. clinicaltrials.gov/ct2/show/NCT00006083 (first received 3 August 2000).

**Goh 2011** *{published data only}*
Goh LJ, Teo HS, Masagoes M. Heparinised saline versus normal saline in maintaining patency of arterial and central venous catheters. *Proceedings of Singapore Healthcare* 2011; **20**(3):190–6.

**Goode 1993** *{published data only}*
Goode CJ, Kleiber C, Titler M, Small S, Rakel B, Steelman VM, et al. Improving practice through research: the case of heparin vs. saline for peripheral intermittent infusion devices. *MEDSURG Nursing* 1993;**2**(1):23–7.

**Griffin 2005** *{published data only}*
Griffin MP, Siadaty MS. Papaverine prolongs patency of peripheral arterial catheters in neonates. *Journal of Pediatrics* 2005;**146**(1):62–5.

**Grosso 1989** *{published data only}*
Grosso P, Martello L, Petrini PL, Massei R. Prevention of vena cava thrombosis during catheterization. Comparison of calciheparin and defibrotide. *Minerva Anestesiologica* 1989;**55**(6):273–6.

**Gyr 1995** *{published data only}*
Gyr P, Burroughs T, Smith K, Mahl C, Pontious S, Swerczek L. Double blind comparison of heparin and saline flush solutions in maintenance of peripheral infusion devices. *Pediatric Nursing* 1995;**21**(4):383-9. 366.

**Hall 2006** *{published data only}*
Hall KF, Bennetts TM, Whitta RK, Welman L, Rawlins P. Effect of heparin in arterial line flushing solutions on platelet count: a randomised double-blind study. *Critical Care and Resuscitation* 2006;**8**(4):294–6.

**Hamilton 1988** *{published data only}*
Hamilton RA, Plis JM, Clay C, Sylvan L. Heparin sodium versus 0.9% sodium chloride injection for maintaining patency of indwelling intermittent infusion devices. *Clinical Pharmacy* 1988;**7**(6):439–43.

**Han 2016** *{published data only}*
Han X, Yang X, Huang B, Yuan L, Cao Y. Low-dose versus high-dose heparin locks for hemodialysis catheters: a systematic review and meta-analysis. *Clinical Nephrology* 2016;**86**(1):1–8.

**Harter 2002** *{published data only}*
Harter C, Salwender HJ, Bach A, Egerer G, Goldschmidt H, Ho AD. Catheter-related infection and thrombosis of the internal jugular vein in hematologic-oncologic patients undergoing chemotherapy: a prospective comparison of silver-coated and uncoated catheters. *Cancer* 2002;**94**(1): 245–51.

**Haynes 2002** *{published data only}*
Haynes BJ, Quarles AW, Vavrinchik J, White J, Pedan A. The LifeSite hemodialysis access system: implications for the nephrology nurse. *Nephrology Nursing Journal* 2002;**29** (1):27-33, 72.

**Hemmelgarn 2011** *{published data only}*
Hemmelgarn BR, Moist LM, Lok CE, Tonelli M, Manns BJ, Holden RM, et al. for the Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin (PreCLOT) Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *New England Journal of Medicine* 2011;**364**(4):303–12.

**Hendrickx 2001** *{published data only}*
Hendrickx L, Kuypers D, Evenepoel P, Maes B, Messiaen T, Vanrenterghem Y. A comparative prospective study on the use of low concentrate citrate lock versus heparin lock in permanent dialysis catheters. *International Journal of Artificial Organs* 2001;**24**(4):208–11.

**Heng 2011** *{published data only}*
Heng A-E, Abdelkader MH, Diaconita M, Nony A, Guerraoui A, Caillot N, et al. Impact of short term use of interdialytic 60% ethanol lock solution on tunneled silicone catheter dysfunction. *Clinical Nephrology* 2011;**75** (6):534–41.

**HGU Gregorio Marañón 2010** *{published data only}*
HGU Gregorio Marañón. Clinical study of ethanol lock-therapy in the prevention of non-tunnelled, short term central venous catheter associated infections. clinicaltrials.gov/ct2/show/NCT01229592 (first received 18 October 2012).

**Hoffer 1999** *{published data only}*
Hoffer EK, Borsa J, Santulli P, Bloch R, Fontaine AB. Prospective randomized comparison of valved versus nonvalved peripherally inserted central vein catheters. *American Journal of Roentgenology* 1999;**173**(5):1393–8.

**Horne 1995** *{published data only}*
Horne MK III, May DJ, Alexander HR, Steinhaus EP, Whitman ED, Chang RC, et al. Venographic surveillance of tunneled venous access devices in adult oncology patients. *Annals of Surgical Oncology* 1995;**2**(2):174–8.

**Hryszko 2013** *{published data only}*
Hryszko T, Brzosko S, Mysliwiec M. Low concentration of heparin used for permanent catheters canal locking is effective and diminishes the risk of bleeding. *International Urology and Nephrology* 2013;**45**(3):825–9.

**Hu 2011** *{published data only}*
Hu HH, Hsu CY, Fang HC, Lee PT, Chen CL, Chang TY, et al. Low-dose heparin retention in temporary hemodialysis double-lumen catheter does not increase catheter occlusion and might reduce risk of bleeding. *Blood Purification* 2011; **32**(3):232–7.

**Imamovic 2009** *{published data only}*
Imamovic G. Randomized control trial on citrate as the central venous catheter lock solution. clinicaltrials.gov/ct2/show/NCT00862966 (first received 13 March 2009).

**Ishii 2013** *{published data only}*
Ishii Y, Mishima S, Yukioka T. Comparison of normal saline and heparinized solutions for maintenance of arterial catheter pressure waves. *Academic Emergency Medicine* 2013;**20**(5 Suppl 1):s248.

**Israel Ministry of Health** *{published data only}*
Israel Ministry of Health. Addition of heparin to taurolock-TM CLS in HD patients with TCC: does it improve catheter patency problems?. clinicaltrials.gov/ct2/show/NCT00749619 (first received 7 September 2008).

**Jasinsky 2007** *{published data only}*
Jasinsky L, Wurster J. Occlusion reduction and heparin elimination trial using an anti-reflux device on central intravenous lines. *Journal of the Association for Vascular Access* 2007;**12**(4):205.

**Jeppesen 2013** *{published data only}*
Jeppesen PB. A double blinded, randomized, controlled investigation of taurolidine-citrate/heparin catheter lock solution versus heparin in patients on home parenteral nutrition with previously proven high risk of catheter related blood stream infections. clinicaltrials.gov/ct2/show/NCT01948245 (first received 16 September 2013).

**Johnson 2002** *{published data only}*
Johnson DW, MacGinley R, Kay TD, Hawley CM, Campbell SB, Isbel NM, et al. A randomized controlled trial of topical exit site mupirocin application in patients with tunnelled, cuffed haemodialysis catheters. *Nephrology Dialysis Transplantation* 2002;**17**(10):1802–7.

**Jonkers 2012** *{published data only}*
Jonkers C, Looman KI, Tabbers MM, Tas TA, Serlie MJ. Incidence of central venous catheter related bloodstream infections in adults and children on home parenteral nutrition: heparin versus taurolidine catheter lock. *Clinical Nutrition Supplements* 2012;**7**(1):203–4.

**Jowett 1986** *{published data only}*
Jowett NI, Stephens JM, Thompson DR, Sutton TW. Do indwelling cannulae on coronary care units need a heparin flush?. *Intensive Care Nursing* 1986;**2**(1):16–9.

**Kankanala 2012** *{published data only}*
Kankanala S, Smith K, Henner DE. Efficacy and safety of a 4% sodium citrate locking solution in cuffed tunneled hemodialysis catheters compared with heparin. *American Journal of Kidney Diseases* 2012;**59**(4):A45.

**Karthaus 2006** *{published data only}*
Karthaus M, Kretzschmar A, Kroning H, Biakhov M, Irwin D, Marschner N, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Annals of Oncology* 2006; **17**(2):289–96.

**Kokenge 2010** *{published data only}*
Kokenge T, Lohofener C, Lange C, Grundemann C, Bergmann K, Januschkewitz K, et al. Efficacy and safety of a low-dose citrate catheter locking solution. A randomized double blind controlled trial. *NDT Plus* 2010;**3**(3):iii162.

**Kovacs 2005** *{published data only}*
Kovacs MJ. A pilot study of central venous catheter survival in cancer patients using low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity. clinicaltrials.gov/ct2/show/NCT00216866 (first received 19 September 2005).

**Kudsk 1985** *{published data only}*
Kudsk KA, Powell C, Mirtallo JM, Fabri PJ, Ruberg RL. Heparin does not reduce catheter sepsis during total parenteral nutrition. *Journal of Parenteral and Enteral Nutrition* 1985;**9**(3):348–9.

**Kulkarni 1994** *{published data only}*
Kulkarni M, Elsner C, Ouellet D, Zeldin R. Heparinized saline versus normal saline in maintaining patency of the radial artery catheter. *Canadian Journal of Surgery* 1994;**37** (1):37–42.

**Lacasaña Bellmunt 2006** *{published data only}*
Lacasaña Bellmunt P, Garcia Ortega MJ, Garcia Ruiz C, Palomino Gutierrez B, Toro Padilla R, Vila Sanchez A, et al. Permeabilisation of peripheral venous catheters of intermittent use: with and without heparin [Permeabilización de catéteres venosos periféricos de uso intermitente: con y sin heparina]. *Metas de Enfermeria* 2006;**9**(7):10–6.

**Lavau-Denes 2013** *{published data only}*
Lavau-Denes S, Lacroix P, Maubon A, Preux PM, Genet D, Venat-Bouvet L, et al. Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study. *Cancer Chemotherapy and Pharmacology* 2013;**72**(1):65–73.

**Le 2003** *{published data only}*
Le Corre I, Delorme M, Cournoyer S. A prospective, randomized trial comparing a transparent dressing and a dry gauze on the exit site of long term central venous catheters of hemodialysis patients. *Journal of Vascular Access* 2003;**4** (2):56–61.

**Leslie 1996** *{published data only}*
Leslie GD, Jacobs IG, Clarke GM. Proximally delivered dilute heparin does not improve circuit life in continuous venovenous haemodiafiltration. *Intensive Care Medicine* 2011;**22**(11):1261–4.

**Liang 1998** *{published data only}*
Liang Y, Wang Y, Li D. Clinical observation on normal saline of tube-sealing solution for vein permanent needle. *Shanxi Nursing Journal* 1998;**12**(2):80–1.

**Liang 2015** *{published data only}*
Liang H, Liu XS, Wu YC, Zhang L, Lin QZ, Jie XN, et al. Ultra-low dose heparin locks perform well on non-tunnelled temporary haemodialysis catheters. Nephrology (Carlton, Vic.) 2015; Vol. 20, issue 4:307–8. PUBMED: 25810232]

**Liao 2002** *{published data only}*
Liao S, Zhang Y, Chen L. Comparison of effects on sealing up the infusion tube by using three different solutions. *Chinese Nursing Research* 2002;**16**(2):87–8.

**Lindblad 1994** *{published data only}*
Lindblad B, Bergqvist D, Wakefield TW, Stanley JC. Time-related anticoagulation after regional and systemic administration of heparin in patients undergoing aortoiliac surgery. *European Journal of Vascular Surgery* 1994;**8**(5): 574–7.

**Lok 2007** *{published data only}*
Lok CE, Appleton D, Bhola C, Khoo B, Richardson RMA. Trisodium citrate 4% - an alternative to heparin capping of haemodialysis catheters. *Nephrology Dialysis Transplantation* 2007;**22**(2):477–83.

**Long 2006** *{published data only}*
Long DA, Coulthard MG. Effect of heparin-bonded central venous catheters on the incidence of catheter-related thrombosis and infection in children and adults. *Anaesthesia and Intensive Care* 2006;**34**(4):481–4.

**Lustig 2011** *{published data only}*
Lustig A, Aflalu S. Novel catheter lock solution in prevention of hemodialysis catheter complications. *Journal of Clinical Pharmacology* 2011;**51**(9):1342.

**Macrae 2008** *{published data only}*
Macrae JM, Dojcinovic I, Djurdjev O, Jung B, Shalansky S, Levin A, Kiaii M. Citrate 4% versus heparin and the

reduction of thrombosis study (CHARTS). *Clinical Journal of the American Society of Nephrology* 2008;**3**(2):369–74.

**Maki 2011** *{published data only}*
Maki DG, Ash SR, Winger RK, Lavin P, AZEPTIC Trial Investigators. A novel antimicrobial and antithrombotic lock solution for hemodialysis catheters: a multi-center, controlled,randomized trial. *Critical Care Medicine* 2011; **39**(4):613–20.

**Malo 2010** *{published data only}*
Malo J, Jolicoeur C, Theriault F, Lachaine J, Senecal L. Comparison between standard heparin and tinzaparin for haemodialysis catheter lock. *ASAIO Journal (American Society for Artificial Internal Organs)* 2010;**56**(1):42–7.

**Marin 2000** *{published data only}*
Marin MG, Lee JC, Skurnick JH. Prevention of nosocomial bloodstream infections: effectiveness of antimicrobial-impregnated and heparin-bonded central venous catheters. *Critical Care Medicine* 2000;**28**(9):3332–8.

**McIntyre 2004** *{published data only}*
McIntyre CW, Hulme LJ, Taal M, Fluck RJ. Locking of tunneled hemodialysis catheters with gentamicin and heparin. *Kidney International* 2004;**66**(2):801–5.

**Meier 2011** *{published data only}*
Meier P, Meier R, Turini P, Friolet R, Blanc E. Prolonged catheter survival in patients with acute kidney injury on continuous renal replacement therapy using a less thrombogenic micropatterned polymer modification. *Nephrology Dialysis Transplantation* 2011;**26**(2):628–35.

**Meyer 1995** *{published data only}*
Meyer BA, Little CJ, Thorp JA, Cohen GR, Yeast JD. Heparin versus normal saline as a peripheral line flush in maintenance of intermittent intravenous lines in obstetric patients. *Obstetrics and Gynecology* 1995;**85**(3):433–6.

**Mismetti 2003** *{published data only}*
Mismetti P, Mille D, Laporte S, Charlet V, Buchmuller-Cordier A, Jacquin JP, et al. Low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial. *Haematologica* 2003;**88**(1):67–73.

**Monreal 1996** *{published data only}*
Monreal M, Alastrue A, Rull M, Mira X, Muxart J, Rosell R, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices - prophylaxis with a low molecular weight heparin (Fragmin). *Thrombosis and Haemostasis* 1996;**75**(2):251–3.

**Moran 2012** *{published data only}*
Moran J, Sun S, Khababa I, Pedan A, Doss S, Schiller B. A randomized trial comparing gentamicin/citrate and heparin locks for central venous catheters in maintenance hemodialysis patients. *American Journal of Kidney Diseases* 2012;**59**(1):102–7.

**Mortazavi 2011** *{published data only}*
Mortazavi M, Alsaeidi S, Sobhani R, Salimi F, Atapour A, Sharif N, et al. Succesful prevention of tunneled, central catheter infection by antibiotic lock therapy using cefotaxime. *Journal of Research in Medical Sciences* 2011;**16** (3):303–9.

**Mudge 1998** *{published data only}*
Mudge B, Forcier D, Slattery MJ. Patency of 24-gauge peripheral intermittent infusion devices: a comparison of heparin and saline flush solutions. *Pediatric Nursing* 1998; **24**(2):142-5, 149.

**Na 2012** *{published data only}*
Na HS. Influence by heparinized flush solution of the radial artery catheter: INTEM and HEPTEM analysis. clinicaltrials.gov/ct2/show/NCT01522846 (first received 9 January 2012).

**NCT03114722** *{published data only}*
NCT03114722. Citrate 4% versus heparinised saline in preventing peripherally inserted central catheter (PICC) occlusions. clinicaltrials.gov/show/NCT03114722 (date first received 14 April 2017).

**Niers 2007** *{published data only}*
Niers TMH, Di Nisio M, Klerk CPW, Baarslag HJ, Buller HR, Biemond BJ. Prevention of catheter-related venous thrombosis with nadroparin in patients receiving chemotherapy for hematologic malignancies: a randomized, placebo-controlled study. *Journal of Thrombosis and Haemostasis* 2007;**5**(9):1878–82.

**Niesen 2003** *{published data only}*
Niesen KM, Harris DY, Parkin LS, Henn LT. The effects of heparin versus normal saline for maintenance of peripheral intravenous locks in pregnant women. *Journal of Obstetric Gynecologic and Neonatal Nursing* 2003;**32**(4):503–8.

**Nieto-Rodriguez 1992** *{published data only}*
Nieto-Rodriguez JA, Garcia-Martin MA, Barreda-Hernandez MD, Hervas MJ, Cano-Real O. Heparin and infusion phlebitis: a prospective study. *Annals of Pharmacotherapy* 1992;**26**(10):1211–4.

**NIH Clinical Centers 2002** *{published data only}*
NIH Clinical Centers. Heparin vs. lepirudin flushes in preventing withdrawal occlusion of tunneled, open-ended venous access devices: a blinded, randomized, clinical trial. clinicaltrials.gov/ct2/show/NCT00039767 (first received 7 June 2002).

**Nori 2006** *{published data only}*
Nori US, Manoharan A, Yee J, Besarab A. Comparison of low-dose gentamicin with minocycline as catheter lock solutions in the prevention of catheter-related bacteremia. *American Journal of Kidney Diseases* 2006;**48**(4):596–605.

**Oguzhan 2012** *{published data only}*
Oguzhan N, Pala C, Sipahioglu MH, Cilan H, Durmaz S, Percin D, et al. Locking tunneled hemodialysis catheters with hypertonic saline (26% NaCl) and heparin to prevent catheter-related bloodstream infections and thrombosis: a randomised, prospective trial. *Renal Failure* 2012;**34**(2): 181–8.

**Oran 2008** *{published data only}*
Oran NT, Eser I. Impact of heparin locking frequency on preventing temporary dialysis catheter dysfunction in

haemodialysis patients. *Journal of Renal Care* 2008;**34**(4): 199–202.

**Periard 2008** ***{published data only}***
Periard D, Monney P, Waeber G, Zurkinden C, Mazzolai L, Hayoz D, et al. Randomized controlled trial of peripherally inserted central catheters vs. peripheral catheters for middle duration in-hospital intravenous therapy. *Journal of Thrombosis and Haemostasis* 2008;**6**(8):1281–8.

**Pervez 2002** ***{published data only}***
Pervez A, Ahmed M, Ram S, Torres C, Work J, Zaman F, et al. Antibiotic lock technique for prevention of cuffed tunnel catheter associated bacteremia. *Journal of Vascular Access* 2002;**3**(3):108–13.

**Phulara 2018** ***{published data only}***
Phulara U. Effectiveness of normal saline flush versus heparin saline flush in maintaining the patency of peripheral intravenous cannula and on occurrence of intravenous focal vascular complications in patients receiving intermittent intravenous medications. *Nursing Journal of India* 2018; **109**(2):51–5.

**Pouw 1995** ***{published data only}***
Pouw L, Kilsby D, Francis P, Tulloh B. Heparin thromboprophylaxis via indwelling subcutaneous teflon cannula. *Australian and New Zealand Journal of Surgery* 1995;**65**(11):793–5.

**Power 2009** ***{published data only}***
Power A, Duncan N, Singh SK, Brown W, Dalby E, Edwards C, et al. Sodium citrate versus heparin catheter locks for cuffed central venous catheters: a single-center randomized controlled trial. *American Journal of Kidney Diseases* 2009;**53**(6):1034–41.

**Quenot 2013** ***{published data only}***
Quenot JP. Citrate versus heparin for the lock of non-tunneled hemodialysis catheters in patients hospitalised in ICU. Multicentre, controlled, randomised superiority trial. clinicaltrials.gov/ct2/show/NCT01962116 (first received 27 August 2013).

**Rajani 1979** ***{published data only}***
Rajani K, Goetzman BW, Wennberg RP, Turner E, Abildgaard C. Effect of heparinization of fluids infused through an umbilical artery catheter on catheter patency and frequency of complications. *Pediatrics* 1979;**63**(4): 552–6.

**Randon 2006** ***{published data only}***
Randon C. Prospective study which compares the use of a closing system without a needle and with positive pressure to a heparin lock with positive pressure for patients with a catheter for chemotherapy. clinicaltrials.gov/ct2/show/NCT00386451 (first received 10 October 2006).

**Ray 1999** ***{published data only}***
Ray CE Jr, Shenoy SS, McCarthy PL, Broderick KA, Kaufman JA. Weekly prophylactic urokinase instillation in tunneled central venous access devices. *Journal of Vascular and Interventional Radiology* 1999;**10**(10):1330–4.

**Reichardt 2002** ***{published data only}***
Reichardt P, Kretzschmar A, Biakhov M, Irwin D, Slabber C, Miller L, et al. A phase III double-blind, placebo-controlled study evaluating the efficacy and safety of daily low-molecular-weight heparin (dalteparin sodium, Fragmin) in preventing catheter-related complications in cancer patients with central venous catheters [abstract]. Journal of Clinical Oncology 2002; Vol. 21(Suppl):703a, Abstract 1474.

**Rijnders 2005** ***{published data only}***
Rijnders BJ, Van WE, Vandecasteele SJ, Stas M, Peetermans WE. Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. *Journal of Antimicrobial Chemotherapy* 2005;**55**(1):90–4.

**Roberts 1994** ***{published data only}***
Roberts GW, Holmes MD, Staugas RE, Day RA, Finlay CF, Pitcher A. Peripheral intravenous line survival and phlebitis prevention in patients receiving intravenous antibiotics: heparin/hydrocortisone versus in-line filters. *Annals of Pharmacotherapy* 1994;**28**(1):11–6.

**Ruggiero 1983** ***{published data only}***
Ruggiero RP, Aisenstein TJ. Central catheter fibrin sleeve - heparin effect. *Journal of Parenteral and Enteral Nutrition* 1983;**7**(3):270–3.

**Sanders 2008** ***{published data only}***
Sanders J, Pithie A, Ganly P, Surgenor L, Wilson R, Merriman E, et al. A prospective double-blind randomized trial comparing intraluminal ethanol with heparinized saline for the prevention of catheter-associated bloodstream infection in immunosuppressed haematology patients. *Journal of Antimicrobial Chemotherapy* 2008;**62**(4):809–15.

**Sang Sook 2012** ***{published data only}***
Sang Sook H, Jee Eun P, Nam Eun K, Hwa Ja K. Effects of normal saline for maintenance of arterial lines of surgical patients. *Journal of Korean Academy of Nursing* 2012;**42**(6): 791–8.

**Saxena 2006** ***{published data only}***
Saxena AK, Panhotra BR, Sundaram DS, Al-Hafiz A, Naguib M, Venkateshappa CK, et al. Tunneled catheters' outcome optimization among diabetics on dialysis through antibiotic-lock placement. *Kidney International* 2006;**70**(9): 1629–35.

**Saxena 2006a** ***{published data only}***
Saxena AK, Panhotra BR, Sundaram DS, Morsy MN, Al-Ghamdi AM. Enhancing the survival of tunneled haemodialysis catheters using an antibiotic lock in the elderly: a randomised, double-blind clinical trial. *Nephrology* 2006;**11**(4):299–305.

**Scherr 2002** ***{published data only}***
Scherr K, Guenther C, Koshal A, Finegan B. Effects of heparinized vs non-heparinized flush solutions on patency of arterial and central pressure monitoring lines in the postoperative cardiac surgical patient. *American Journal of Critical Care* 2002;**11**(3):277.

**Schouten 2013** *{published data only}*
Schouten H. Concentrated citrate locking to reduce the incidence of central venous catheter-related infections and thrombosis: a randomized phase III study in a hematological patient population. clinicaltrials.gov/ct2/show/NCT01820962 (first received 12 March 2013).

**Schroder 2008** *{published data only}*
Schroder H. A randomised study of taurolock for the locking of tunneled central venous catheters in children with malignant diseases. clinicaltrials.gov/ct2/show/NCT00735813 (first received 14 August 2008).

**Shirzad 2013** *{published data only}*
Shirzad M, Espahbodi F, Baboli MT, Samakoosh MA, Khalilian A. Effects of heparin lock - antibiotics to prevent infections in patients undergoing hemodialysis: a clinical trial. *Journal of Mazandaran University of Medical Sciences* 2013;**22**(96):99–104.

**Silva 2008** *{published data only}*
Silva J, Teixeira e Costa, Baptista A, Ramos A, Ponce P. Catheter-related bacteremia in hemodialysis: which preventive measures to take?. *Nephron* 2008;**110**(4):251–7.

**Silva 2013** *{published data only}*
Silva TNV, Mendes ML, Abrao JMG, Caramori JT, Ponce D. Successful prevention of tunneled central catheter infection by antibiotic lock therapy using cefazolin and gentamicin. *International Urology and Nephrology* 2013;**45**(5):1405–13.

**Smith 1990** *{published data only}*
Smith I, Hathaway M, Goldman C, Ng J, Brunton J, Simor AE, et al. A randomized study to determine complications associated with duration of insertion of heparin locks. *Research in Nursing and Health* 1990;**13**(6):367–73.

**Sofroniadou 2012** *{published data only}*
Sofroniadou S, Revela I, Smirloglou D, Makriniotou I, Zerbala S, Kouloubinis A, et al. Linezolid versus vancomycin antibiotic lock solution for the prevention of nontunneled catheter-related blood stream infections in hemodialysis patients: a prospective randomized study. *Seminars in Dialysis* 2012;**25**(3):344–50.

**Solomon 2001** *{published data only}*
Solomon B, Moore J, Arthur C, Prince HM. Lack of efficacy of twice-weekly urokinase in the prevention of complications associated with Hickman catheters: a multicentre randomised comparison of urokinase versus heparin. *European Journal of Cancer* 2001;**37**(18):2379–84.

**Solomon 2010** *{published data only}*
Solomon LR, Cheesbrough JS, Ebah L, Al-Sayed T, Heap M, Millband N, et al. A randomized double-blind controlled trial of taurolidine-citrate catheter locks for the prevention of bacteremia in patients treated with hemodialysis. *American Journal of Kidney Diseases* 2010;**55**(6):1060–8.

**Stas 2001** *{published data only}*
Stas KJF, Vanwalleghem J, De Moor B, Keuleers H. Trisodium citrate 30% vs heparin 5% as catheter lock in the interdialytic period in twin- or double-lumen dialysis catheters for intermittent haemodialysis. *Nephrology Dialysis Transplantation* 2001;**16**(7):1521–2.

**Thomson 2011** *{published data only}*
Thomson PC, Morris ST, Mactier RA. The effect of heparinized catheter lock solutions on systemic anticoagulation in hemodialysis patients. *Clinical Nephrology* 2011;**75**(3):212–7.

**Thurlimann 1992** *{published data only}*
Thurlimann B, Bachmann I. Effective prevention of chemotherapy-induced phlebitis by low-dose heparin: a prospective randomised trial. *Annals of Oncology* 1992;**3**(4):311–3.

**Tolar 1996** *{published data only}*
Tolar B, Gould JR. The timing and sequence of multiple device-related complications in patients with long-term indwelling Groshong catheters. *Cancer* 1996;**78**(6):1308–13.

**Trottier 1995** *{published data only}*
Trottier SJ, Veremakis C, O'Brien J, Auer AI. Femoral deep vein thrombosis associated with central venous catheterization: results from a prospective, randomized trial. *Critical Care Medicine* 1995;**23**(1):52–9.

**Tuncali 2005** *{published data only}*
Tuncali BE, Kuvaki B, Tuncali B, Capar E. A comparison of the efficacy of heparinized and nonheparinized solutions for maintenance of perioperative radial arterial catheter patency and subsequent occlusion. *Anesthesia and Analgesia* 2005;**100**(4):1117–21.

**Tuten 1991** *{published data only}*
Tuten SH, Gueldner SH. Efficacy of sodium chloride versus dilute heparin for maintenance of peripheral intermittent intravenous devices. *Applied Nursing Research* 1991;**4**(2):63–71.

**Venditto 2010** *{published data only}*
Venditto M, du Montcel ST, Robert J, Trystam D, Dighiero J, Hue D, et al. Effect of catheter-lock solutions on catheter-related infection and inflammatory syndrome in hemodialysis patients: heparin versus citrate 46% versus heparin/gentamicin. *Blood Purification* 2010;**29**(3):268–73.

**Vercaigne 2011** *{published data only}*
Vercaigne L. Efficacy and safety of an ethanol/sodium citrate locking solution to prevent hemodialysis catheter-related infections: a pilot study. clinicaltrials.gov/ct2/show/NCT01394458 (first received 4 July 2011).
Vercaigne LM. Efficacy and safety of an ethanol/sodium citrate locking solution: a pilot study. Vascular Access 2014; Vol. 8, issue 1:25.
* Vercaigne LM, Allan DR, Armstrong SW, Zacharias JM, Miller LM. An ethanol/sodium citrate locking solution compared to heparin to prevent hemodialysis catheter-related infections: a randomized pilot study. *Journal of Vascular Access* 2016;**17**(1):55–62.

**Verso 2005** *{published data only}*
Verso M, Agnelli G, Bertoglio S, Di Somma FC, Paoletti F, Ageno W, et al. Enoxaparin for the prevention of venous

thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *Journal of Clinical Oncology* 2005;**23**(18): 4057–62.

**Wang 2012** ***{published data only}***
Wang R, Luo O, He L, Li JX, Zhang MG. Preservative-free 0.9% sodium chloride for flushing and locking peripheral intravenous access device: a prospective controlled trial. *Journal of Evidence-Based Medicine* 2012;**5**(4):205–8.

**Warkentin 1998** ***{published data only}***
Warkentin TE, Ling E, Ho A, Sheppard JI. 'Incidental' unfractionated heparin (UFH) vs normal saline (NS) flushes for intraoperative invasive catheters and the frequency of formation of heparin induced thrombocytopenia IgG antibodies (HIT-IgG): a randomized controlled trial. *Blood* 1998;**92**(10 Suppl 1 (Pt 2)):91.

**Weijmer 2005** ***{published data only}***
Weijmer MC, van den Dorpel MA, Van de Ven PJ, ter Wee PM, van Geelen JA, Groeneveld JO, et al. Randomized, clinical trial comparison of trisodium citrate 30% and heparin as catheter-locking solution in hemodialysis patients. *Journal of the American Society of Nephrology* 2005; **16**(9):2769–77.

**Whitta 2006** ***{published data only}***
Whitta RK, Hall KF, Bennetts TM, Welman L, Rawlins P. Comparison of normal or heparinised saline flushing on function of arterial lines. *Critical Care and Resuscitation* 2006;**8**(3):205–8.

**Witkovski 2010** ***{published data only}***
Witkovski MC. Continuous or intermittent for keeping arterial catheter in children: a randomized clinical trial. clinicaltrials.gov/show/NCT01097031 (first received 30 March 2010).

**Wolf 2011** ***{published data only}***
Wolf J. A double-blind, randomized, placebo-controlled trial of ethanol lock therapy for treatment and secondary prophylaxis of central line associated bloodstream infection (CLABSI) in children and adolescents. clinicaltrials.gov/show/NCT01472965 (first received 14 November 2011).

**Wong 2009** ***{published data only}***
Wong FSY, Cheng YL, Chow NY, Cheung ALC, Chau SK, Ngai MS, et al. Effect of 3 different solutions used for locking hemodialysis catheter on systemic coagulation: a randomized study. *Hemodialysis International* 2009;**13**(3): 403.

**Xu 2017** ***{published data only}***
Xu L, Hu Y, Huang X, Fu J, Zhang J. Heparinized saline versus normal saline for maintaining peripheral venous catheter patency in China: an open-label, randomized controlled study. *Journal of International Medical Research* 2017;**45**(2):471–80.

**Young 2009** ***{published data only}***
Young AM, Billingham LJ, Begum G, Kerr DJ, Hughes AI, Rea DW, et al. WARP Collaborative Group, UK. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. *Lancet* 2009;**373**(9663):567–74.

**Zacharski 2005** ***{published data only}***
Zacharski LR, Prandoni P, Monreal M. Warfarin versus low-molecular-weight heparin therapy in cancer patients. *Oncologist* 2005;**10**(1):72–9.

**Zhang 2009** ***{published data only}***
Zhang P, Yuan J, Tan HZ, Lv R, Chen JH. Successful prevention of cuffed hemodialysis catheter-related infection using an antibiotic lock technique by strictly catheter-restricted antibiotic lock solution method. *Blood Purification* 2009;**27**(2):206–11.

**Ziyaeifard 2015** ***{published data only}***
Ziyaeifard M, Alizadehasl A, Aghdaii N, Sadeghi A, Azarfarin R, Masoumi G, Golbargian G. Heparinized and saline solutions in the maintenance of arterial and central venous catheters after cardiac surgery. *Anesthesiology and Pain Medicine* 2015;**5**(5):e28056.

## References to studies awaiting assessment

**Klein 2017** ***{published data only}***
Klein J, Patterson A, Jepsen A, Badgero K, Moore M, Warrell WA, et al. Effectiveness of heparin versus saline flushing for managing central venous catheters (CVCs) in the blood and marrow transplant (BMT) patients: a pilot study. *Biology of Blood and Marrow Transplantation* 2017; **23**(3 Suppl 1):S386.

**Klein 2018** ***{published data only}***
Klein J, Jepsen A, Patterson A, Reich RR, Mason TM. Heparin versus normal saline: flushing effectiveness in managing central venous catheters in patients undergoing blood and marrow transplantation. *Clinical Journal of Oncology Nursing* 2018;**22**(2):1–5.

## References to ongoing studies

**NCT02354118** ***{published data only}***
NCT02354118. Maintaining patency in implanted port catheters. clinicaltrials.gov/ct2/show/NCT02354118 (first received 29 January 2015).

**NCT02923830** ***{published data only}***
NCT02923830. Maintaining patency in BioFlo implanted port catheters with saline only flushes. clinicaltrials.gov/ct2/show/NCT02923830 (first received 30 September 2016).

**RBR-3ht499** ***{published data only}***
RBR-3ht499. Effectiveness of heparin solution in preventing Hickman® catheter occlusion: clinical trial. RBR-3ht499 [Efetividade da solução de heparina na prevenção de oclusão do cateter de Hickman®: ensaio clínico]. ensaiosclinicos.gov.br/rg/RBR-3ht499/ (first received 16 March 2017):(UTN Number: U1111-1194-3653).

## Additional references

**Battistelli 2010**
Battistelli S, Genovese A, Gori T. Heparin-induced thrombocytopenia in surgical patients. *American Journal of Surgery* 2010;**199**(1):43–51.

**Bern 1990**
Bern MM, Lokich JJ, Wallach SR, Bothe A, Benotti PN, Arkin CF, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. *Annals of Internal Medicine* 1990;**112**(6): 423–8.

**Bishop 2009**
Bishop L. Aftercare and management of central venous access devices. In: Hamilton H, Bodenham A editor(s). *Central Venous Catheters*. 1st Edition. Chichester: Wiley & Blackwell, 2009:221–37.

**Bradford 2015**
Bradford NK, Edwards RM, Chan RJ. Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children. *Cochrane Database of Systematic Reviews* 2015, Issue 11. DOI: 10.1002/14651858.CD010996.pub2

**Bradford 2016**
Bradford NK, Edwards RM, Chan RJ. Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children: a systematic review. *International Journal of Nursing Studies* 2016;**59**:51–9.

**Burns 2008**
Burns KE, McLaren A. A critical review of thromboembolic complications associated with central venous catheters. *Canadian Journal of Anaesthesia* 2008;**55**(8):532–41.

**Dal Molin 2014**
Dal Molin A, Allara E, Montani D, Milani S, Frassati C, Cossu S, et al. Flushing the central venous catheter: is heparin necessary?. *Journal of Vascular Access* 2014;**15**(4): 241–8.

**Eisen 2006**
Eisen LA, Narasimhan M, Berger JS, Mayo PH, Rosen MJ, Schneider RF. Mechanical complications of central venous catheters. *Journal of Intensive Care Medicine* 2006;**21**(1): 40–6.

**Goode 1991**
Goode CJ, Titler M, Rakel B, Ones DS, Kleiber C, Small S, et al. A meta-analysis of effects of heparin flush and saline flush: quality and cost implications. *Nursing Research* 1991; **40**(6):324–30.

**GRADEproGDT 2015 [Computer program]**
McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed August 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

**Guyatt 2008**
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* 2008;**336**(7650):924–6.

**Higgins 2003**
Higgins JPT, Thompson SG, Deeks JJ, Altmann DG. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003;**327**(7414):557–60.

**Higgins 2011**
Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

**INS 2016**
Gorski LA. INS Learning Center: Infusion Therapy Standards of Practice 2016. learningcenter.ins1.org/products/infusion-therapy-standards-of-practice-2016 (accessed 9 May 2017).

**Jacobs 2003**
Jacobs BR. Central venous catheter occlusion and thrombosis. *Critical Care Clinics* 2003;**19**(3):489–514.

**Jonker 2010**
Jonker MA, Osterby KR, Vermeulen LC, Kleppin SM, Kudsk KA. Does low-dose heparin maintain central venous access device patency? A comparison of heparin versus saline during a period of heparin shortage. *Journal of Parenteral and Enteral Nutrition* 2010;**34**(4):444–9. [PUBMED: 20631392]

**Klerk 2003**
Klerk CPW, Smorenburg SM, Büller HR. Thrombosis prophylaxis in patient populations with a central venous catheter. *Archives of Internal Medicine* 2003;**163**(16): 1913–21.

**Lee 2007**
Lee DH, Warkentin TE. Frequency of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A editor (s). *Heparin-Induced Thrombocytopenia*. 4th Edition. New York: Informa Healthcare, 2007:67–116.

**López-Briz 2005**
López-Briz E, Ruiz-Garcia V. Effectiveness of heparin versus NaCl 0.9% in central venous catheter flushing. A systematic review [Heparina frente a cloruro sódico 0,9% para mantener permeables los catéteres venosos centrales. Una revisión sistemática]. *Farmacia Hospitalaria* 2005;**29** (4):258–64.

**Martel 2005**
Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005;**106**(8):2710–5.

**McGee 2003**
McGee DC, Gould MK. Preventing complications of central venous catheterization. *New England Journal of Medicine* 2003;**348**(12):1123–33.

**McNulty 2005**
McNulty I, Katz E, Kim KY. Thrombocytopenia following heparin flush. *Progress in Cardiovascular Nursing* 2005;**20**(4):143–7.

**McQuay 1997**
McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Annals of Internal Medicine* 1997;**126**(9):712–20.

**Mermel 2000**
Mermel LA. Prevention of intravascular catheter-related infections. *Annals of Internal Medicine* 2000;**132**(5):391–402.

**Merrer 2001**
Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy E, Barre E, et al. French Catheter Study Group in Intensive Care. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *Journal of the American Medical Association* 2001;**286**(6):700–7.

**Mitchell 2009**
Mitchell MD, Anderson BJ, Williams K, Umscheid CA. Heparin flushing and other interventions to maintain patency of central venous catheters: a systematic review. *Journal of Advanced Nursing* 2009;**65**(10):2007–21.

**Raad 1997**
Raad I, Darouiche R, Dupuis J, Abi-Said D, Gabrielli A, Hachem R, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. The Texas Medical Center Catheter Study Group. *Annals of Internal Medicine* 1997;**127**(4):267–74.

**Randolph 1998a**
Randolph AG. An evidence-based approach to central venous catheter management to prevent catheter-related infection in critically ill patients. *Critical Care Clinics* 1998;**14**(3):411–21.

**Randolph 1998b**
Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. *Chest* 1998;**113**(1):165–71.

**Shah 2008**
Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. *Cochrane Database of Systematic Reviews* 2008, Issue 2. DOI: 10.1002/14651858.CD002772.pub3

**Smith 2013**
Smith RN. Central venous catheters. *British Medical Journal* 2013;**347**:f6570. DOI: 10.1136/bmj.f6570

**Sona 2012**
Sona C, Prentice D, Schallom L. National survey of central venous catheter flushing in the intensive care unit. *Critical Care Nurse* 2012;**32**(1):e12–9.

**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**
Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *Journal of the American Medical Association* 1999;**281**(3):261–7.

**Verso 2003**
Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *Journal of Clinical Oncology* 2003;**21**(19):3665–75.

**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-Marti 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-Marti 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 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| 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:<br>• Heparin 100 IU/mL locking (3 mL)<br>• 0.9% sodium chloride locking (10 mL) |
| 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 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| 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 |

**Dal Molin 2015**

| | |
|---|---|
| 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 |

**Dal Molin 2015** (*Continued*)

| | | |
|---|---|---|
| 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:<br>• 10 mL 0.9% NaCl and after 3 mL heparin (100 IU/mL)<br>• 10 mL 0.9% NaCl |
| 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 Leuvens 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 |

**Heidari 2015** (*Continued*)

| | | |
|---|---|---|
| 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:<br>• 20 mL 0.9% NaCl + 2 mL heparin 1000 IU/mL lock<br>• 20 mL 0.9% NaCl |
| 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 |

| | | |
|---|---|---|
| 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 |

**Lyons 2014** (*Continued*)

| | | |
|---|---|---|
| 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 | 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:<br>• If the lumen could not be flushed, the participant was repositioned and the flush re-attempted<br>• If still unable to flush, the syringe was changed and the flush re-attempted<br>Secondary outcome: heparin-induced thrombocytopaenia (HIT), assessed by daily platelet count, starting on day 4 from the time of giving heparin flushes for all participants in Group H |
| Notes | Exclusion criteria: known heparin allergy, diagnosis of HIT, bleeding risk identified by attending physician, age < 18 years or > 58 years, requiring prolonged ICU stay with ailments such as terminal illness, severe septicaemia, MODS, etc<br>Follow-up: average 1 week<br>Unit of randomisation: the participant<br>Source of support: none declared |

***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 |

**Mahesh 2014** (*Continued*)

| | | |
|---|---|---|
| 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:<br>• 5 mL 0.9% NaCl<br>• 5 mL heparin 100 IU/mL |
| 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:<br>• Heparin 5000 IU/mL<br>• 0.9% NaCl<br>• Vitamin C 200 mg/mL |
| 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) 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:<br>• 3 mL heparin 10 IU/mL<br>• 10 mL 0.9% NaCl |
| Outcomes | Rate of lumen non-patency, blood loss return, flush failure, rate of catheter-related bloodstream 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) 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 thrombocytopaenia.
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 |
|---|---|
| AACCN 1993 | Arterial catheters were used |
| Abdelkefi 2004 | Interventions do not fulfil inclusion criteria (continuous infusion) |
| Abdelkefi 2005 | Interventions do not fulfil inclusion criteria (continuous infusion) |
| Abdelkefi 2005a | Interventions do not fulfil inclusion criteria (heparin-coated catheters) |
| Abdelkefi 2007 | Interventions do not fulfil inclusion criteria (heparin-bonded catheter + normal saline vs non-coated catheter + continuous infusion heparin) |
| Abdelkefi 2008 | Interventions do not fulfil inclusion criteria (impregnated catheters) |
| Agnelli 2009 | Interventions do not fulfil inclusion criteria (systemic nadroparin) |
| Akyuz 2010 | Comparison does not fulfil inclusion criteria (heparin vs taurolidine + citrate) |
| Alexander 2010 | 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 |
| Betjes 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*)

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

(*Continued*)

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

**Klein 2018** (*Continued*)

| | |
|---|---|
| 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:<br>• Able to read and understand English<br>• Has an implanted port in place less than 1 year<br>• Evidence of a patent (unobstructed) port catheter before enrolment in the study<br>• Is receiving active treatment (i.e. is receiving a therapeutic drug through the implanted port)<br>• Current treatment protocol projected to continue for a minimum of 3 months<br>• Anticipates receiving care at identified centres for 12 months following enrolment in the study<br>• Does not receive care for implanted port at any other facility |
| 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:<br>• Able to read and understand English<br>• Has a BioFlo implanted port in place less than 1 year<br>• Evidence of a patent BioFlo port catheter before enrolment in the study<br>• Is receiving active treatment (i.e. is receiving a therapeutic drug) through the BioFlo implanted port<br>• Current treatment protocol projected to continue for a minimum of 3 months |

**NCT02923830** (*Continued*)

| | |
|---|---|
| | • Anticipates receiving care at identified centres for 12 months following enrolment in the study<br>• Does not receive care for BioFlo implanted port at any other facility |
| 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 | • Planned date of first enrolment: 22-03-2017<br>• Planned date of last enrolment: 20-10-2017 |
| Contact information | Sandra Regina da Silva<br>Address: Rua Congo, 271<br>Pinhais<br>Brazil 8320-320 |

**RBR-3ht499** (*Continued*)

| | |
|---|---|
| | 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 thrombocytopaenia | 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 ≥ 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

| Study or subgroup | Heparin n/N | NS n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Participants | | | | | |
| Beigi 2014 | 0/50 | 0/50 | | | Not estimable |
| Bowers 2008 | 0/52 | 3/50 | | 1.1 % | 0.14 [ 0.01, 2.60 ] |
| Dal Molin 2015 (1) | 10/217 | 15/213 | | 13.4 % | 0.65 [ 0.30, 1.42 ] |
| Goosens 2013 | 73/398 | 78/404 | | 49.0 % | 0.95 [ 0.71, 1.27 ] |
| Kaneko 2004 | 1/22 | 1/26 | | 1.3 % | 1.18 [ 0.08, 17.82 ] |
| Lyons 2014 (2) | 6/62 | 7/28 | | 8.7 % | 0.39 [ 0.14, 1.05 ] |
| Mahesh 2014 | 2/50 | 4/50 | | 3.4 % | 0.50 [ 0.10, 2.61 ] |
| **Subtotal (95% CI)** | **851** | **821** | | **76.9 %** | **0.79 [ 0.58, 1.08 ]** |
| Total events: 92 (Heparin), 108 (NS) | | | | | |
| Heterogeneity: $Tau^2$ = 0.02; $Chi^2$ = 5.35, df = 5 (P = 0.37); $I^2$ =7% | | | | | |
| Test for overall effect: Z = 1.46 (P = 0.15) | | | | | |
| 2 Catheters | | | | | |
| Pumarola 2007 | 0/125 | 0/125 | | | Not estimable |
| Rabe 2002 | 3/33 | 9/33 | | 6.1 % | 0.33 [ 0.10, 1.12 ] |
| Schallom 2012 | 12/314 | 25/395 | | 17.0 % | 0.60 [ 0.31, 1.18 ] |


(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Heparin n/N | NS n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **472** | **553** | | **23.1 %** | **0.53 [ 0.29, 0.95 ]** |
| Total events: 15 (Heparin), 34 (NS) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.70, df = 1 (P = 0.40); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.15 (P = 0.032) | | | | | |
| **Total (95% CI)** | **1323** | **1374** | | **100.0 %** | **0.70 [ 0.51, 0.95 ]** |
| Total events: 107 (Heparin), 142 (NS) | | | | | |
| Heterogeneity: $Tau^2$ = 0.03; $Chi^2$ = 8.11, df = 7 (P = 0.32); $I^2$ =14% | | | | | |
| Test for overall effect: Z = 2.28 (P = 0.023) | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.43, df = 1 (P = 0.23), $I^2$ =30% | | | | | |


(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

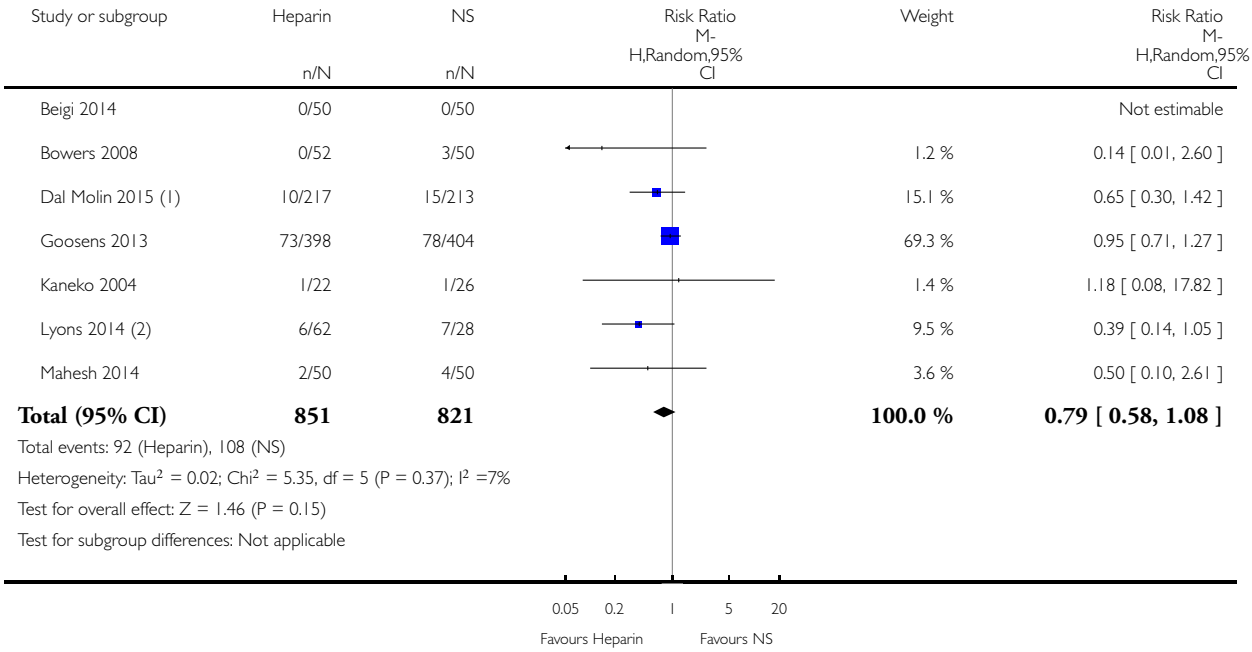
(2) We combined results from low and high dose heparin groups

## 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

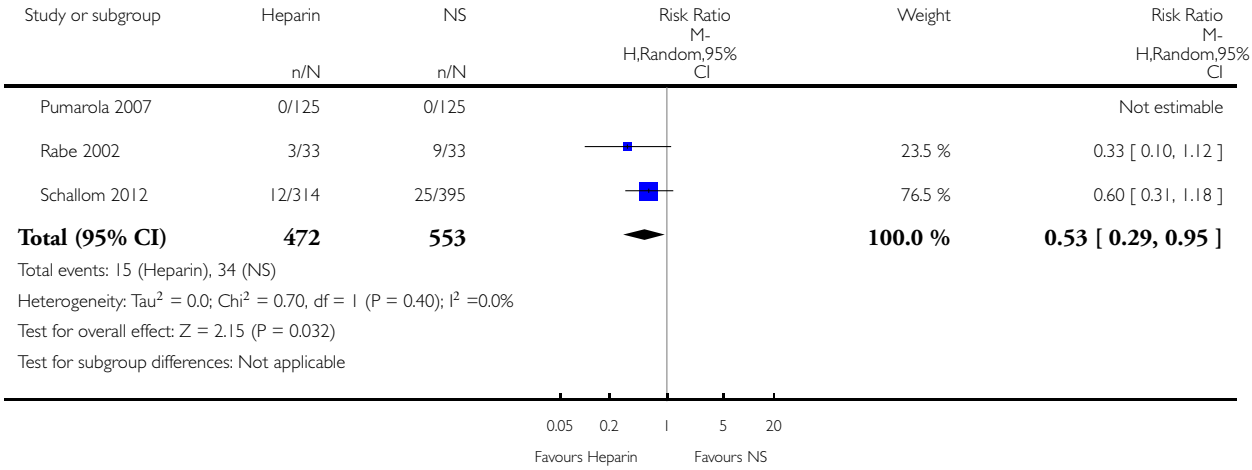
(2) We combined results from low and high dose heparin groups

### 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)

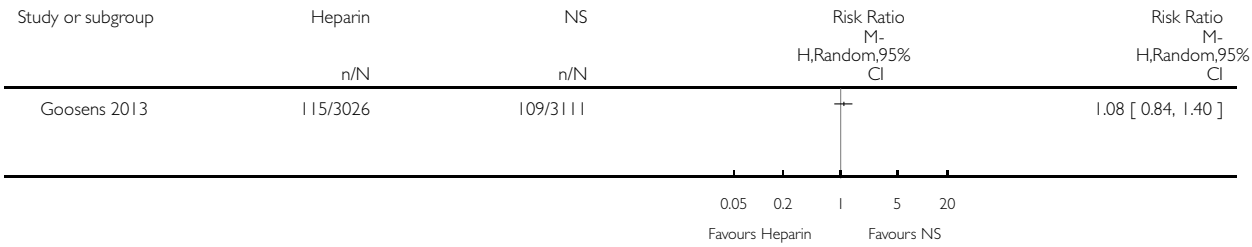



### Analysis 2.3. Comparison 2 Occlusion of CVCs, Outcome 3 Occlusion of CVCs (unit of analysis line access).

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)

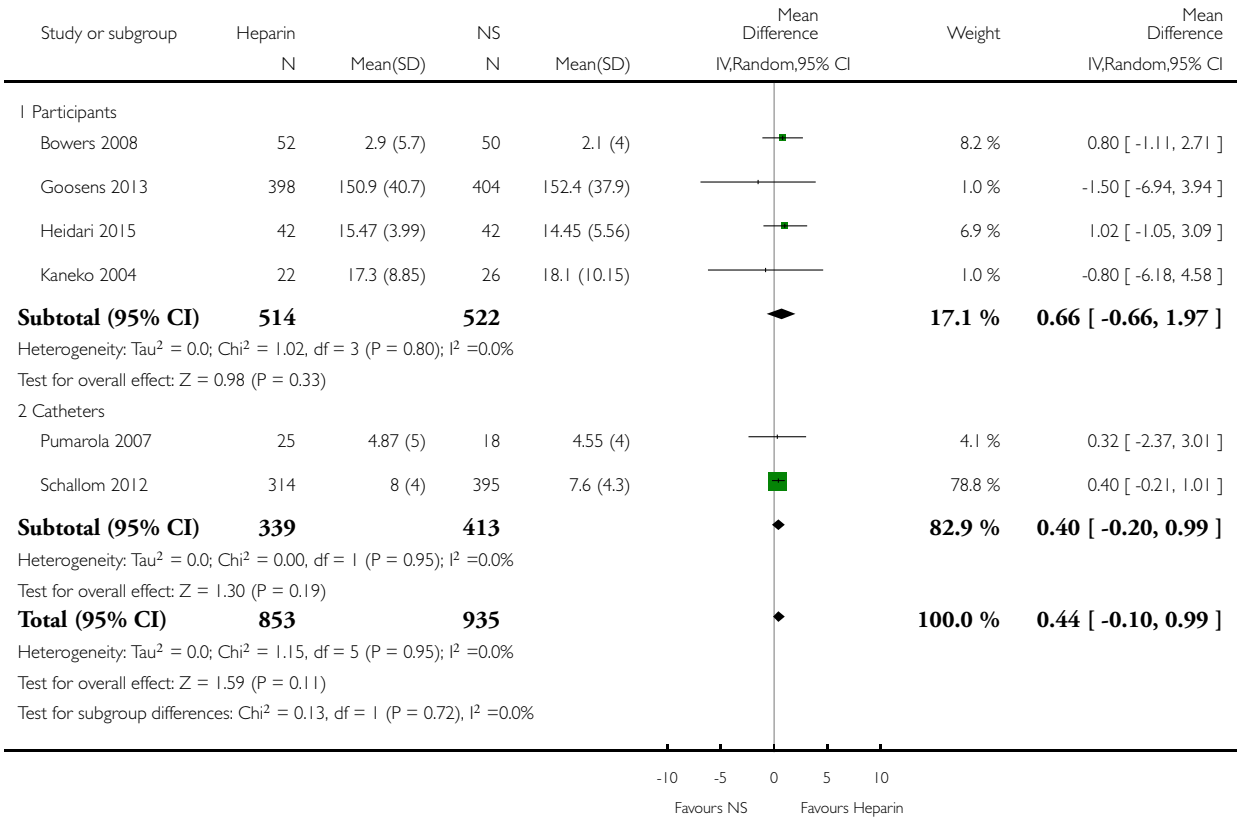


## Analysis 3.1. Comparison 3 All patency, Outcome 1 All studies.

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)

| Study or subgroup | Heparin N | Mean(SD) | NS N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Bowers 2008 | 52 | 2.9 (5.7) | 50 | 2.1 (4) | | 47.7 % | 0.80 [ -1.11, 2.71 ] |
| Goosens 2013 | 398 | 150.9 (40.7) | 404 | 152.4 (37.9) | | 5.8 % | -1.50 [ -6.94, 3.94 ] |
| Heidari 2015 | 42 | 15.47 (3.99) | 42 | 14.45 (5.56) | | 40.4 % | 1.02 [ -1.05, 3.09 ] |
| Kaneko 2004 | 22 | 17.3 (8.85) | 26 | 18.1 (10.15) | | 6.0 % | -0.80 [ -6.18, 4.58 ] |
| **Total (95% CI)** | **514** | | **522** | | | **100.0 %** | **0.66 [ -0.66, 1.97 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.02$, df = 3 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable

## 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)

| Study or subgroup | Heparin | | NS | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Random,95% CI | | IV,Random,95% CI |
| Pumarola 2007 | 25 | 4.87 (5) | 18 | 4.55 (4) | | 4.9 % | 0.32 [ -2.37, 3.01 ] |
| Schallom 2012 | 314 | 8 (4) | 395 | 7.6 (4.3) | | 95.1 % | 0.40 [ -0.21, 1.01 ] |
| **Total (95% CI)** | **339** | | **413** | | | **100.0 %** | **0.40 [ -0.20, 0.99 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 1.30 (P = 0.19)

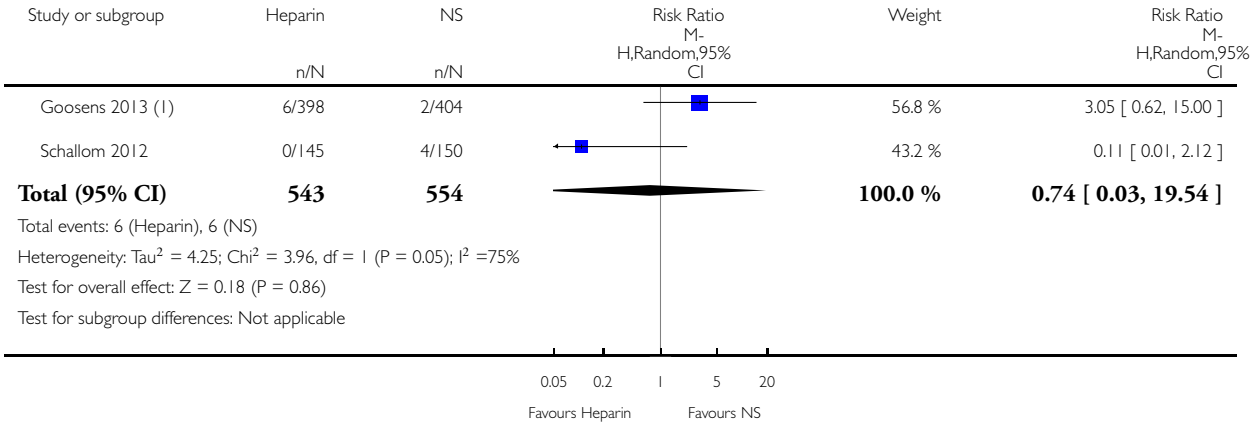
Test for subgroup differences: Not applicable

## 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



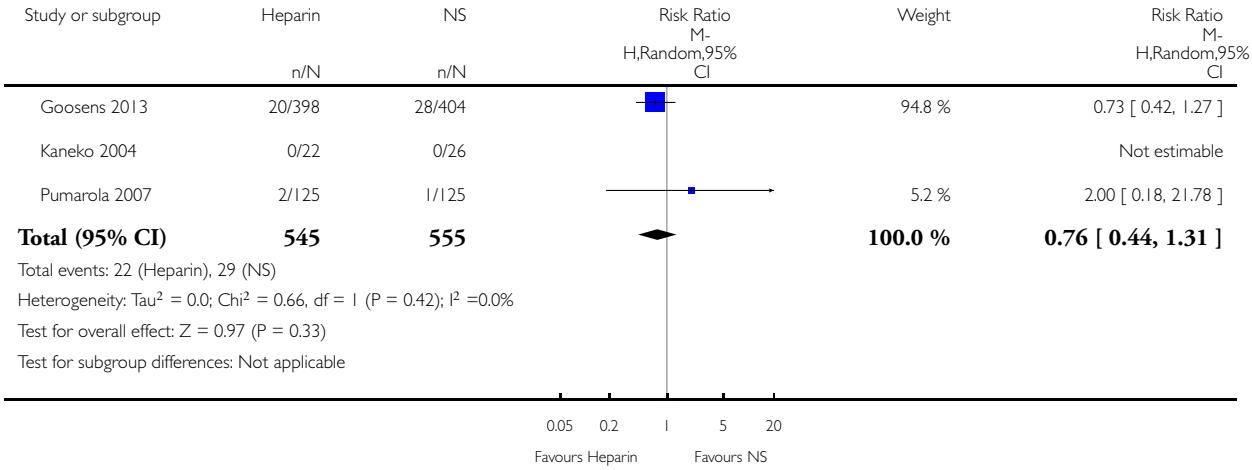

(1) Staphylococcus aureus 2, Staphylococcus epidermidis 3, Candida glabatra 1 in heparin group and Staphylococcus epidermidis 1 and Staphylococcus homini 1 in saline group

## 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

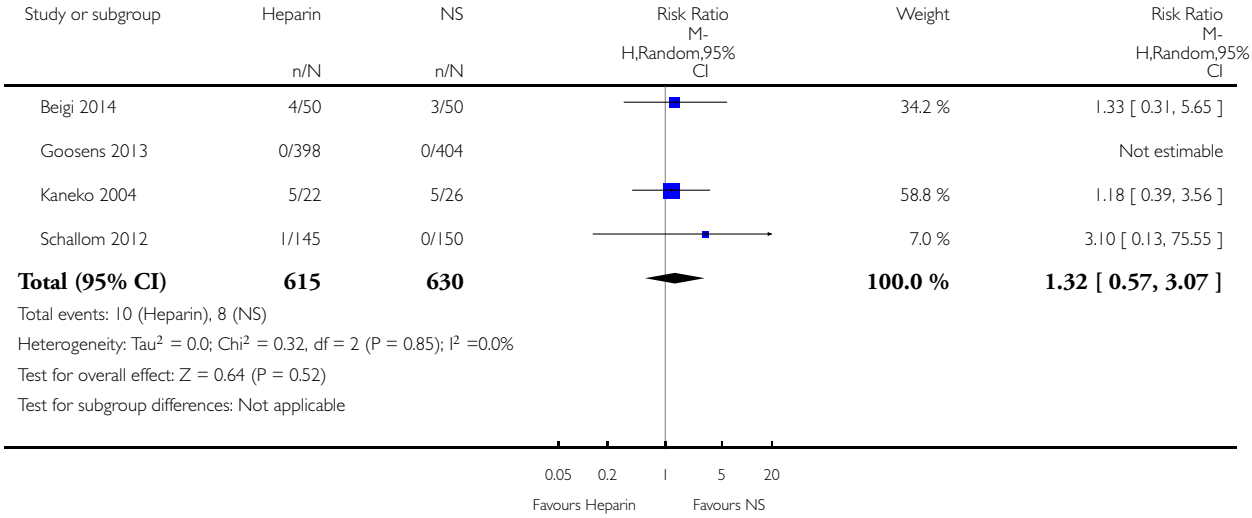


### Analysis 5.3. Comparison 5 Safety, Outcome 3 Haemorrhage from any site.

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

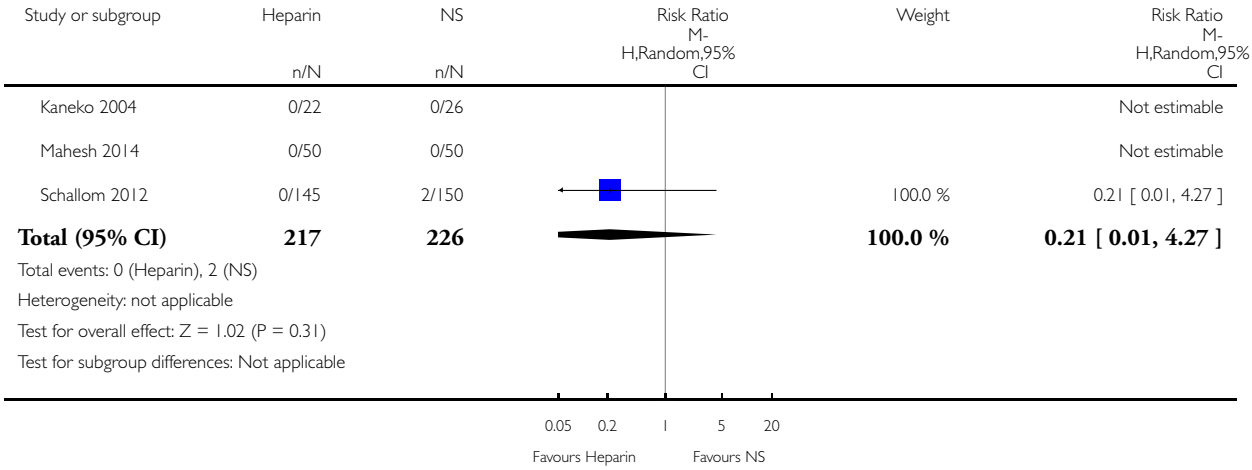


### Analysis 5.4. Comparison 5 Safety, Outcome 4 Heparin-induced thrombocytopaenia.

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 thrombocytopaenia

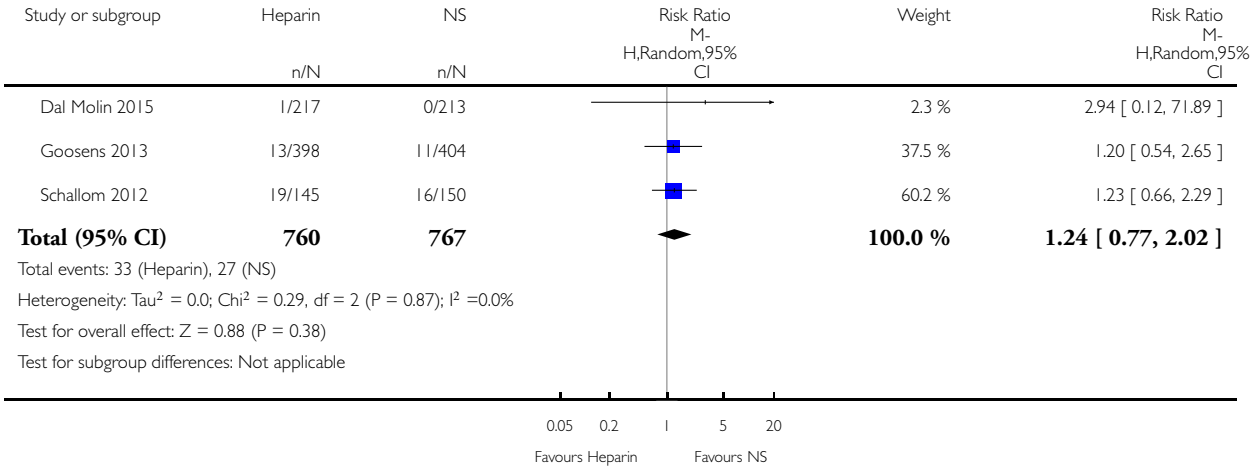


### Analysis 5.5. Comparison 5 Safety, Outcome 5 CVC-related thrombosis.

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

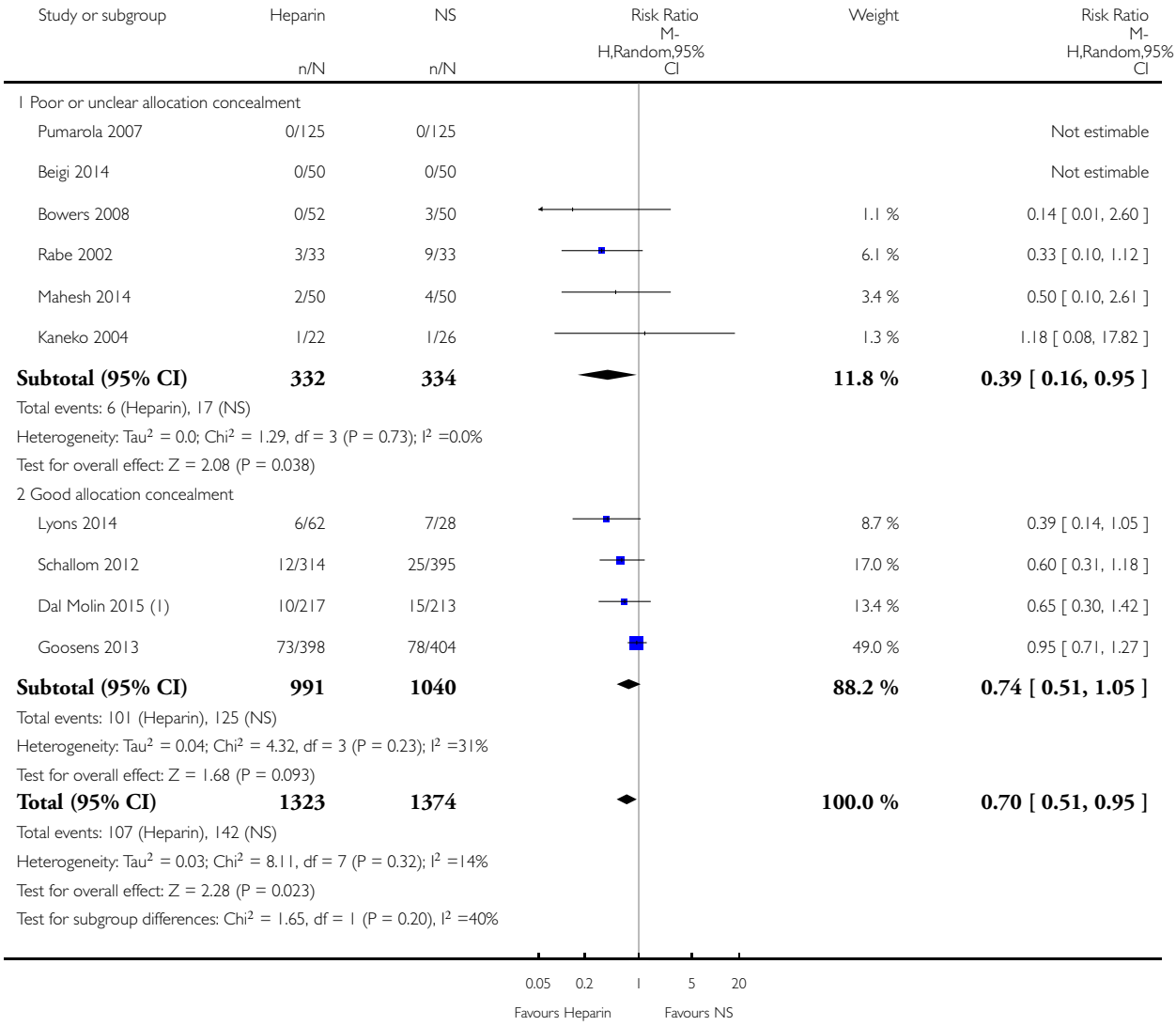


## Analysis 6.1. Comparison 6 Sensitivity analysis, Outcome 1 Occlusion of CVCs related to quality.

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



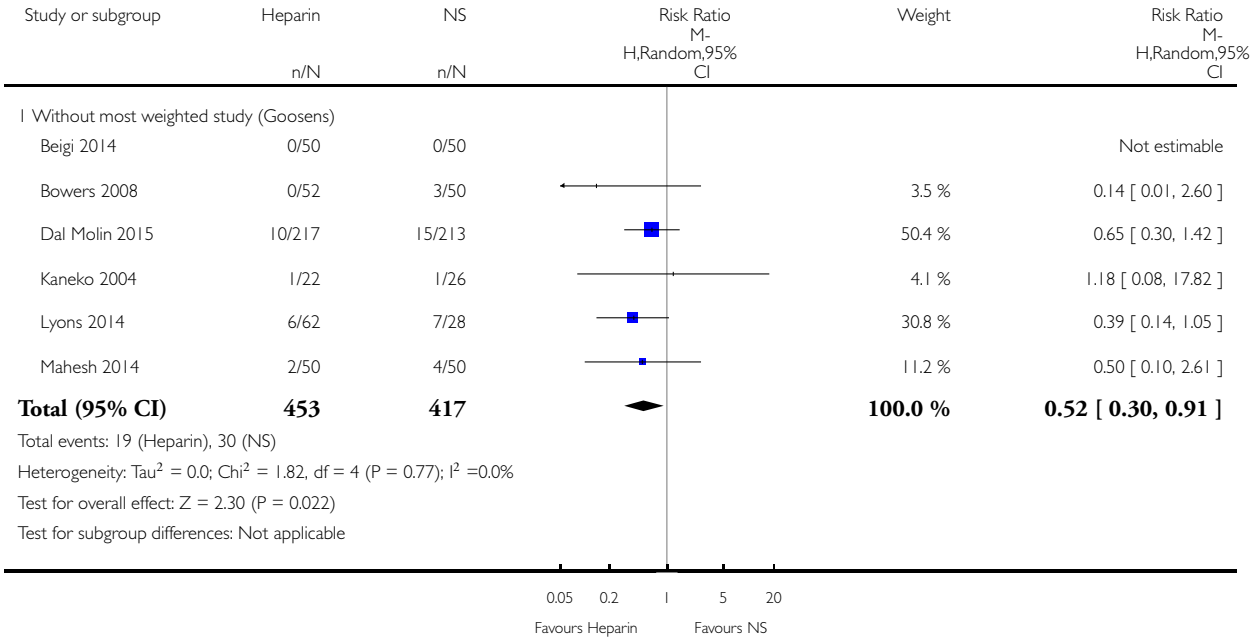

(1) The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in the saline group

### 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

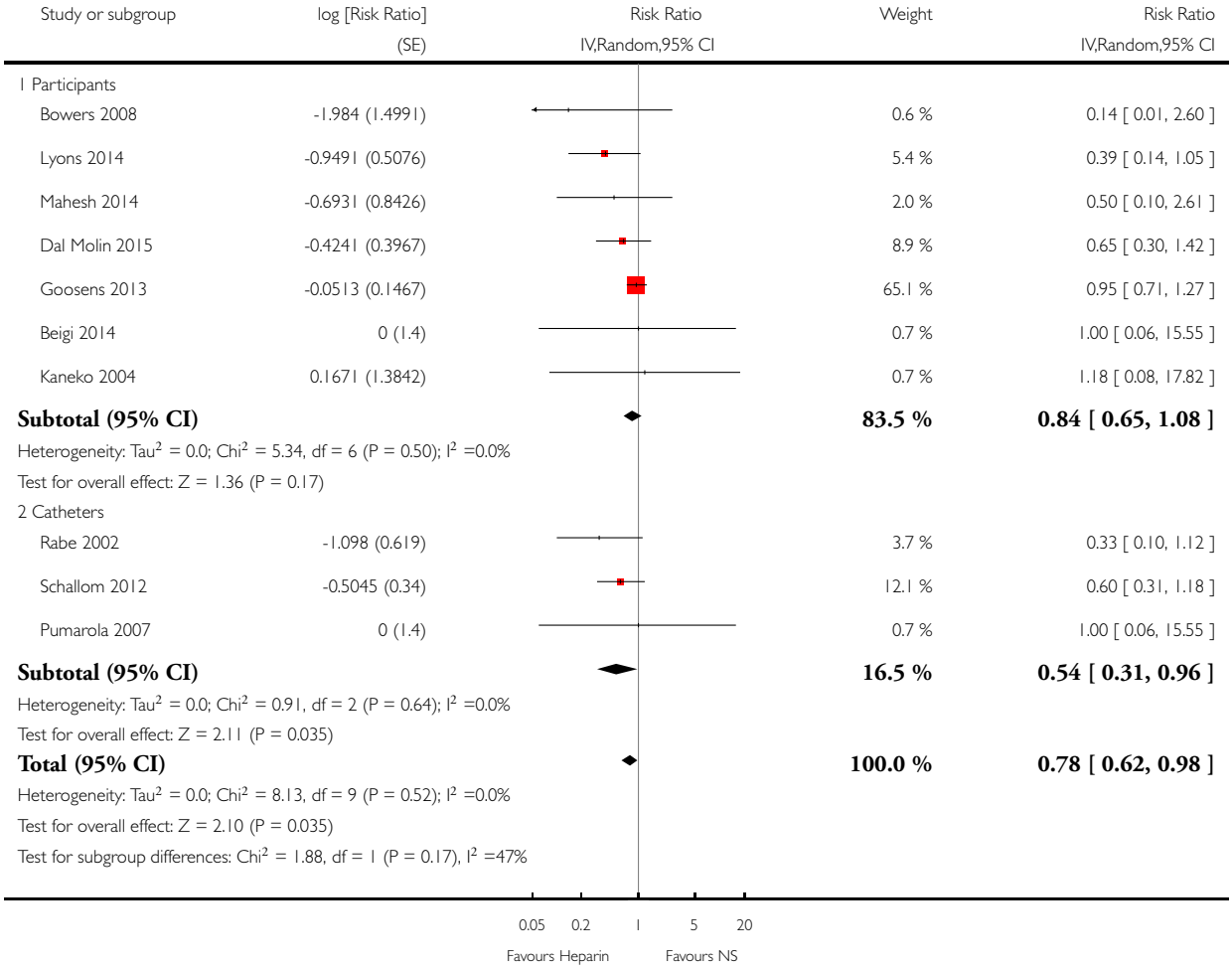


### Analysis 6.3. Comparison 6 Sensitivity analysis, Outcome 3 All occlusions effect size.

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

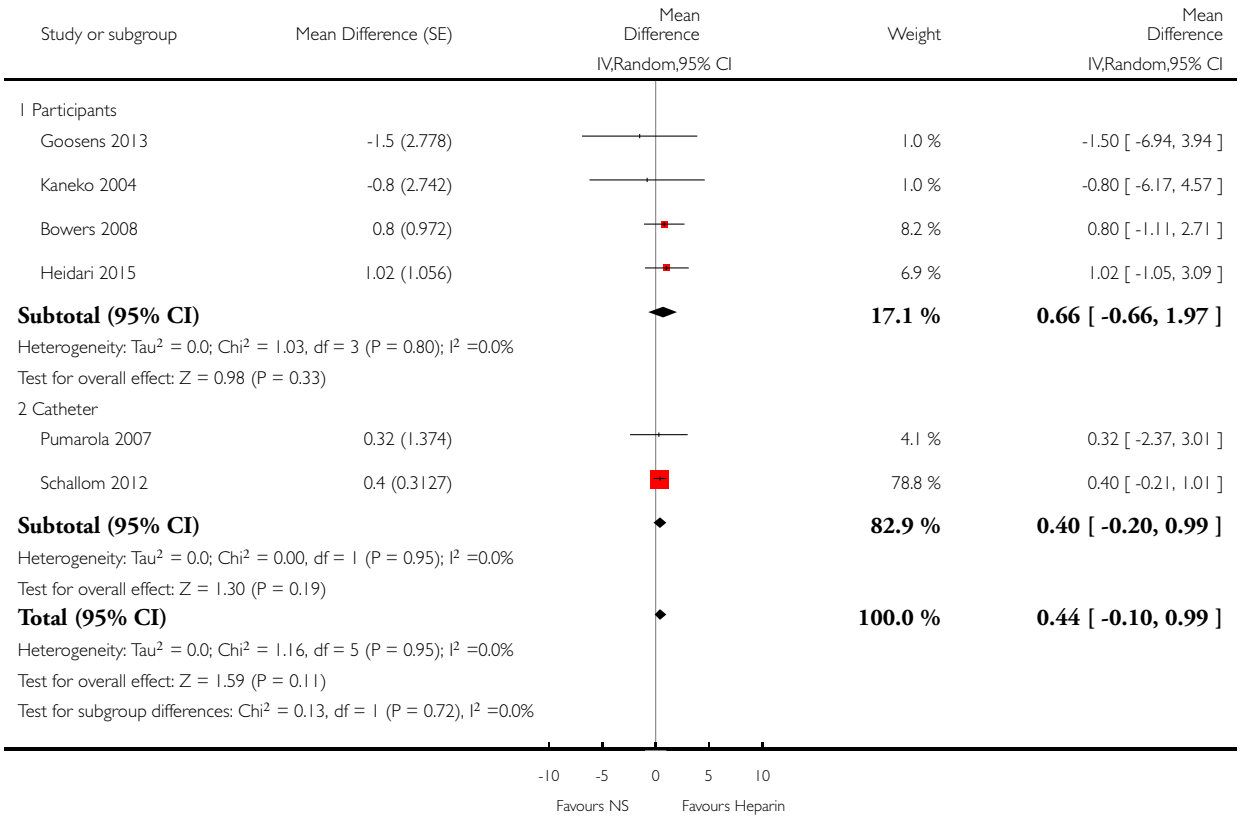


### Analysis 6.4. Comparison 6 Sensitivity analysis, Outcome 4 All patency effect size.

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

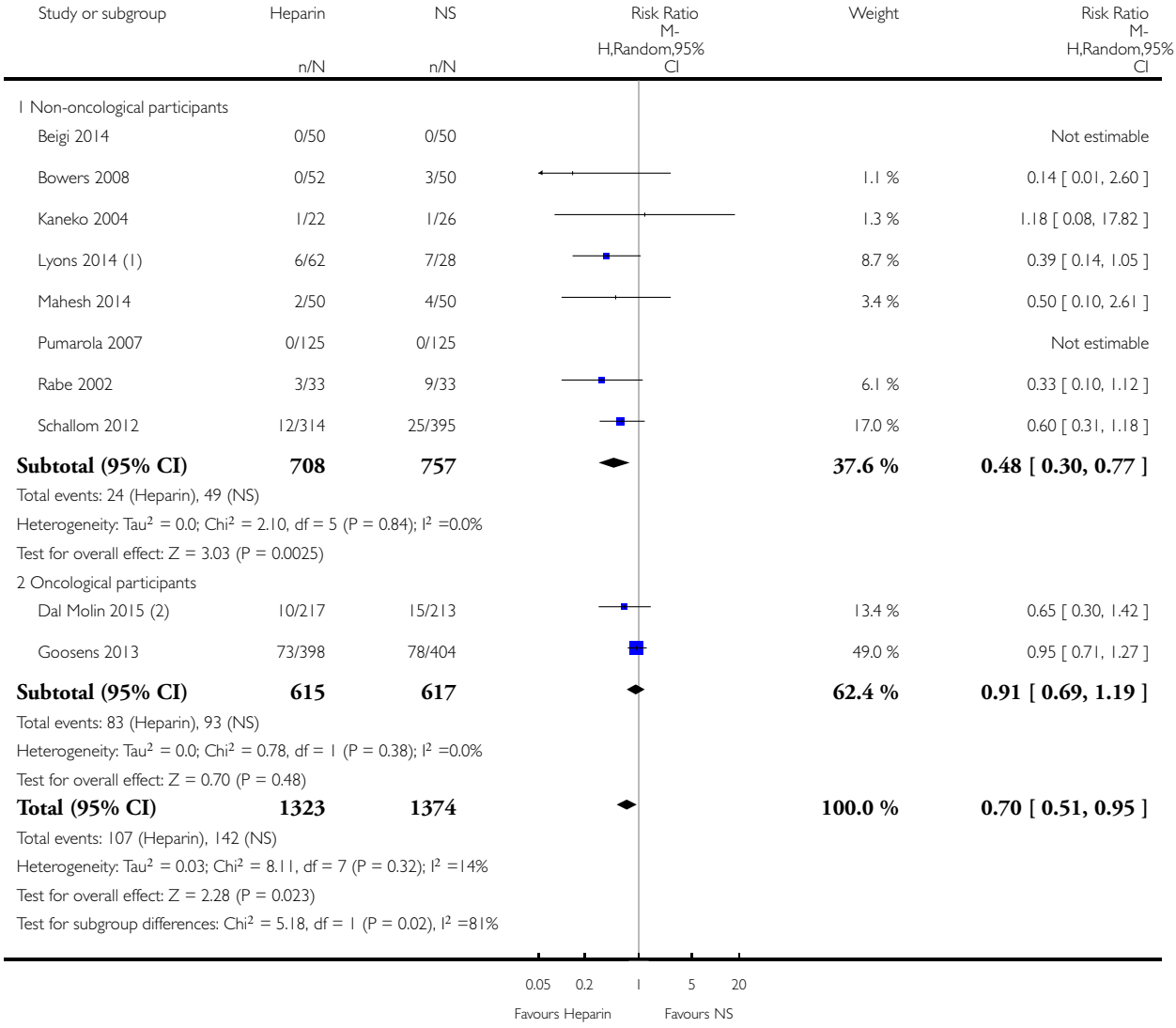


## Analysis 7.1. Comparison 7 Analysis of subgroups, Outcome 1 Occlusion of CVCs oncology vs non-oncology participants.

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

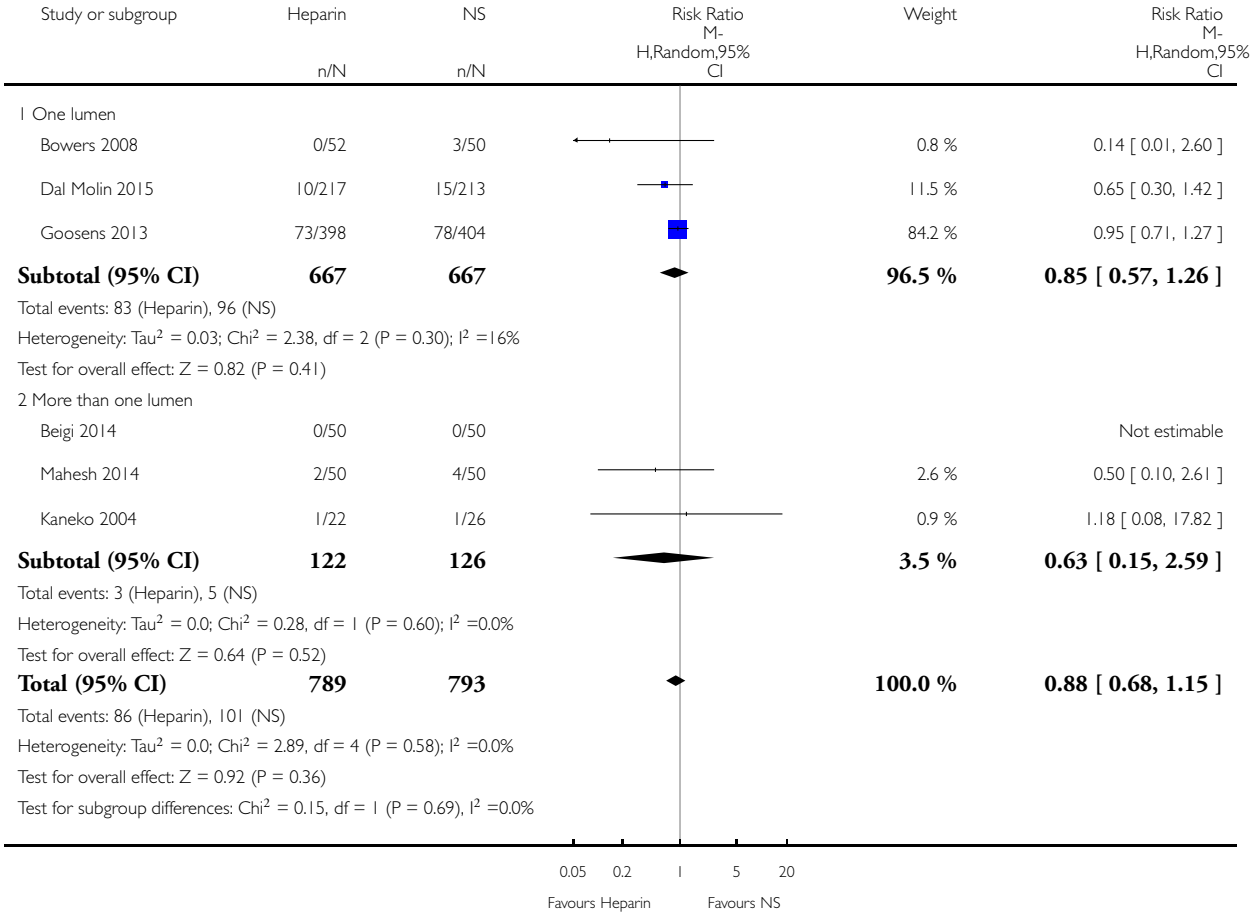
(2) The study included partial occlusions (when fluids can be flushed freely but blood cannot be withdrawn) and total occlusion (defined as impossibility to flush and draw blood). Only one total occlusion was reported in the saline group

## 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)

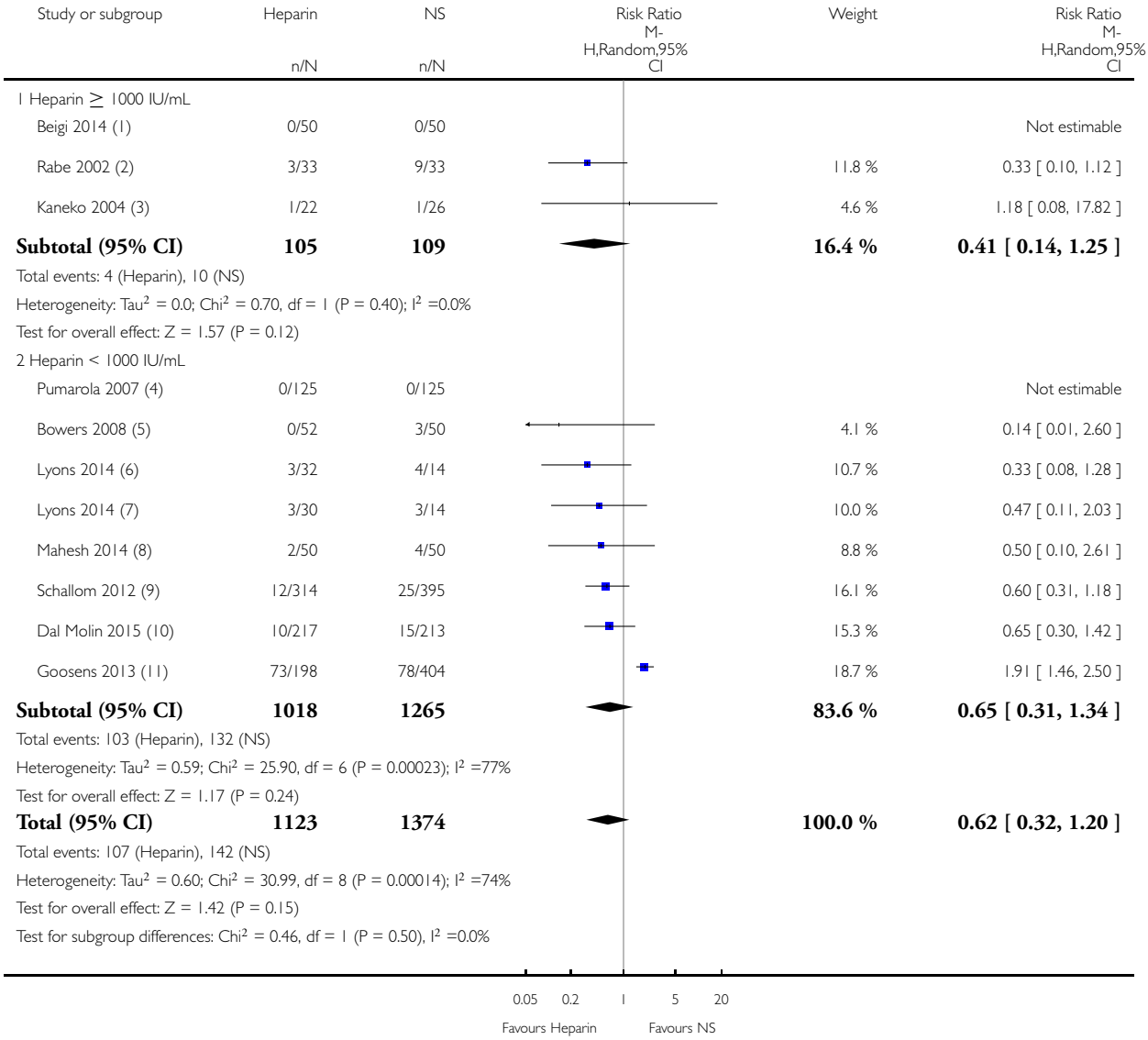


### Analysis 7.3. Comparison 7 Analysis of subgroups, Outcome 3 All occlusions - heparin concentration.

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.

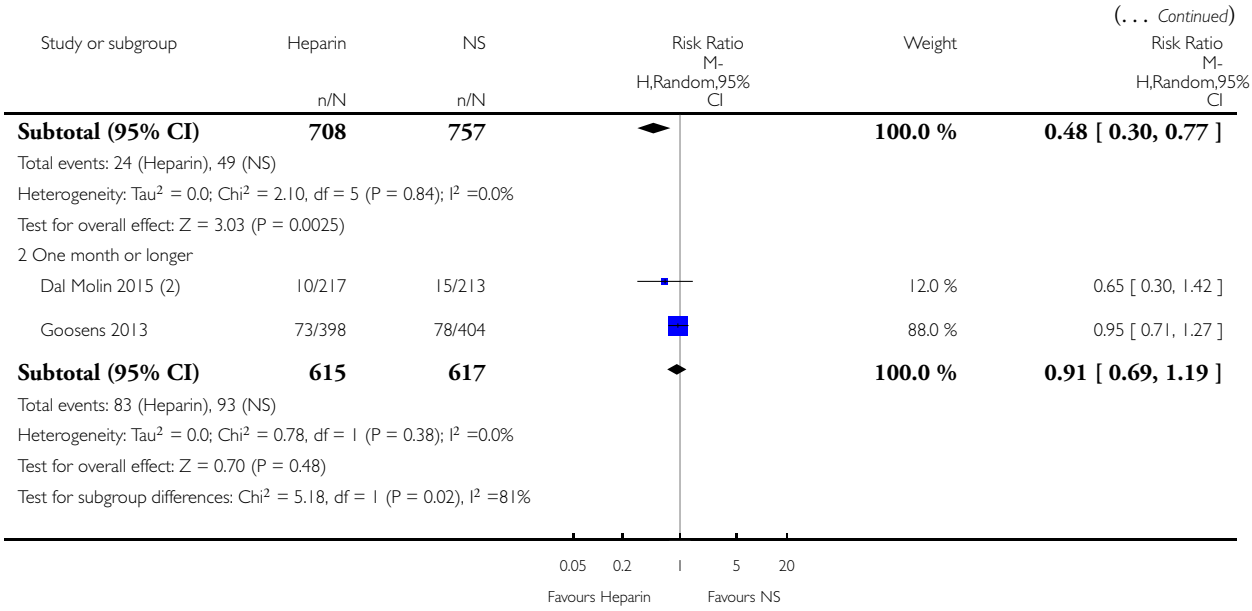
Review: Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults

Comparison: 7 Analysis of subgroups

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

| Study or subgroup | Heparin n/N | NS n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Less than one month | | | | | |
| Beigi 2014 | 0/50 | 0/50 | | | Not estimable |
| Pumarola 2007 | 0/125 | 0/125 | | | Not estimable |
| Bowers 2008 | 0/52 | 3/50 | | 2.6 % | 0.14 [ 0.01, 2.60 ] |
| Rabe 2002 | 3/33 | 9/33 | | 15.0 % | 0.33 [ 0.10, 1.12 ] |
| Lyons 2014 (1) | 6/62 | 7/28 | | 22.4 % | 0.39 [ 0.14, 1.05 ] |
| Mahesh 2014 | 2/50 | 4/50 | | 8.1 % | 0.50 [ 0.10, 2.61 ] |
| Schallom 2012 | 12/314 | 25/395 | | 49.0 % | 0.60 [ 0.31, 1.18 ] |
| Kaneko 2004 | 1/22 | 1/26 | | 3.0 % | 1.18 [ 0.08, 17.82 ] |


(*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*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rabe 2002 | NR | NR | NR | NR | NR | NR | NR | NR |
| Schallom 2012 | 19/145 | 16/150 | 0/145 | 4/150 | NR | NR | 0/145 | 2/150 |

CVC: central venous catheter.
H: heparin.
HIT: heparin-induced thrombocytopaenia.
NR: not reported.
NS: normal saline (0.9% NaCl).

# APPENDICES

## Appendix 1. 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.

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## 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