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Anticoagulants and antiplatelet agents for preventing central venous haemodialysis catheter malfunction in patients with end-stage kidney disease (Review)

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[Intervention Review]

Anticoagulants and antiplatelet agents for preventing central venous haemodialysis catheter malfunction in patients with end-stage kidney disease

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ABSTRACT

Background

Catheter malfunction, including thrombosis, is associated with reduced dialysis adequacy, as well as an increased risk of catheter-related bacteraemia and mortality. The role of anticoagulants in the prevention of catheter malfunction remains uncertain.

Objectives

This review aimed to compare the prophylactic effect of different anticoagulant agents, preparations, doses and administration on the incidence of central venous haemodialysis catheter-related malfunction and sepsis in patients with end-stage kidney disease (ESKD).

Search methods

We searched the Cochrane Renal Group's Specialised Register to 7 January 2016 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included all randomised controlled trials (RCT) assessing anticoagulants compared with conventional care for the prevention of catheter malfunction in adult patients receiving haemodialysis for ESKD.

Data collection and analysis

The primary outcome was catheter malfunction defined as a catheter blood flow of 200 mL/min or less, or as defined by study authors. Secondary outcomes were catheter-related bacteraemia, all-cause mortality and bleeding events. Relative risks (RR) with 95% confidence intervals (CI) for individual studies were pooled using random effects models within treatment classes. Analyses were conducted by class, with subgroup analyses performed of individual agents within classes.

Main results

We included 27 studies (3003 participants) that were followed up for a median of six months. Study interventions included alternative anticoagulant locking solutions (19 studies, 2216 patients), systemic agents (6 studies, 664 patients) and low or no dose heparin (2 studies, 123 patients). The most common comparison treatment was a locking solution of heparin 5000 IU/mL, used in 17 studies. No significant

effect on catheter malfunction was observed for alternative anticoagulant locking solutions (RR 0.96, 95% CI 0.74 to 1.26), systemic agents (RR 0.59, 95% CI 0.28 to 1.23), or low or no dose heparin (RR 0.90, 95% CI 0.10 to 8.31). A significant reduction on incidence of catheter-related bacteraemia was observed for alternative anticoagulant locking solutions (RR 0.46, 95% CI 0.32 to 0.66) but not systemic agents (RR 2.41, 95% CI 0.89 to 6.55), and could not be assessed in reports of low or no dose heparin studies. No significant effect on all-cause mortality was observed for alternative anticoagulant locking solutions (RR 0.88, 95% CI 0.54 to 1.43) or systemic agents (RR 0.78, 95% CI 0.37 to 1.65), and was not reported in studies of low or no dose heparin. Bleeding events were only reported in eight studies, including only 2/5 studies of systemic warfarin, with no clear effect demonstrated (RR 1.43, 95% CI 0.86 to 2.39). For individual agents, recombinant tissue plasminogen (rt-PA) was the only locking solution shown to reduce catheter malfunction (RR 0.58, 95% CI 0.37 to 0.91) based on the results of a single study. No significant on catheter malfunction was observed for other individual classes of alternative anticoagulant locking solutions (citrate: RR 1.14, 95% CI 0.76 to 1.69; antibiotic: RR 1.48, 95% CI 0.79 to 2.77; ethanol: RR 0.88, 95% CI 0.21 to 3.67). On the other hand, all individual classes of alternative anticoagulant locking solutions, except ethanol, reduced catheter-related bacteraemia (citrate: RR 0.49, 95% CI 0.36 to 0.68; antibiotic: RR 0.27, 95% CI 0.11 to 0.70; rt-PA: RR 0.35, 95% CI 0.13 to 0.93; ethanol: RR 0.33, 95% CI 0.03 to 4.05). No significant effect on all-cause mortality was observed for any individual agent within the class of alternative locking solutions. Studies were mainly of low quality and underpowered with an average participant number of 75 and study duration of six months. The interpretation of the study evidence was further limited by the variation in tested interventions and outcome reporting.

Authors' conclusions

The relative net benefit of anticoagulant therapies for prevention of catheter malfunction remains uncertain. Multiple agents appear to reduce catheter-related bacteraemia although the lack of clear assessment of harms and the limitations of study quality mean these results should be interpreted with caution. Methodological approaches can be used to avoid methods of reporting unduly affecting on the results of meta-analyses incorporating studies employed mixed reporting methods. Further high quality randomised studies, including safety outcomes, are needed.

PLAIN LANGUAGE SUMMARY

Anticoagulants and antiplatelet agents for preventing central venous haemodialysis catheter malfunction in patients with end-stage kidney disease

Background

Patients with end-stage kidney disease require vascular access during haemodialysis. Central venous haemodialysis catheters are frequently used when permanent vascular access is not available. Catheter problems contribute to greater morbidity and mortality. Catheter malfunction leads to requirements for additional interventions, increased risk of catheter-related infection and hospitalisation.

Standard care for the prevention of catheter malfunction is the use of heparin solutions as a post dialysis ‘lock’ in the catheter ports. The potential impact of heparin treatment on bleeding risk is an acknowledged concern. Therefore newer approaches have been proposed to seek improvements in catheter patency or treatment-associated harm rates.

Study characteristics

This review focused on randomised controlled trials (RCTs) of anticoagulants compared with conventional care for the prevention of catheter malfunction patients receiving haemodialysis.

Key results

We found 27 studies, involving 3003 patients followed for an average six months, which assessed alternative anticoagulant locking solutions, systemic agents and low or no dose heparin. Catheter malfunction were not affected by any of these classes of agents. Subgroup analysis showed that the only agent reducing catheter malfunction was recombinant tissue plasminogen locking solution based on the results of a single study. A significant reduction was observed on the incidence of catheter-related bacteraemia for alternative anticoagulant locking solutions. There was no evidence to suggest that alternative anticoagulants to heparin locking solutions had an effect on death rates or bleeding events, although only a small proportion of studies reported bleeding events.

Quality of the evidence

Further high quality information is needed on both potential benefits and safety of alternative approaches to maintaining dialysis access catheter function.

BACKGROUND

Central venous haemodialysis catheters are a necessary but problematic component of dialysis practice. Central venous catheters (CVC) are used for approximately 57% of incident dialysis patients in Australia among whom they are associated with significantly increased dialysis-related mortality (Hariharan 2006; Polkinghorne 2013; Schwab 1999; USRDS 2009). CVC are associated with the risk of catheter-related thrombosis which can result in catheter malfunction (Suhocki 1996).

Description of the condition

Catheter-related thrombosis can be classified as either extrinsic or intrinsic (Beathard 2001) based on the site at which the thrombosis forms. The main consequences from catheter-related thrombotic events are deep venous thrombosis (Vanherweghem 1994), shortened access life and requirement for extra procedures (Linenberger 2006), inadequate dialysis (Little 2001) and increased risk of sepsis (Timsit 1998). The incidence of catheter-related thrombosis varies by catheter location (Trerotola 2000), sex, systemic prothrombotic states, site of insertion (subclavian compared with internal jugular) (Trerotola 2000), previous catheter-related thrombosis and catheter malposition (Liangos 2006; Trerotola 2000).

Description of the intervention

Current guidelines recommend antithrombotic locking solutions to prevent catheter-related malfunction in dialysis patients but do not refer to specific agents or concentrations in recognition of the lack of definitive evidence for individual regimens (UK Renal Association 2011; KDOQI 2006). Newer approaches including alternative anticoagulant containing locking solutions, antibiotic containing lock solutions, systematic anticoagulants, antiplatelet agents (Abdul-Rahman 2007), catheter flushing regimes (Pepper 2007) and recombinant tissue-type plasminogen activator (rt-PA) (Schenk 2000) have been investigated to seek improvements in catheter patency or treatment-associated harm rates.

How the intervention might work

Standard care in the prevention of catheter malfunction is the use of heparin solutions as a post dialysis 'lock' in the catheter ports. Heparin is a mucopolysaccharide with in vitro and in vivo anticoagulant properties. It exerts anticoagulant effect by deactivating activated factor X and inhibiting conversion of prothrombin to thrombin. Heparin locking solutions have been recommended for maintaining catheter patency, though the nominated wide concentration range of 1000 to 10,000 U/mL reflects the lack of evidence on optimal dosing (Besarab 2011). The potential impact on bleeding risk is an acknowledged concern (Moritz 2003; Yevzlin 2007). Other adverse events associated with heparin use include major bleeding, heparin-induced thrombocytopenia and thrombosis, and osteoporosis (Thomas 2007).

Alternative approaches, therefore, have been tested to improve catheter function and reduce adverse events. These potentially include alternative anticoagulant based locking solutions (e.g. citrate locking solutions), systemic anticoagulation, and impregnated catheters. These may improve efficacy by their anticoagulant properties. For example, solutions containing 4% to 5% of trisodium citrates express anticoagulant activity (von Brecht 1986) by binding Ca^{2+} to prevent progression of the coagulation cascade (Pinnick 1983). Alternative approaches to reducing adverse events include reduced heparin or no heparin saline flushes.

Why it is important to do this review

Catheter thrombosis is associated with negative outcomes including reduced dialysis adequacy, requirement for repeated invasive interventions, increased risk of catheter-related bacteraemia and higher rates of hospitalisation and mortality.

OBJECTIVES

This review aimed to compare the prophylactic effect of different anticoagulant agents, preparations, doses and administration on the incidence of central venous haemodialysis catheter-related malfunction and sepsis in patients with ESKD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (studies in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which any locking solutions containing anticoagulant, systemic anticoagulants and antiplatelet agents were used for catheter-related thrombosis prophylaxis. The first phase of randomised cross-over studies were also included.

Types of participants

Inclusion criteria

Studies conducted in people with ESKD who require CVC for initiation or maintenance haemodialysis access were included. Studies enrolling patients who had been treated previously with anticoagulants for thrombotic events were included in the review.

Exclusion criteria

Studies that included patients who were receiving systemic therapeutic anticoagulation for non catheter-related thromboembolic events were excluded. Patients with acute kidney injury were also excluded.

Types of interventions

The review compared the prophylactic effect of different anticoagulant or antiplatelet agents, preparations, doses and administration on the incidence of central venous haemodialysis catheter-related malfunction and sepsis in patients with ESKD. We conducted comparisons of placebos or comparators versus:

- anticoagulant catheter locking solutions;
- systemic anticoagulants;
- antiplatelet agents.

Types of outcome measures

Primary outcomes

- Reported thrombotic outcomes: Incidence of catheter malfunction presumed due to thrombosis defined as a persistent inability to achieve a blood flow of greater than 200

mL/min despite positional changes of the patient and additional flushing or both, or as defined by the study authors.

Secondary outcomes

- Incidence of major bleeding, defined as a reduction in haemoglobin of 20 g/L; bleeding requiring blood transfusion, bleeding requiring hospital admission, or as defined by the authors
- Incidence of minor bleeding, defined as a reduction in haemoglobin of less than 20 g/L, change from baseline less than 19.9 g/L; bleeding not requiring hospital admission, bleeding not requiring blood transfusion, or as defined by the authors
- Other thrombotic events, defined as thromboses in vessels in the region of the vascular catheter, or as defined by the study authors
- Requirement for replacement of CVC
- Requirement for thrombolytic agents
- Infection related to vascular access, defined as catheter-related exit site infection, bacteraemia in the absence of another clear source of infection, or as defined by the study authors
- Thrombocytopenia, defined as a new platelet count less than 150,000/µL (150 x 10^9/L), or as defined by the study authors
- Hypocalcaemia, defined as a serum corrected calcium level less than 2.20 mmol/L, or as defined by the study authors
- All-cause mortality
- Other adverse events including allergic reactions, urticaria, and anaphylaxis
- Other adverse events, as defined by the study authors
- Economic costs to health services funders.

Search methods for identification of studies

Electronic searches

We searched Cochrane Kidney and Transplant's Specialised Register to 7 January 2016 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms.

Searching other resources

Relevant studies were also obtained from the following sources.

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

Two authors independently reviewed the abstracts of all studies from the initial search. Those that meet the inclusion criteria were collated. Two authors independently applied the inclusion criteria to each full text article. A third author resolved any conflicts by acting as arbitrator. There were three ways we dealt with duplicate publications. Firstly, we used Endnote's 'find duplicate' function to automatically remove duplicates. Secondly, we manually screened the duplications when we went through abstracts review. Thirdly, when one study produced more than one publication, we combined reports together and used the publication with the most complete data in the analyses. The number of duplicates is reported in the study flow chart.

Data extraction and management

Two authors independently extracted information using a standardised data collection form. These data were extrapolated from tables and graphs in published papers. If this is not possible, the study authors were contacted for further information. Extracted data included clinical measures such as participants' comorbidities, and length and frequency of dialysis. We also scrutinised information regarding interventions, different anticoagulants, and assess data related to our primary and secondary outcomes measures.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (*see* Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel
  - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Were reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For the primary outcome, incidence of thromboembolic events, and secondary outcomes with continuous variables (such as rates of bleeding and rates of other adverse effects), we treated data as continuous and use mean differences to estimate the difference

that one treatment has on the average outcome to another. However, if results were reported as time to a first event, we used time-to-event data to measure treatment effect.

For binary outcomes, such as all-cause mortality, we compared proportions and 95% confidence intervals, and calculate numbers-needed-to-treat and numbers-needed-to-harm to establish a standardised, clinically relevant measure of data.

An a priori decision was made to calculate summary estimates within three therapeutic classes (i.e. alternative anticoagulant locking solutions, systemic agents, and low or no dose heparin locking solutions) given the different mechanisms of action between classes and the plausible true heterogeneity of effect. Studies varied in the method of outcome reporting. We nominated heparin 5000 IU/ml as the comparison arm where possible, based on clinical practice despite the lack of evidence-based recommendations from current guidelines on optimal heparin lock concentration (Besarab 2011).

Unit of analysis issues

We analysed outcomes at the individual patient level. If the unit of randomisation was not the same as the level of analysis, i.e. the patient, adjustments were made to address the potential impact of clustering on the outcome.

Dealing with missing data

Missing data were requested by written correspondence (e.g. emailing corresponding author) from the authors.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

An a priori decision was made to calculate summary estimates within three therapeutic classes (i.e. alternative anticoagulant locking solutions, low or no dose heparin locking solutions and systemic agents) given the different mechanisms of action between classes and the plausible true heterogeneity of effect.

Assessment of reporting biases

If possible, funnel plots were to be used to assess for the potential existence of small study bias (Higgins 2011). If there was funnel plot asymmetry we planned to use the trim-and-fill method to estimate the volume of unpublished studies on this concept.

Data synthesis

Relative risks (RR) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes. By preference we selected data reported as the number of patients with an event. However, where data was not available for the number of patients with an event, we included data reported as events per study and then as events per catheter day, by deriving a RR for each study and pooling the RRs as below.

Given the heterogeneity of the interventions involved, our pre-specified preference was to use random effects models to derive the summary estimates. However, we observed a variety of methods of outcome reporting including reporting by patients and reporting of repeated events. The random effects model weights individual studies by confidence interval with the consequence that any given study will have greater influence on the overall result if repeated events measures are used compared with if patient counts are used. Having the results influenced by decisions on reporting method appears arbitrary and could have the overall effect of favouring smaller studies as these may be more likely to report event rates rather than counts, and so does not seem consistent with the conservative approach underlying our initial decision to use random effects models. We therefore modified our analysis methods as follows. Summary estimates of relative risks were derived from individual study risks in a two-step process. Firstly random effects models were constructed pooling individual studies that reported by each method. Secondly the results of these models were weighted by average study sample size.

Analyses were performed using RevMan 5.3 if possible, i.e. where all studies reported the raw counts of participants experiencing an event. When this was not possible, analyses were performed using STATA 11.0.

Subgroup analysis and investigation of heterogeneity

Planned a priori subgroup analyses were used to explore possible sources of heterogeneity. Heterogeneity in prevention of catheter malfunction in alternative anticoagulant locking solutions could be related to different class of interventions, i.e. citrate, rt-PA, LMWH and antibiotic locking solutions. Whether the use of a co-intervention or not can also cause heterogeneity of the results, which was also analysed.

Sensitivity analysis

Sensitivity study was performed according to Cochrane methodology, i.e. by substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear, including the omission of single studies whose inclusion alters the analysis outcome.

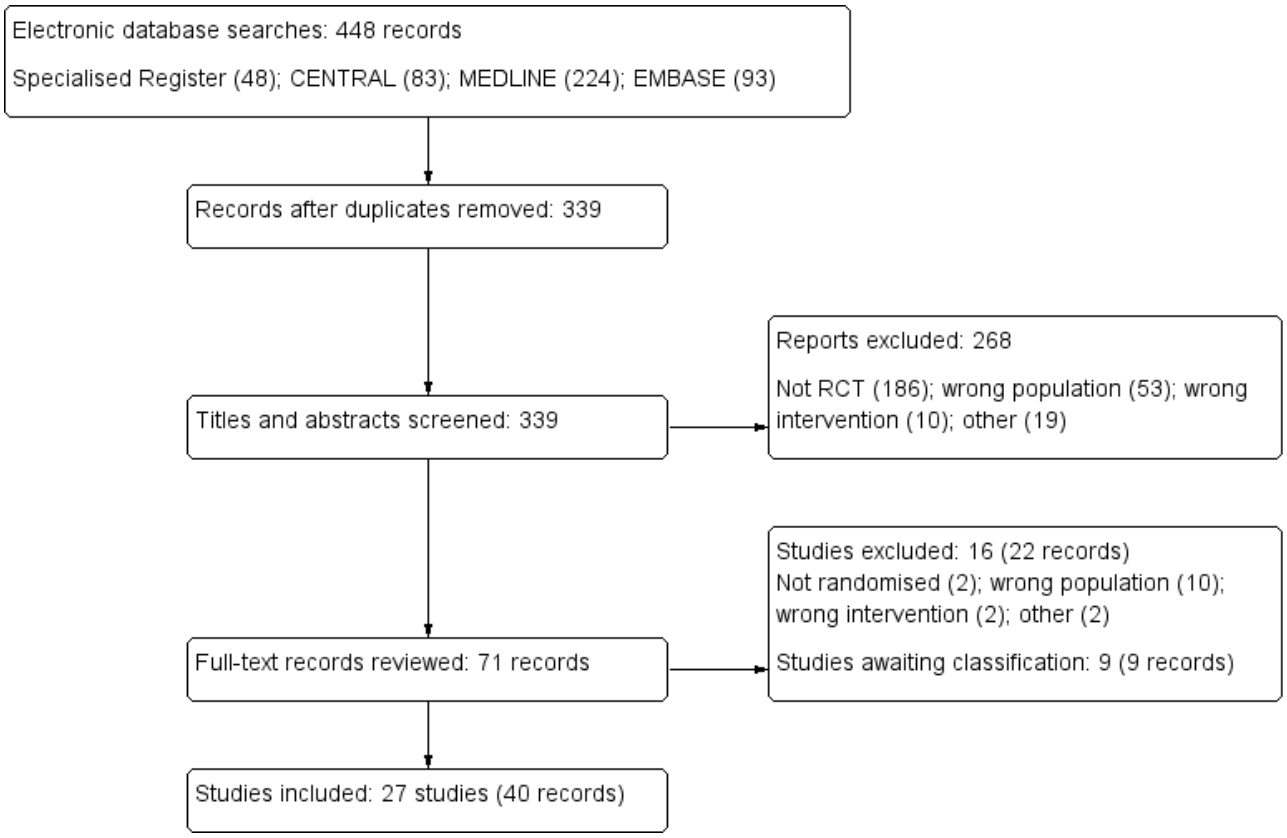
RESULTS

Description of studies

Results of the search

The search identified 448 potentially relevant studies, of which 52 studies with 71 reports were reviewed in full text (Characteristics of included studies). Twenty seven studies were included, 16 studies excluded and there are nine studies awaiting assessment: seven were abstract-only publications (Bonkain 2013; Clement 1998; Freudiger 1990; Geron 2008; Hemmelder 2003; Shi 2008; Sishir 2014); one study was recently completed and no data are available (ISRCTN27307877); and one study was identified just prior to publication and will be assessed in a future update of this review (Ray 1999) (Figure 1). There were no citations in languages other than English were identified.

Figure 1. Study flow diagram.



Included studies

Interventions included alternative anticoagulant locking solutions (19 studies, 2216 patients) (AZEPTIC Study 2011; Betjes 2004; Bleyer 2005; Buturovic 1998; Campos 2011; CHARTS Study 2008; Corbett 2013; Dogra 2002; Filiopoulos 2011; HEALTHY-CATH Study 2009; Hendrickx 2001; Lustig 2011; Malo 2010; Moran 2012; Nori 2006; Pervez 2002; Power 2009; PreCLOT Study 2006; Solomon 2010), systemic agents (aspirin (1 study, 180 patients) (Mozafar 2013); warfarin (5 studies, 479 patients) (Abdul-Rahman 2007; Coli 2006; Mokrzycki 2001; Traynor 2001; Wilkieson 2011), and low or no dose heparin (2 studies, 123 patients (Hryszko 2013; Kaneko 2004).

Within the class of alternative anticoagulant locking solutions, agents tested included citrate locking solutions (14 studies, 1656 patients) (AZEPTIC Study 2011; Betjes 2004; Buturovic 1998; CHARTS Study 2008; Corbett 2013; Dogra 2002; Filiopoulos 2011; Hendrickx 2001; Lustig 2011; Moran 2012; Nori 2006; Pervez 2002; Power 2009; Solomon 2010); recombinant tissue plasminogen activator locking solutions (1 study, 225 patients) (PreCLOT Study 2006), antibiotic locking solutions (2 studies, 244 patients) (Bleyer 2005; Campos 2011), low molecular weight heparin (LMWH) locking solutions (1 study, 42 patients) (Malo 2010), and ethanol locking solution (1 study, 49 patients) (HEALTHY-CATH Study 2009).

Excluded studies

Sixteen studies (22 reports) were excluded after review of the full article (Characteristics of excluded studies). Two studies were not randomised (Aslam 2008; Ota 1996); two studies were cross-over studies with no extractable data (Meeus 2005; Schenk 2000);10 studies enrolled the wrong population (Betjes 2006; Caruana 1991; Gittins 2007; Hu 2011; Huraib 1994; Lange 2007; Oguzhan 2012; Plamondon 2005; Thomson 2011; Weijmer 2005); and two studies did not use anticoagulant or antiplatelet agents (Oran 2008; Saxena 2012).

Risk of bias in included studies

Risk of bias was variable as illustrated in overall Figure 2 and by individual study in Figure 3. In the majority of studies as reported, the risk of bias was unclear for random sequence generation and allocation concealment, unclear or high for blinding of participants or personnel, and for outcome assessment. Most studies as reported were low risk for incomplete outcome data reporting and high risk for selective reporting.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

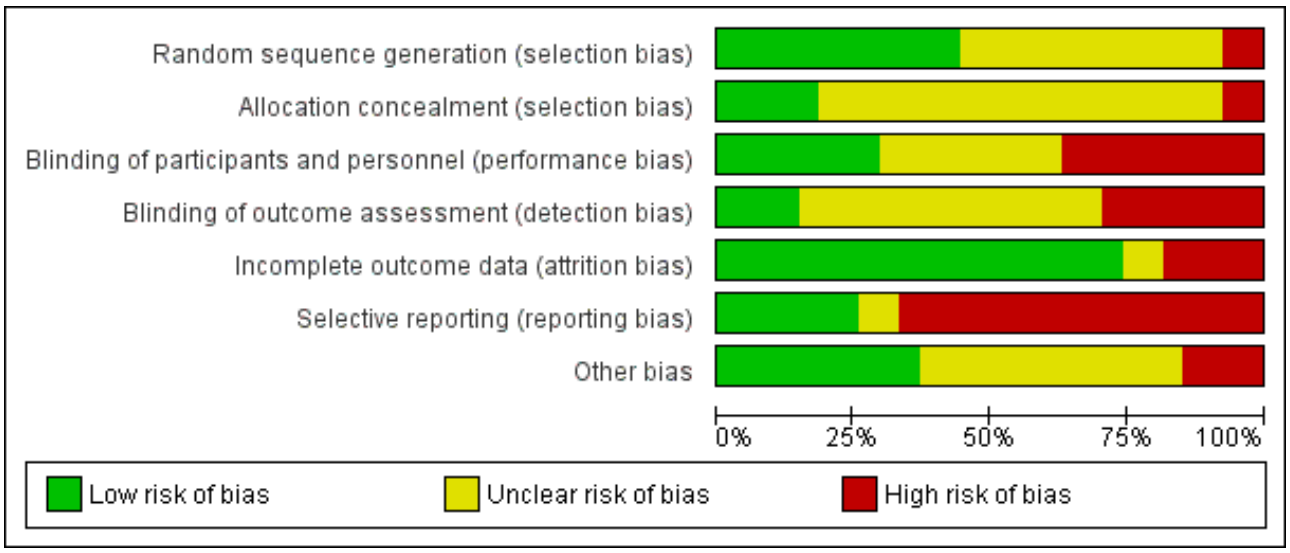


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

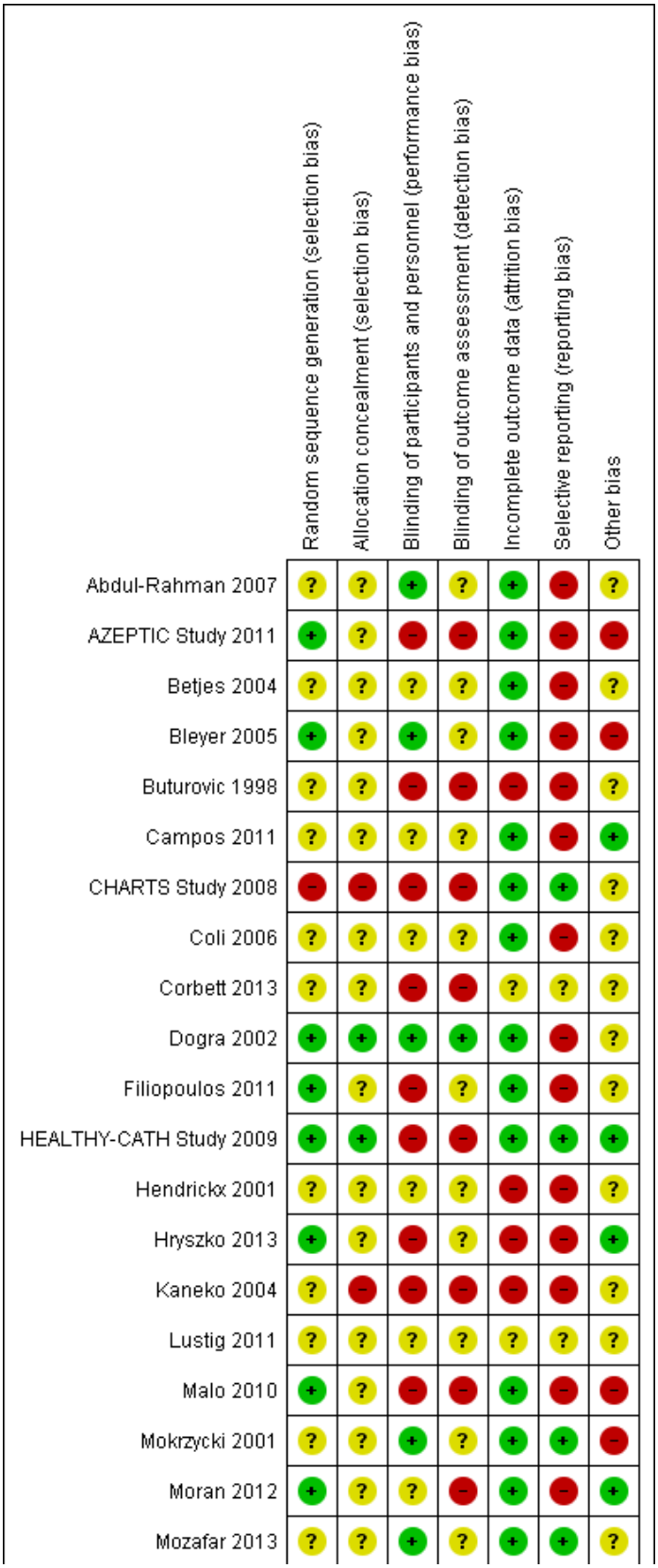
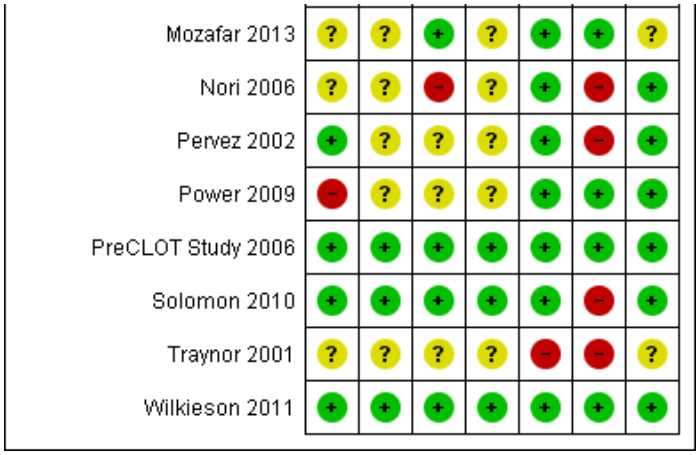


Figure 3. (Continued)



Allocation

Random sequence generation

Random sequence generation was judged to be at low risk of bias in 12/27 (45%) studies (AZEPTIC Study 2011; Bleyer 2005; Dogra 2002; Filiopoulos 2011; HEALTHY-CATH Study 2009; Hryszko 2013; Malo 2010; Moran 2012; Pervez 2002; PreCLOT Study 2006; Solomon 2010; Wilkieson 2011); unclear in 13/27 (48%) studies (Abdul-Rahman 2007; Betjes 2004; Buturovic 1998; Campos 2011; Coli 2006; Corbett 2013; Hendrickx 2001; Kaneko 2004; Lustig 2011; Mokrzycki 2001; Mozafar 2013; Nori 2006; Traynor 2001) and at high risk of bias in 2/27 (7%) studies (CHARTS Study 2008; Power 2009).

Allocation concealment

Allocation concealment was judged to be of low risk in 5/27 (19%) studies (Dogra 2002; PreCLOT Study 2006; Solomon 2010;Wilkieson 2011; HEALTHY-CATH Study 2009); unclear in 20/27 (74%) studies (Abdul-Rahman 2007; Betjes 2004; Bleyer 2005; Buturovic 1998; Campos 2011; Coli 2006; Filiopoulos 2011; Hendrickx 2001; AZEPTIC Study 2011; Malo 2010; Mokrzycki 2001; Moran 2012; Nori 2006; Pervez 2002; Power 2009; Traynor 2001; Corbett 2013; Hryszko 2013; Lustig 2011; Mozafar 2013); and at high risk of bias in 2/27 (7%) studies (Kaneko 2004; CHARTS Study 2008).

Blinding

Blinding of participants and personnel (performance bias) was judged to be at low risk of bias in 8/27 (30%) studies (Abdul-Rahman 2007; Bleyer 2005; Dogra 2002; Mokrzycki 2001; Mozafar 2013; PreCLOT Study 2006; Solomon 2010; Wilkieson 2011); unclear in 9/27 (33%) studies (Betjes 2004; Campos 2011; Coli 2006; Hendrickx 2001; Lustig 2011; Moran 2012; Pervez 2002; Power 2009; Traynor 2001) and at high risk of bias in 10/27 (37%) studies (AZEPTIC Study 2011; Buturovic 1998; CHARTS Study 2008; Corbett 2013; Filiopoulos 2011; HEALTHY-CATH Study 2009; Hryszko 2013; Kaneko 2004; Malo 2010; Nori 2006).

Blinding of outcome assessors (detection bias) was judged to be of low risk in 3/27 (11%) studies (Dogra 2002; Solomon 2010; Wilkieson 2011), unclear in 15/27 (56%) studies (Abdul-Rahman 2007; Betjes 2004; Bleyer 2005; Campos 2011; Coli 2006; Filiopoulos 2011; PreCLOT Study 2006; Hendrickx 2001; Lustig 2011; Mozafar 2013; Mokrzycki 2001; Nori 2006; Pervez 2002; Power 2009; Traynor 2001); and of high risk in 9/27 (33%) studies (Buturovic 1998; Kaneko 2004; CHARTS Study 2008; AZEPTIC Study 2011; Malo 2010; Moran 2012; HEALTHY-CATH Study 2009; Corbett 2013; Hryszko 2013).

Incomplete outcome data

Incomplete data was judged to be of low risk in 18/27 (67%) studies (Betjes 2004; Campos 2011; Bleyer 2005; Coli 2006; Dogra 2002; PreCLOT Study 2006; CHARTS Study 2008; AZEPTIC Study 2011; Malo 2010; Mokrzycki 2001; Moran 2012; Nori 2006; Pervez 2002; Power 2009; Solomon 2010;Wilkieson 2011; HEALTHY-CATH Study 2009; Mozafar 2013); and unclear in 3/27 (11%) studies (Corbett 2013; Lustig 2011; Filiopoulos 2011); and of high risk in 6/27 (22%) studies (Abdul-Rahman 2007;Buturovic 1998; Hendrickx 2001; Kaneko 2004; Hryszko 2013; Traynor 2001).

Selective reporting

Low risk for selective reporting was defined as report with at least one catheter malfunction type outcome and safety outcome (bleeding), which was judged in 7/27 (26%) studies (PreCLOT Study 2006; CHARTS Study 2008; Mokrzycki 2001; Power 2009; Wilkieson 2011;Mozafar 2013; HEALTHY-CATH Study 2009); unclear risk in 2/27 (7%) studies (Corbett 2013; Lustig 2011); and of high risk in 18/27 (67%) studies (Abdul-Rahman 2007; Betjes 2004; Bleyer 2005; Buturovic 1998; Coli 2006; Campos 2011; AZEPTIC Study 2011; Malo 2010; Hryszko 2013; Dogra 2002; Moran 2012; Nori 2006; Pervez 2002; Solomon 2010; Filiopoulos 2011; Hendrickx 2001; Kaneko 2004; Traynor 2001).

Other potential sources of bias

Intention-to-treat analysis

Intention-to-treat analysis was used in 8/27 (30%) studies (Dogra 2002; Filiopoulos 2011; AZEPTIC Study 2011; Moran 2012; Power 2009; Solomon 2010; Wilkieson 2011; HEALTHY-CATH Study 2009), and was not reported in 19/27 (70%).

Funding

Four studies were assessed as being at high risk of bias (AZEPTIC Study 2011; Bleyer 2005; Malo 2010; Mokrzycki 2001); 10 studies were judged to be at low risk of bias (Campos 2011; HEALTHY-CATH Study 2009; Hryszko 2013; Moran 2012; Nori 2006; Pervez 2002; Power 2009; PreCLOT Study 2006; Solomon 2010; Wilkieson 2011),

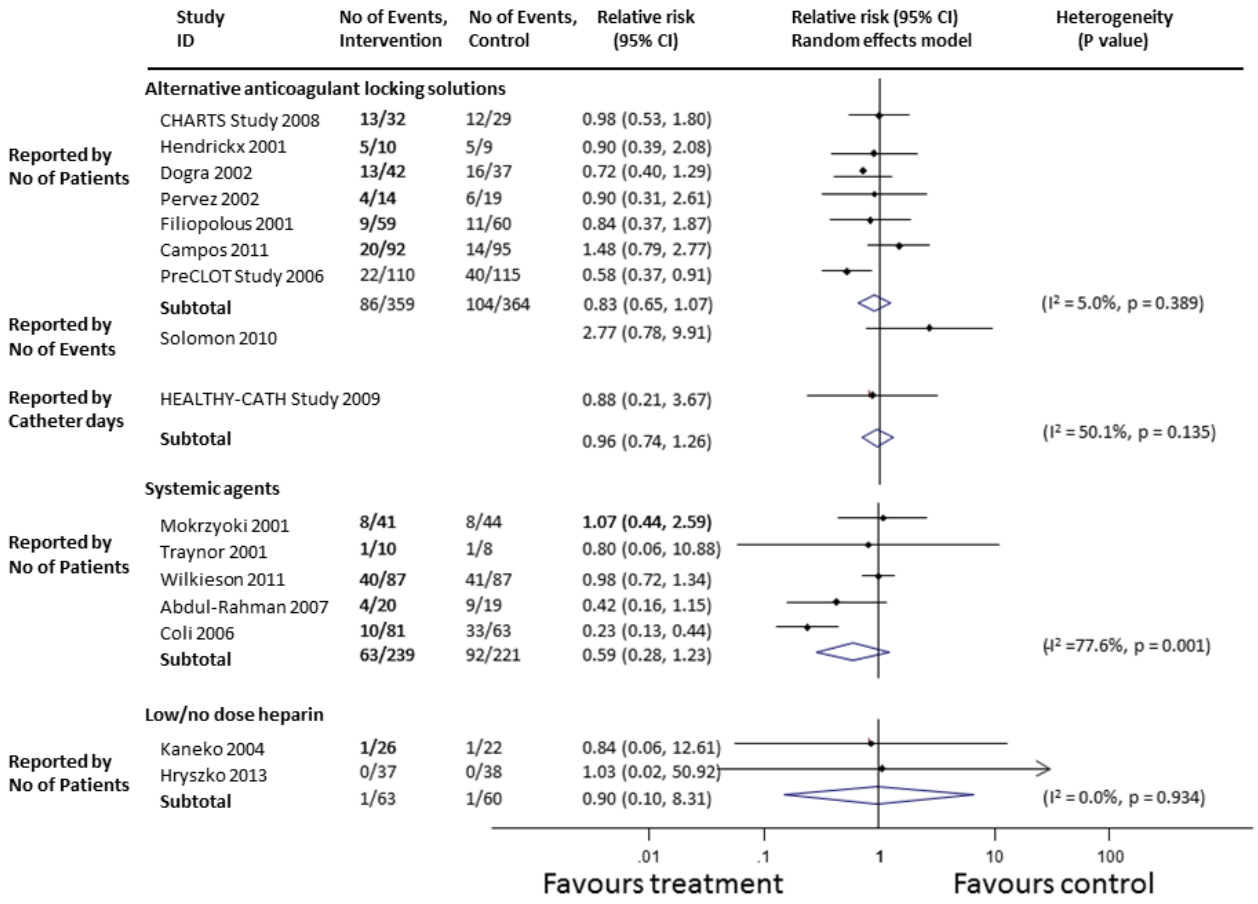
and bias was unclear in 13 studies (Abdul-Rahman 2007; Betjes 2004; Buturovic 1998; CHARTS Study 2008; Coli 2006; Corbett 2013; Dogra 2002; Filiopoulos 2011; Hendrickx 2001; Kaneko 2004; Lustig 2011; Mozafar 2013; Traynor 2001).

Effects of interventions

Prevention of catheter malfunction

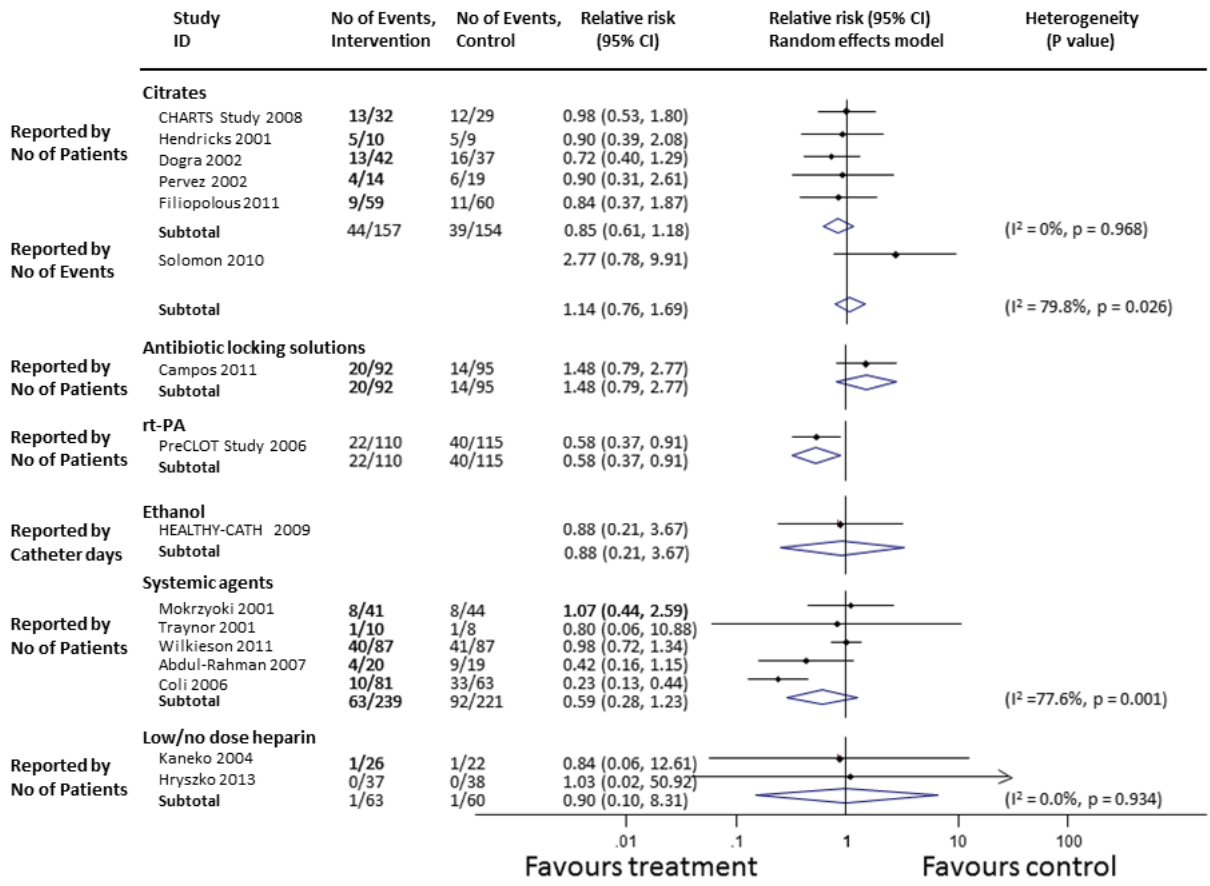
We were able to assess the incidence of catheter malfunction in 16/27 studies (1490 patients) with a median follow-up of six months. There were 159 catheter malfunction events in 753 participants in the intervention group, and 199 events in 737 participants in the control group. In addition, catheter malfunction events were reported in different ways. Four studies assessed catheter loss, five studies assessed thrombosis, and one study assessed requirement for intervention to maintain catheter function (Table 1). There was no effect for alternative anticoagulant locking solutions (Figure 4 (9 studies, 908 patients): RR 0.96, 95% CI 0.74 to 1.26), systemic warfarin (Figure 4 (6 studies, 460 patients): RR 0.59, 95% CI 0.28 to 1.23), and low or no dose heparin (Figure 4 (2 studies, 123 patients): RR 0.90, 95% CI 0.10 to 8.31).

Figure 4. Catheter malfunction



Subgroup analysis of the impact of individual locking solution agents demonstrated that only rt-PA was associated with a reduction of catheter malfunction (Figure 5 (1 study, 225 patients): RR 0.58, 95% CI 0.37 to 0.91). Citrate locking solutions of concentrations ranging from 4% to 46.7% did not significantly reduce catheter malfunction (Figure 5 (6 studies, 447 patients): RR 1.14, 95% CI 0.76 to 1.69), regardless of use in isolation or in conjunction with anti-microbial solutions including gentamicin, taurolidine or methylene blue (regression coefficient for adjuvant antibiotics compared with none: 0.455, P = 0.167). High citrate concentration was not superior to low concentration (regression coefficient for citrate concentration 0.143, P = 0.605).

Figure 5. Catheter malfunction (subgroup analysis)



Among the studies of systemic anticoagulation, there was no suggestion of a dose related effect of warfarin on prevention of catheter malfunction although only five eligible studies were identified (regression coefficient for warfarin dose -0.992, P = 0.108). The dosage of warfarin and the target INRs in systemic anticoagulants studies was summarised in Table 2.

Sensitivity analysis demonstrated the impact of citrate solutions remained non-significant when a single study of citrate and taurolidine (Solomon 2010) was excluded (RR 0.85, 95% CI 0.61 to 1.18). Use of warfarin demonstrated a 42% reduction in the incidence of catheter malfunction, however, high heterogeneity among the five warfarin studies exist (I^2 = 77.6%, P = 0.001).

Prevention of catheter-related bacteraemia

Catheter-related bacteraemia was assessed in 16 studies (2214 patients, median follow-up 4 months). The incidence of catheter-related bacteraemia was reported as the rate per 1000 catheter days in 10 studies, the rate per patient in 14 studies and both in 8 studies. A significant reduction on the rate of catheter-related bacteraemia was found from alternative anticoagulant locking solutions (Figure 6: RR 0.46, 95% CI 0.32 to 0.66), but not from systemic warfarin (Figure 7: RR 2.41, 95% CI 0.89 to 6.55).

Figure 6. Catheter-related bacteraemia

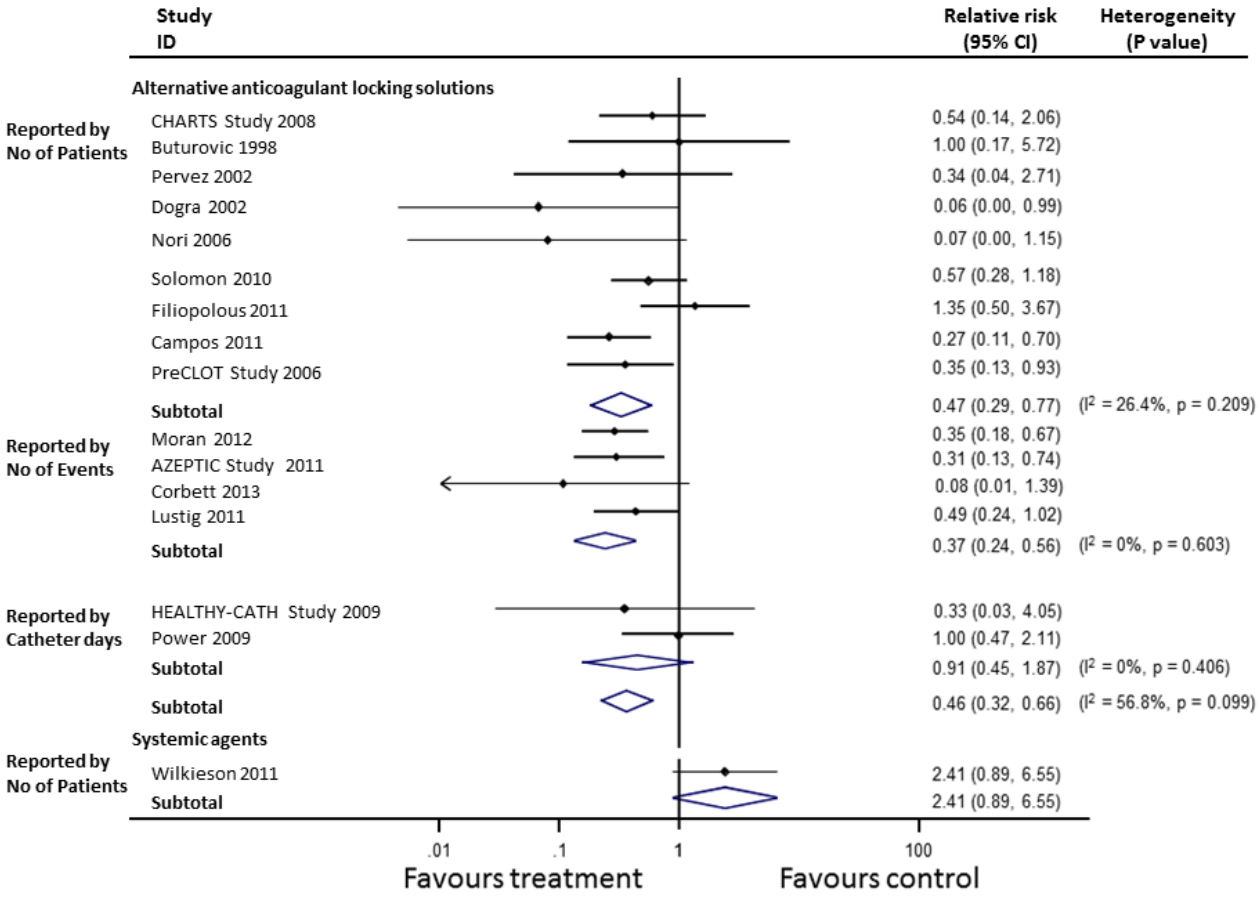
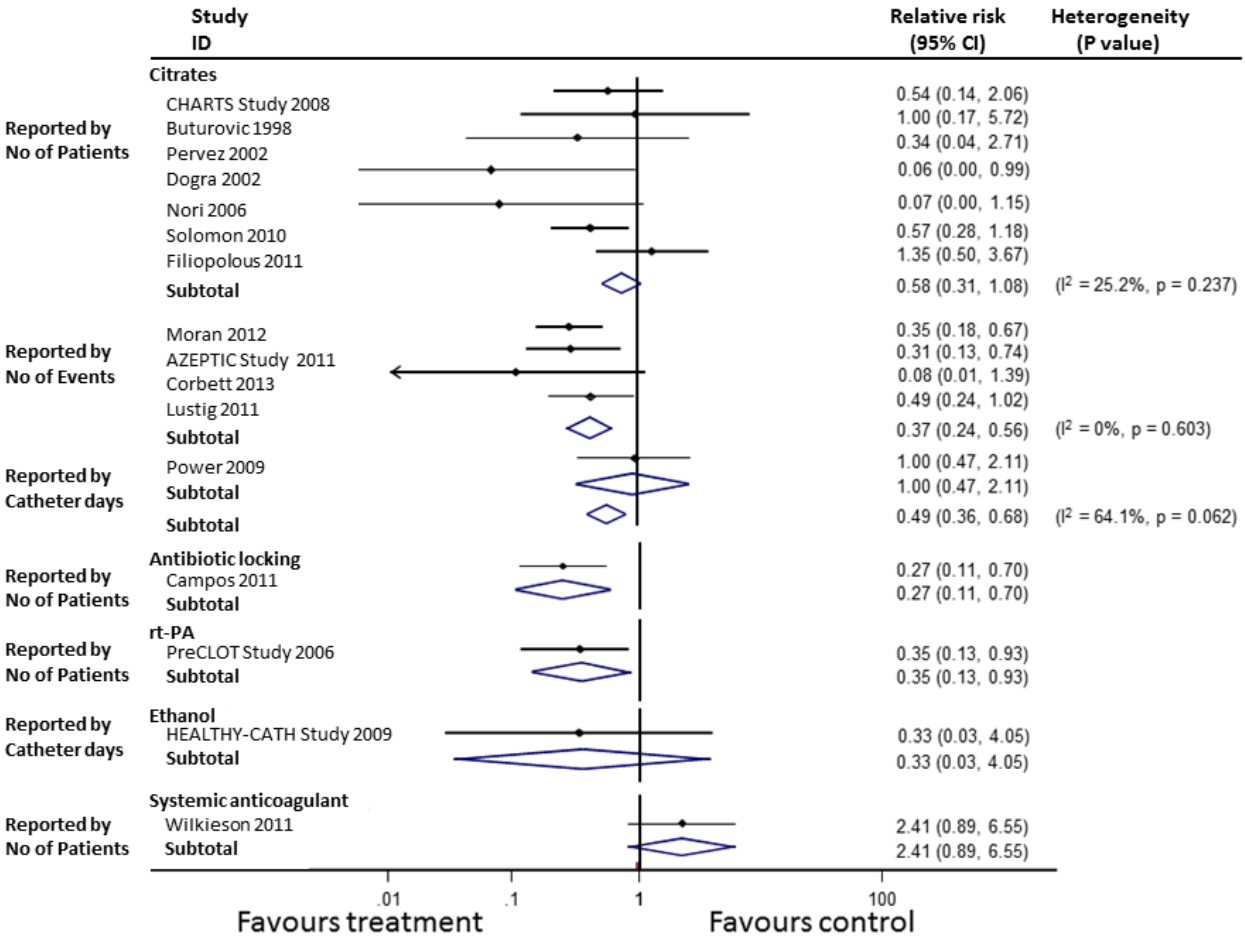


Figure 7. Catheter-related bacteraemia (subgroup analysis)

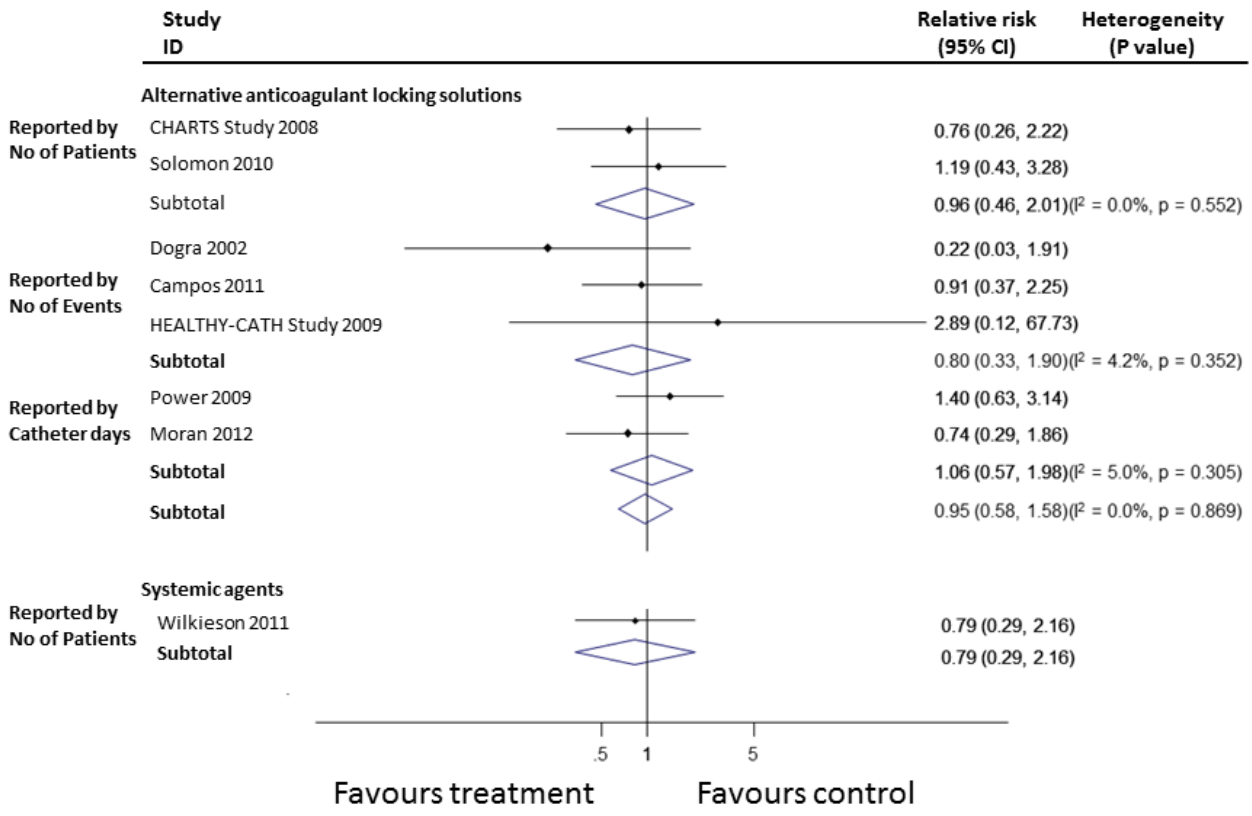


Subgroup analysis showed a reduction in the rate of catheter-related bacteraemia by all the individual classes of alternative anticoagulant locking solutions (Figure 7) (citrate locking solutions: RR 0.49, 95% CI 0.36 to 0.68; antibiotic locking solutions: RR 0.27, 95% CI 0.11 to 0.70; rt-PA locking solutions RR 0.35, 95% CI 0.13 to 0.93) except for ethanol locks (RR 0.33, 95% CI 0.03 to 4.05). The impact on catheter-related bacteraemia was not affected by the addition or otherwise of antimicrobial solutions to citrate locking solution (P = 0.387).

Prevention of exit site infection

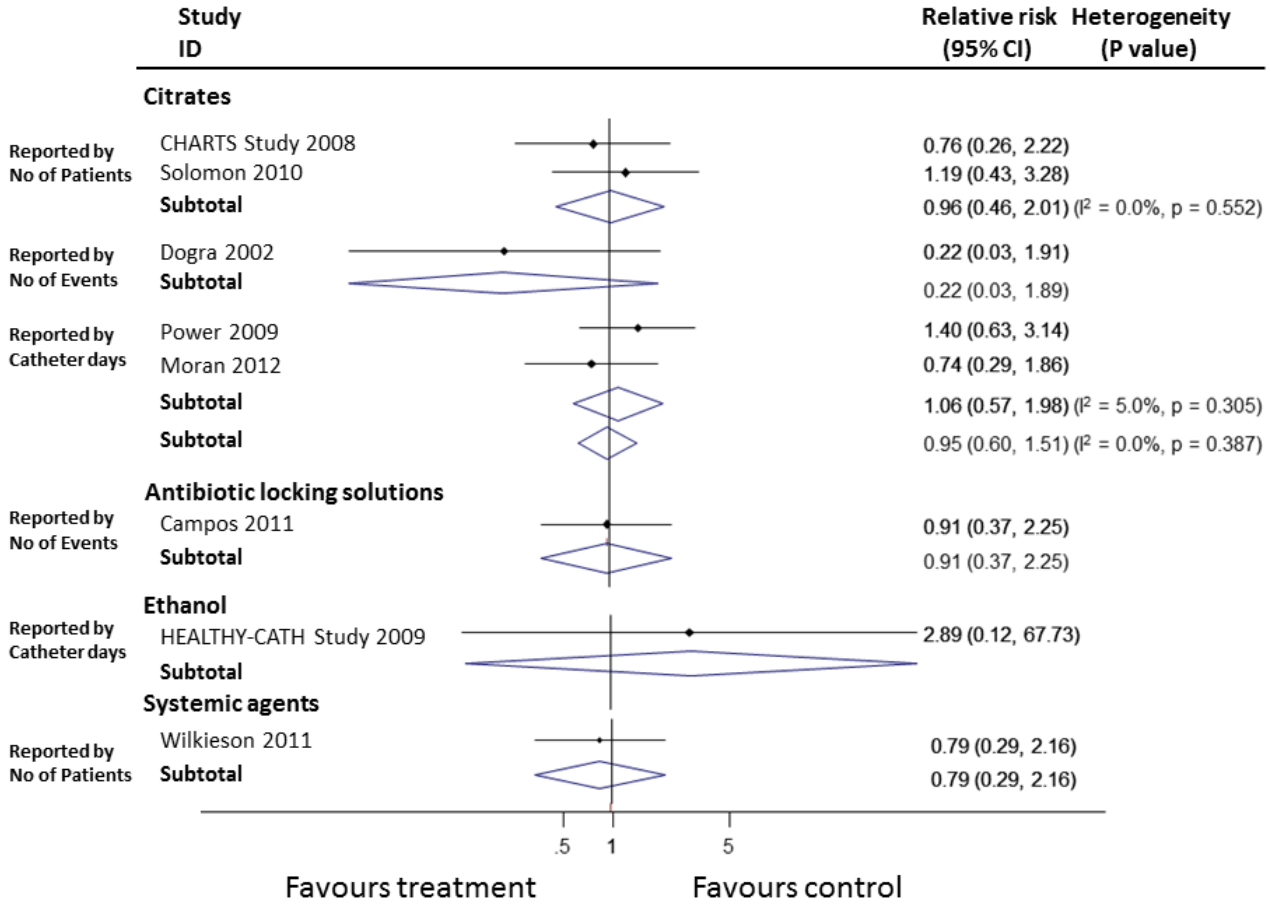
Exit site infection was assessed in eight studies (1199 participants, median follow-up 4.4 months). The incidence of exit site infection was reported as the rate per patient in six studies and the rate per 1000 catheter days in two studies. No significant difference in the rate of exit site infection was found from alternative anticoagulant locking solutions (RR 0.95, 95% CI 0.58 to 1.58), nor from systemic warfarin (RR 0.79, 95% CI 0.29 to 2.16) (Figure 8).

Figure 8. Exit site infection



Subgroup analysis did not show a reduction in the rate of exit site infection by all the individual classes of alternative anticoagulant locking solutions (citrate locking solutions: RR 0.95, 95% CI 0.60 to 1.51; antibiotic locking solutions: RR 0.91, 95% CI 0.37 to 2.25; ethanol locks: RR 2.89, 95% CI 0.12 to 67.73) (Figure 9).

Figure 9. Exit site infection (subgroup analysis)



All-cause mortality

All-cause mortality was reported in 11 studies (1828 participants, median follow-up 4.4 months) assessing alternative locking solutions and systemic warfarin. No treatment class improved mortality: alternative anticoagulant locking solutions (Analysis 1.1.1 (8 studies, 1425 participants): RR 0.88, 95% CI 0.54 to 1.43; I^2 = 0%); warfarin Analysis 1.1.2 (3 studies, 403 participants): RR 0.78, 95% CI 0.37 to 1.65; I^2 = 0%).

No individual alternative anticoagulant locking solutions showed survival benefits compared with standard heparin: citrate (Analysis 1.2.1 (6 studies, 1151 participants): RR 0.89, 95% CI 0.52 to 1.51; I^2 = 1%); rt-PA (Analysis 1.2.2 (1 study, 225 participants): RR 0.63, 95% CI 0.15 to 2.56); ethanol (Analysis 1.2.3 (1 study, 49 participants): RR 2.88, 95% CI 0.12 to 67.53).

Safety profile

The safety outcomes of the interventions were reported less often than efficacy outcomes. Only eight studies reported bleeding events, among which data were able to be pooled in seven studies (849 participants, median follow-up 3.7 months) meaning these analyses maybe affected by bias associated with incomplete outcome and selective reporting. Two studies reported major bleeding only, four reported total bleeding only, and two studies reported both.

There was no significant differences in total bleeding events for alternative anticoagulant locking solutions (Analysis 1.3.1 (3 studies, 335 participants): RR 0.69, 95% CI 0.47 to 1.01; I^2 = 0%), and systemic agents (Analysis 1.3.2 (3 studies, 439 participants): RR 1.30, 95% CI 0.93 to 1.83; I^2 = 0%). Low dose heparin reduced bleeding events by 55% although this result was based on a single study (Analysis 1.3.3 (1 study, 75 participants): RR 0.45, 95% CI 0.21 to 0.96). Subgroup analysis did not show the effect on bleeding events by any individual classes of alternative anticoagulant locking solutions: citrate locking solutions (Analysis 1.4.1 (2 studies, 286 participants): RR 0.70, 95% CI 0.47 to 1.02; I^2 = 0%); ethanol (Analysis 1.4.2 (1 study, 49 participants): RR 0.32, 95% CI 0.01 to 7.50); warfarin (Analysis 1.4.3 (2 studies, 259 participants): RR 1.43, 95% CI 0.86 to 2.39; I^2 = 0%); aspirin (Analysis 1.4.4 (1 study, 180 participants): RR 1.21, 95% CI 0.77 to 1.90); rt-PA (Analysis 1.4.5 (1 study, 225 participants): RR 0.85, 95% CI 0.43 to 1.68).

Five studies (633 participants) reported other adverse events, including two citrate studies (311 participants), one rt-PA study (225 participants), one ethanol study (49 participants), and one low or no dose heparin study (48 participants). There were 53 adverse events in 335 participants in the intervention group, while 39 adverse events occurred in 298 participants in the control group. Participants receiving citrate locking solutions experienced more adverse events, including thrombocytopenia (1 study), intermittent nonspecific dizziness (1 study), metallic taste (1 study) and facial and/or digital paraesthesia (1 study).

Requirement for thrombolytic agents

The requirement for rescue thrombolytic agents due to catheter malfunction was reported in eight studies, among which data were able to be meta-analysed in seven studies (1168 participants, median follow-up 6 months). All of the studies assessed alternative anticoagulant locking solutions. Overall, no significant effect on the requirement for thrombolytic agents was observed (Figure 10: RR 0.87, 95% CI 0.55 to 1.38). With regards to individual alternative anticoagulant locking solutions, rt-PA and LMWH reduced the use of thrombolytic agents by 79% and 47%, respectively (LMWH (1 study, 42 participants): RR 0.53, 95% CI 0.32 to 0.86; rt-PA (1 study, 225 participants): RR 0.21, 95% CI 0.07 to 0.59), while use of citrates did not show a significant impact on the thrombolytic use (5 studies, 877 participants: RR 1.18, 95% CI 0.95 to 1.47) (Figure 11).

Figure 10. Requirement for thrombolytic agents

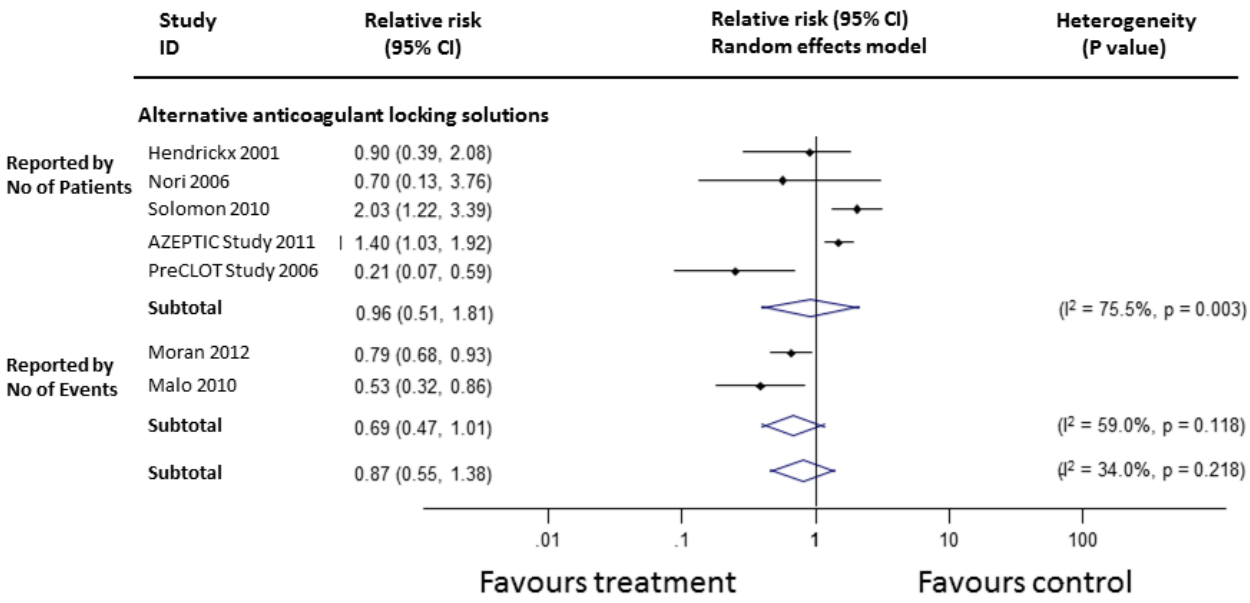
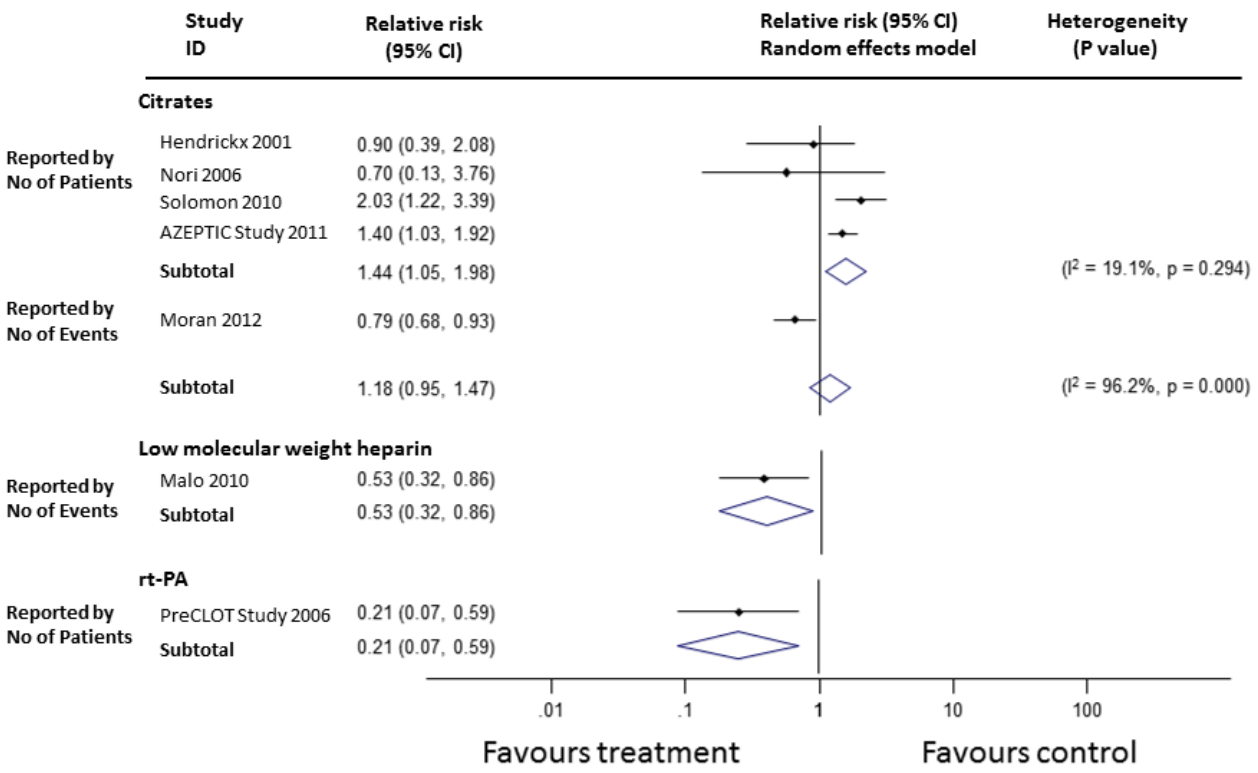


Figure 11. Requirement for thrombolytic agents (subgroup analysis)



DISCUSSION

Summary of main results

This systematic review of RCTs assessing the relative effects of different strategies for prevention of catheter malfunction in adults with ESKD identified 27 relatively small studies, with an average of 75 participants and 6 months follow up. Newer approaches, including alternative anticoagulant locking solutions, systemic agents and low or no dose heparin, did not affect rates of catheter malfunction compared with usual care. The only individual agent demonstrating statistically significant improvement for catheter malfunction compared with conventional care was rt-PA-based locking solution in a result that was based on a single study. No significant effect on all-cause mortality was observed for individual classes of anticoagulants. Use of rt-PA and LMWH locking solutions reduced the use of thrombolytic agents but the results were based on a single study. The relative effectiveness of other interventions remains inconclusive and, of concern, the reporting of safety outcomes was infrequent. Specifically, bleeding rates were only reported in 8 studies, despite the use of anticoagulants in a patient population with recognised bleeding risk.

Citrate locking solutions, antibiotic locking solutions and rt-PA locking solutions were associated with a significant reduction in catheter-related bacteraemia. However, the additional use of antibiotic locks to citrate did not have an impact on incidence of catheter-related bacteraemia. The effectiveness of an alternative mechanism for preventing infectious complications in haemodialysis patients with CVC, topical interventional strategies, was the subject of a Cochrane review last updated in 2010 (McCann 2010). Interventions that assessed included prophylactic topical antimicrobials, topical antiseptics, medicated and non-medicated dressings. The review found mupirocin ointment appears effective in reducing the risk of catheter-related bacteraemia, while the effect of povidone-iodine ointment, polysporin ointment, topical honey and types of dressing on catheter-related bacteraemia remain uncertain.

Among individual alternative anticoagulant agents, rt-PA was effective in reducing catheter malfunction in a single study of Canadian centres for the prevention of catheter malfunction at no increased bleeding risk. These results are promising but, as a single study of 225 participants, require replication in other settings (PreCLOT Study 2006). The author's cost-effectiveness analysis found the incremental cost of rt-PA was CAD 13,956 per episode of prevented catheter-related bacteraemia in the setting where the rate of catheter-related bacteraemia in the control group was 13%. Differences of background bacteraemia prevalence will obviously influence the cost-effectiveness of the intervention.

Citrate solutions reduced catheter-related bacteraemia, but there was no clear evidence they reduced catheter malfunction. Based on a single study, citrate did not show a reduction in bleeding events. There was a suggestion that patients receiving citrate locking solutions experienced more adverse events, although these were only reported in two studies with 311 participants with one of them showing statistically significant result. Cardiac arrhythmia rates were not reported in any despite safety concerns that high concentration citrate may promote the induction of cardiac arrhythmia via systemic hypocalcaemia. Future studies should of citrate solutions are warranted and should address the uncertainty for both efficacy and safety outcomes.

Ethanol locking solutions were not inferior to heparin locks in prevention of catheter malfunction in a single reported study. Ethanol appears to possess intrinsic anticoagulant activity and is therefore effective at restoring catheter patency (Pennington 1987). In addition, in vitro studies suggested that ethanol also has broad-spectrum antimicrobial activity, which seems to be based on denaturization rather than a specific molecular target (Sherertz 2006). Our review did not show a benefit for ethanol on prevention of catheter-related bacteraemia based on only one small study; future large studies should test it as a promising alternative locking solution to heparin.

Our analysis indicates it is possible low or no dose heparin may not be inferior to heparin locking in preventing catheter malfunction based on two small studies. The uptake of heparin locking solutions for temporary dialysis access catheters appears to have developed as the default without RCT evidence. The priority that should be assigned to future research of lower dosing heparin is unclear given the scarcity of information on the rates of adverse effects associated with current heparin usage.

The broad inclusiveness of interventions included in our review meant we anticipated heterogeneity of effects and hence planned to use random effects models. However we also found heterogeneity in the reporting methodologies. Individual studies variously reported numbers of patients experiencing events – the information conventionally used in meta-analyses - or by repeated event rates. Relative risks generated by the latter can be utilized in meta-analysis but the narrower CI generated by repeated events mean that these studies have greater impact in the random effects models than if they had reported by individual patients. None of these studies made statistical adjustments for the potential lack of independence of repeated events in a given individual. We have developed a methodology for analysis in these situations.

Overall completeness and applicability of evidence

This is the first systematic review assessing all RCTs investigating anticoagulants for the prevention of catheter malfunction in adults undergoing haemodialysis. Twenty-seven studies with a large variety of interventions involving six different catheter locking solutions and systemic agents were included in our review. The relative net benefit of anticoagulant therapies over conventional care for prevention of catheter malfunction remains uncertain. However, a significant reduction in catheter-related bacteraemia was observed for citrate locking solutions, antibiotic locking solutions and rt-PA locking solutions. Currently there is no adequate information on locking solutions collected in the Australian, USA or UK registries. The inclusion of locking solution type is warranted in large registries to facilitate the monitoring of bleeding rates and infrequent events such as cardiac arrhythmias.

Quality of the evidence

The studies were predominantly of low quality, and underpowered with an average participant number of 75 and study duration of 6 months. The interpretation of the study evidence was further limited by the variation in tested interventions and outcome reporting differences.

Potential biases in the review process

One limitation of this study was the reliance on the published data. Therefore, incomplete data reporting (attribution bias) in some studies could lead to potential loss of statistical power. In addition, assessment of potential net benefit, including efficacy and harms, was prevented by the limited safety reporting, notably of bleeding events.

Agreements and disagreements with other studies or reviews

The only agent that appeared to have prophylactic effect in our review is rt-PA locking solution but the result was only based on a single study. This finding is consistent with those of a current systematic review (Firwana 2011) assessing three RCTs comparing rt-PA versus heparin for locking dialysis catheters. Only one of these was eligible for our study with the other two being excluded because they were conducted in a paediatric population (Gittins 2007) and another because it included patients with both acute kidney injury and chronic kidney disease Schenk 2000.

Our review also found that use of citrate locking solutions significantly reduced incidence of catheter-related bacteraemia but not for catheter malfunction or requirement for thrombolytic agents in 14 studies. The review is consistent in the main with a previous systematic review (Zhao 2014) which included 13 studies. We found citrate locking solutions had no impact on bleeding events (one eligible study), while Zhao 2014 identified reduced bleeding with citrate locking solutions which included two studies with the results driven by inclusion of a study assessing patients with both acute kidney injury and chronic kidney disease (Weijmer 2005).

AUTHORS' CONCLUSIONS

Implications for practice

The current evidence does not show a clear benefit for alternative anticoagulants compared with conventional practice. Despite the frequency with which this basic aspect of a costly health care service is delivered, we have a limited understanding of its efficacy, safety and cost effectiveness. A net benefit of rt-PA for prevention of catheter malfunction needs to be confirmed in other settings. Effect of citrate locking solutions on a reduction of catheter-related bacteraemia is promising, which could potentially replace conventional heparin locking solutions for dialysis patients. However, it warrants further investigation on its benefits and harms before widespread use in clinical practice.

Implications for research

Further high quality blinded RCTs on alternative anticoagulant locking solutions that are adequately powered to report on both potential benefits and harms are needed. Interventions for prevention of catheter malfunction that warrant further investigation include studies of rt-PA, citrate, and ethanol locking solutions as well as non-inferiority studies of lower heparin dosing. Given that our review did not show that high citrate concentrations were more efficacious than lower concentrations in preventing catheter malfunction and catheter-related bacteraemia, it would also appear reasonable that future studies of citrate therapy assess the impact of low concentration citrate locking solutions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abdul-Rahman 2007

Methods	• Study design: parallel RCT • Study duration: December 2004 to December 2005 • Duration of follow-up: 12 months
Participants	• Country: Saudi Arabia • Setting: single centre • Adult HD patients dialysed with tunnelled CVC • Number: treatment group 1 (20): treatment group 2 (19); control group (19) • Mean age ± SD (years): treatment group 1 (48.3 ± 11.5); treatment group 2 (44.7 ± 7.4); control group (45.4 ± 9.5) • Sex (M/F): treatment group 1 (12/8); treatment group 2 (10/9); control group (12/7) • Number with diabetes: treatment group 1 (6); treatment group 2 (6); control group (8)

Abdul-Rahman 2007 *(Continued)*

	• Exclusion criteria: previous history of blood loss requiring either hospitalisation or transfusion in the previous 3 months; demonstrated advanced proliferative diabetic retinopathy; life expectancy < 12 months because of advanced organ-systemic disease or malignancy; uncontrolled hypertension (defined as SBP, > 200 mm Hg or DBP > 110 mm Hg on three different occasions in a period of 2 weeks); platelet count < 100,000/cm^3, INR > 1.3, or partial thromboplastin time 5 seconds longer than control, or demonstrated other medical conditions that would make anticoagulant or antiplatelet therapy dangerous; receiving dipyridamole, sulfinpyrazone, ticlopidine, clopidogrel, or NSAID
Interventions	Treatment group 1 • Warfarin: adjusted dose with the target INR of 1.5 to 2 Treatment group 2 • Aspirin: 81 mg single dose/d Control group • No treatment
Outcomes	• Time to the first episode of catheter thrombosis (defined as the detection of a visible catheter clotting or the inability to successfully initiate or continue dialysis via the tunnelled central catheter with a blood flow < 250 mL/min in the absence of other causes of catheter malfunction) • Major bleeding events: confirmed retroperitoneal, intra-articular or cerebral haemorrhage, or any bleeding episode that resulted in a 2 g/dL decrease in haemoglobin concentration.
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the details of the randomisation sequence nor the identity of the medication assignment was known to the participants or the assigned physician
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	High risk	Bleeding not reported; did not report catheter-related bacteraemia
Other bias	Unclear risk	Insufficient information to permit judgement

AZEPTIC Study 2011

Methods	• Study design: open-label, parallel RCT • Study duration: not reported • Duration of follow-up: 26 weeks
Participants	• Country: USA • Setting: multicentre (25 outpatient HD units in USA) • Patients with ESKD > 18 years receiving HD 3 times weekly through a cuffed and tunnelled internal jugular venous catheter with a mean baseline flow rate 300 mL/min • Number: treatment group (201): control group (206) • Mean age ± SD (years): treatment group (62.2 ± 15.4); control group (61.7 ±15.2) • Sex (males): treatment group (48.8%); control group (51.5%) • Proportion with DKD: treatment group (46.8%); control group (48.5%)\ • Exclusion criteria: no clinical or laboratory evidence of active infection within the preceding 30 days and a negative pre-enrolment blood culture; femoral and subclavian catheters; catheters with antithrombotic or antimicrobial coatings; pregnancy; thrombocytopenia or other chronic coagulopathy; history of heparin-induced thrombocytopenia; antibiotic therapy within 14 days of enrolment (30 days for vancomycin); hypersensitivity to heparin, sodium citrate, methylene blue, methylparaben, or propylparaben
Interventions	Treatment group • C-MB-P: 0.24 M (7.0%) sodium citrate, 0.15% methylene blue, 0.15% methylparaben, and 0.015% propylparaben (Zuragen; Ash Access Technology, Lafayette, IN) Control group • UFH: 5000 U in sterile saline
Outcomes	• Patency failure from thrombosis (defined as a decrease of Qb200 > 20% with failure to restore flow after one to three interventions that culminated in removal of the catheter) • CRBSI: defined as fever (temperature > 38°C) with concordant positive blood cultures drawn from the catheter and a peripheral vein or a peripheral blood culture and a concordant exit site culture. Concordant CRBSI was defined as two concordant positive blood cultures but with temperature not exceeding 38.0°C. Probable CRBSI was defined as fever with one positive blood culture. In each category, there was no clinically identifiable source of bloodstream infection other than the catheter) • Adverse events • Catheter blood flow rate over the course of the study • All-cause mortality • Composite end points introduced to address multiple outcomes and to control type I error associated with multiple testing for overall treatment effect • Combining CRBSI, patency failure, adverse events, and death from any cause
Notes	• Funding: "National Institute of Diabetes and Digestive and Kidney Diseases 5 R44 DK071369-03; the Indiana 21st Century Research and Technology Fund; the Oscar Rennebohm Foundation of Madison, WI; the National Institutes of Health; and Ash Access Technology" • "Dr. Ash is the founder and reports ownership of Ash Access Technology. Dr. Ash has stock ownership and options in Ash Access Technology and received patents from Ash Access Technology related to this product. Mr. Winger is employed by Ash Access Technology and reports ownership and stock options. Dr. Lavin is employed by Averion International. Averion International was compensated by Ash Access Technology for clinical monitoring, statistical analysis, and clinical event committee support for this study"

Risk of bias

Bias	Authors' judgement	Support for judgement

AZEPTIC Study 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generalised list of random numbers at each site using a permuted block design stratified by dialysis catheter age
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT performed
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	High risk	Second investigator is the owner of Ash Access

Betjes 2004

Methods	• Study design: parallel RCT • Study duration: May 2002 to June 2003 • Duration of follow-up: 90 days
Participants	• Country: the Netherlands • Setting: single centre • Adult HD patients dialysing with tunnelled and non tunnelled CVC • Number: treatment group (37): control group (39) • Mean age ± SE (years): treatment group (58.3 ± 16.3); control group (50.3 ± 20.4) • Sex (males): treatment group (56.8%); control group (61.5%) • Proportion with diabetes: treatment group (22%); control group (33%) • Exclusion criteria: dialysis catheter was used on the intensive care unit or for reasons other than HD; using antibiotics
Interventions	Treatment group • Citrate–taurolidine: 1.35% taurolidine and 4% sodium citrate (Neutrolin TM, Biolink, Norwell, MA, USA) Control group • Heparin: 5000 U/mL
Outcomes	• Catheter-related sepsis: symptomatic patients with a positive bacterial blood culture drawn from the dialysis catheter with no other apparent source of infection • Exit site infection according to the Centers for Disease Control criteria: erythema, tenderness and/or induration within 2 cm of the exit site with or without a purulent exudate or microbiological exit-site infection where the exudate yields a micro-organism on culture • Bacterial colonisation of the catheter

Betjes 2004 *(Continued)*

	• Catheter-related sepsis or bacterial colonization-free survival: defined as the number of days from catheter insertion to diagnosis of catheter-related sepsis or positive bacterial blood culture
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Bleyer 2005

Methods	• Study design: parallel RCT • Study duration: 1 August 1998 to 17 November 1999 • Duration of follow-up: 360 days
Participants	• Country: USA • Setting: single centre; follow-up at a local HD centre • Adult HD patients ≥ 18 years dialysing with CVC; catheter inserted within 72 hours of entering the study; signed informed consent • Number: treatment group (30): control group (27) • Mean age ± SD (years): treatment group (50.1 ± 19.6); control group (58.7 ± 13.5) • Sex (males): treatment group (63.3%); control group (51.8%) • Proportion with diabetes: treatment group (33.3%); control group (44.4%) • Exclusion criteria: active catheter infection; active infection at any site within the previous 48 hours; known allergies to heparin, minocycline, or EDTA; serum calcium < 7.5 mg/dL with symptoms; previous enrolment in the study
Interventions	Treatment group • Minocycline: 3 mg/mL

Bleyer 2005 *(Continued)*

	• EDTA: 30 mg/mL Control group • Heparin as a flush after each dialysis session Other information • If patients met the criteria for inclusion, they received one of the two study solutions within 72 hours of catheter placement. Thereafter, at the end of each HD session, catheters were locked with the designated solution • When patients were transferred to the outlying dialysis centres, the solutions were supplied weekly to the nursing staff of these centres
Outcomes	• Catheter clotting (defined as the use of urokinase or tissue plasminogen activator or catheter removal for clotting.) • CRSBI (defined as catheter colonization plus a peripheral blood culture growing the same organism. Catheter colonization was defined as growth of 15 or more CFU)by roll-plate culture, ≥ 100 CFU by sonication culture, ≥ 100 CFU by flush culture, or a ratio of 5:1 or more of catheter blood CFU to peripheral blood CFU) • Catheter malfunction (defined as blood flow rate of < 200 mL/min for three consecutive dialyses and/or the use of urokinase) • Adverse events
Notes	• Funding: "One of the investigators at the study site (RJS) is a co-patent holder on the minocycline–EDTA flush solution being studied. Another author at a distant site (IIR) is the other patent holder. The study was blinded and the data analyses were done by AJB and GR to minimize any potential conflicts."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block design - random numbers in blocks of 4
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	High risk	Author holds patent on intervention being tested

Buturovic 1998

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: removal of catheters when they were no longer required or had to be removed for complications
Participants	• Country: Slovenia • Setting: not reported • ESKD patients with subclavian or jugular single lumen catheters as temporary vascular access for HD • Number: treatment group 1 (10): treatment group 2 (10); control group (10) • Mean age ± SD: 63 ± 8 years • Sex (M/F): 13/17 • Exclusion criteria: not reported
Interventions	Treatment group 1 • Trisodium citrate: 4% Treatment group 2 • Polygeline: 3.5% Control group • Heparin: 5000 U in 2 mL of saline
Outcomes	• Catheter usage time • Clot volume: the volume of the aspirated clot was determined by sinking it in a calibrated syringe and measuring its displacement volume
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No
Blinding of outcome assessment (detection bias) All outcomes	High risk	No
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete, no catheter-related bacteraemia was reported; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported

Buturovic 1998 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

Campos 2011

Methods	• Study design: open-label, parallel RCT • Study duration: March 2008 to July 2009 • Duration of follow-up: 90 days
Participants	• Country: Brazil • Setting: multicentre (3) • Adult HD patients with ESKD dialysing with CVC (jugular and subclavian) for at least 2 weeks • Number: treatment group (92): control group (95) • Mean age ± SD (years): treatment group (54.56 ± 16.86); control group (55.55 ± 15.35) • Sex (males): treatment group (62.0%); control group (53.7%) • Proportion with diabetes: treatment group (35.9%); control group (40.0%) • Exclusion criteria: active infection; on antibiotics within seven days before catheter implantation; in the first two sessions of HD, the catheter did not allow a pump blood flow rate of 200 mL/min for non-tunnelled catheters and 250 mL/min for tunnelled catheters; protocol violation
Interventions	Treatment group • Minocycline with EDTA solution: CATH-SAFE®, 3 mg/mL of minocycline and 30 mg/mL of EDTA, Laborato´ rio Lebon, Porto Alegre, Brazil). The solution was prepared by diluting the lyophilised syringe content with 3 mL of isotonic saline. The maximum size of the syringes used was 3 mL Control group • UFH-sodium: 5000 U/mL
Outcomes	• CRBSI within 90 d from catheter insertion: suspicious when a temperature of > 37.8 °C, chills, hypotension, mental confusion, or pain occurred. The study protocol required obtaining blood cultures both from peripheral blood and from the catheter. An exit site swab was also collected, if indicated). The criteria to make the diagnosis of bacterial infection were based on KDOQI 2006. "Blood stream infection in a symptomatic patient with no other apparent source of infection. We decided not to include “possible” blood stream infection, defined as clinical pointers in the absence of laboratory confirmation of blood stream infection." • Catheter dysfunction: the need for catheter removal because, during HD, a pump blood flow < 200 mL/min for non-tunnelled catheters and 250 mL/min for tunnelled catheters was not achieved • Catheter-related bacteraemia-free survival: number of days from catheter insertion to diagnosis of catheter-related bacteraemia as defined above
Notes	• Funding: Pro-Renal Foundation of Brazil for financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Campos 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Low risk	Funding from Pro-Renal Foundation of Brazil for financial support

CHARTS Study 2008

Methods	• Study design: open-label, parallel RCT • Study duration: not reported • Duration of follow-up: median length of follow up of 64 days (IQR 32 to 132)
Participants	• Country: Canada • Setting: single centre • Patients undergoing chronic HD 3 times/week, 4 h/session with cuffed catheters as primary vascular access • Number: treatment group (32): control group (29) • Mean age ± SD (years): treatment group (63 ± 16); control group (69 ± 15) • Sex (males): treatment group (65.6%); control group (48.3%) • Proportion with diabetes: treatment group (56.3%); control group (48.3%) • Exclusion criteria: previously randomised to the study; arteriovenous fistula or arteriovenous graft was already in use at the time of the study; currently on antibiotics; unable or unwilling to give informed consent

Interventions	Treatment group
	• Citrate: 4%
	  * Prepackaged by the manufacturer (MEDXL, Montreal, Quebec, Canada) in a 5 mL syringe containing citrate 4%/patient/dialysis run (one syringe for both venous and arterial lumen). From these prefilled syringes, citrate was instilled at a volume determined by the manufacturer specifications of the lumen volume
	  * Locking agent remained in the catheter lumen until the next HD run, and at the beginning of the next run the solution was withdrawn and discarded.
	Control group
	• Heparin solution: 5000 U/mL
	  * 1 mL of 10,000 U/mL of heparin was aspirated into a 2 mL syringe and added 1 mL of sterile normal saline to produce 2 mL of heparin 5000 U/mL as per the current standard of care (one syringe/catheter lumen

Outcomes	• Development of catheter dysfunction: blood pump speed < 250 mL/min or the use of rt-PA • catheter-related bacteraemia

CHARTS Study 2008 *(Continued)*

	• Development of an exit-site infection • Bleeding complications (either local or systemic)
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Patients were randomised according to their last name
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	Low risk	Bleeding reported
Other bias	Unclear risk	Insufficient information to permit judgement

Coli 2006

Methods	• Study design: parallel RCT • Study duration: June 2001 and June 2005 • Duration of follow-up: 12 months
Participants	• Country: Italy • Setting: single centre • Adult HD patients with ESKD dialysing with CVC • Number: treatment group (81): control group (63) • Mean age ± SD (years): treatment group (65 ± 12); control group (69 ± 11) • Sex (M/F): treatment group (41/40); control group (32/31) • Proportion with DKD: treatment group (15%); control group (14%) • Exclusion criteria: active infection in the last 30 days; patients with bleeding or coagulative disorders, immunological diseases or acute cardiovascular events in the last 3 months
Interventions	Treatment group • Prophylactic dose of warfarin (received 12 hours after catheter placement) with INR 1.8-2.5 in association with ticlopidine 250 mg/d Control group

Coli 2006 *(Continued)*

	• Patients received warfarin only after TCC thrombosis or malfunction with INR 1.8-2.5 in association with ticlopidine 250 mg/d Other information • All patients received LMWH (nadroparin calcium, Fraxiparin, Danofi-Synthelabo) at a dose of 64 IU anti-Xa/kg subcutaneously once/d until the target INR was reached
Outcomes	• Occurrence of an episode of blood flow rate < 300 mL/min during HD when this episode met the following criteria * Not associated with mechanical problems or tunnelled cuffed catheter tip displacement * Need for inversion of dialysis lines * Need for urokinase therapy or infusion in accordance with Twasrdowsk
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Corbett 2013

Methods	• Study design: open-label, parallel RCT • Study duration: not reported • Duration of follow-up: 6 months
Participants	• Country: UK • Setting: single centre • HD patients established on dialysis for > 90 days who dialyse in-centre at any of the satellite dialysis units of Imperial College Healthcare NHS Trust; all patients with a recent catheter-related bacteraemia with an identified organism grown on microbiological culture and treated without catheter removal were eligible for inclusion

Corbett 2013 *(Continued)*

- Number: treatment group (14); control group (13)
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: individuals in whom attempted catheter salvage is clinically not indicated; unable to provide informed consent; known allergy to sodium citrate, heparin or taurolidine; bleeding diathesis or physical cause for active bleeding

Interventions	Treatment group • Taurolidine-citrate-heparin line-lock (500 U/mL) Control group • Heparin: 5000 U/mL
Outcomes	• Bacteraemia-free catheter survival
Notes	• Abstract-only publication; some additional data available from clinicaltrials.gov • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Dogra 2002

Methods	• Study design: parallel RCT • Study duration: May 1999 to June 2001 • Duration of follow-up: 270 days
Participants	• Country: Australia • Setting: multicentre (2 tertiary referral centres and their associated satellite dialysis units)

Dogra 2002 *(Continued)*

- Adult HD patients with insertion of a tunnelled catheter for the maintenance or commencement of HD (dual-lumen, cuffed catheters); patients having reinsertion of a tunnelled catheter through a new entry site were also included
- Number: treatment group (42): control group (37)
- Mean age ± SD (years): treatment group (55.7 ± 2.5); control group (59.3 ± 2.1)
- Sex (males): treatment group (45%); control group (47%)
- Proportion with diabetes: treatment group (30%); control group (40%)
- Exclusion criteria: active sepsis; allergy to gentamicin and/or citrate; failure to randomise a patient within three dialysis sessions of new catheter insertion and rewiring of a tunnelled; catheter through the same exit site were also exclusion criteria

Interventions	Treatment group
	• Gentamicin + citrate in a 3 mL syringe
	  * Gentamicin: 2 mL of 40 mg/mL
	  * Tri-sodium citrate: 1 mL of 3.13%
	Control group
	• Heparin: 5000 U/mL in a 3 mL syringe
	Other information
	• Each patient was provided with two 3 mL syringes/dialysis, and nurses were advised to withdraw the lock solution before dialysis and to lock the catheters after dialysis with a volume equivalent to the lumen volume plus 0.2 mL

Outcomes	• Catheter-related bacteraemia: according to the Centers for Disease Control • Infection-free catheter survival: number of days from catheter insertion to diagnosis of CRI as previously defined • Catheter malfunction: blood flow rate of < 200 mL/min for 3 consecutive dialyses and/or the use of urokinase • Adverse events
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation using random number tables
Allocation concealment (selection bias)	Low risk	Performed by clinical trials pharmacists
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT reported

Dogra 2002 *(Continued)*

Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Filiopoulos 2011

Methods	• Study design: parallel, open-label RCT • Study duration: April 2008 to November 2009 • Duration of follow-up: 60 days
Participants	• Country: Greece • Setting: single centre • Adult patients with CKD stage 5 requiring an uncuffed catheter insertion for starting or maintaining chronic HD; patients with a newly inserted, well-positioned uncuffed catheter that was expected to be needed for at least 1 week • Number: treatment group (59): control group (60) • Mean age, range (years): treatment group (75, 36 to 95); control group (72, 50 to 80) • Sex (M/F): treatment group (33/26); control group (29/31) • Proportion with diabetes: treatment group (64%); control group (67%) • Exclusion criteria: active or current infection; on antibiotics or immunosuppressive medications

Interventions	Treatment group
	• Taurolidine + citrate (TauroLock TM, TauroPharm GmbH)
	  * Taurolidine: 1.35%
	  * Sodium citrate: 4%
	Control group
	• Gentamicin + heparin (ratio 1:3)
	  * Gentamicin: 40 mg/mL
	  * UFH: 5,000 U/mL
	Other information
	• Solutions given at the end of each dialysis session and continuously since catheter insertion

Outcomes	• Time to the first catheter-related bacteraemia episode: positive blood culture obtained, using an aseptic technique, during dialysis through the dialysis circuit linked to the catheter in a symptomatic patient and after other potential sources of infection has been excluded through the appropriate clinical and laboratory testing • Catheter thrombosis: catheter dysfunction with blood flow < 200 mL/min in 3 consecutive dialysis sessions and after other potential causes, such as malposition or kinking, had been excluded
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers

Filiopoulos 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No patient was lost to follow-up or discontinued the catheter-lock solution"
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Unclear risk	Insufficient information to permit judgement

HEALTHY-CATH Study 2009

Methods	• Study design: open-label, parallel RCT • Study duration: October 2006 to November 2010 • Duration of follow-up: patients were followed until removal of CVC
Participants	• Country: Australia • Setting: multicentre study (3) • Incident or prevalent adult HD patients with tunnelled IV catheters; able to give informed consent • Number: treatment group (25); control group (24) • Mean age ± SD (years): treatment group (52 ± 18); control group (64 ± 16) • Sex (M/F): treatment group (13/12); control group (11/13) • Proportion of diabetic nephropathy: treatment group (32%); control group (25%) • Exclusion criteria: intolerance to ethanol; personal, cultural or other objection to the use of ethanol; history of an exit site, tunnel, or bloodstream infection associated with the current catheter; pregnancy
Interventions	Treatment group • 3 mL 70% ethanol lock weekly after HD • Heparin lock twice weekly after other HD sessions Control group • Heparin lock 5000 IU/mL thrice weekly after HD
Outcomes	• Time to first episode of CRBSI • Adverse reactions • Incidence of CRBSI caused by different pathogens • Time to infection-related catheter removal • Time to exit site infection • Mechanical dysfunction: any dysfunction of the catheter such as a split, but not including catheter blockage, which required catheter removal

HEALTHY-CATH Study 2009 *(Continued)*

Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised computer generated block randomisation procedure
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment was ensured using a centralised computer generated block randomisation procedure
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	No
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT was reported
Selective reporting (reporting bias)	Low risk	Bleeding was reported
Other bias	Low risk	Study appears free of other potential biases

Hendrickx 2001

Methods	• Study design: parallel RCT • Study duration: between April and October 2000 • Duration of follow-up: not reported
Participants	• Country: Belgium • Setting: single centre • Adult HD patients dialysing with single lumen tunnelled CVC as permanent vascular dialysis access (internal jugular) • Number: treatment group (10): control group (9) • Mean age: treatment group (74.6 years); control group (71.4 years) • Sex (M/F): treatment group (4/6); control group (4/5) • Proportion with diabetes: not reported • Exclusion criteria: patients with temporary catheters; previous history of catheter position related inadequate blood flow; known history of haemorrhagic diathesis; systemic thromboembolic events; liver failure; receiving anticoagulation therapy
Interventions	Treatment group • Trisodium citrate solution: 5% Control group • UFH solution: 5000 U/mL

Hendrickx 2001 *(Continued)*

Outcomes	• Incidence of flow problem: the inability to maintain an effective blood flow above 150 mL/min) • Complete occlusion of the catheter with the inability to withdraw the lock * Clots: the presence of clotting material on the gauze (depending on their size, a difference was noted between small, medium and large clots) • Intradialytic blood flow rates • catheter-related bacteraemia
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete report on number of patients with clots formation; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Hryszko 2013

Methods	• Study design: open-label, parallel RCT • Study duration: • Duration of follow-up:
Participants	• Country: Poland • Setting: single centre • Adult HD patients dialysing with dual lumen cuffed CVC (internal jugular or femoral vein) • Number: treatment group (37); control group (38); • Mean age ± SD (years): treatment group (64 ± 15); control group (65 ± 14) • Sex (M/F): treatment group (19/18); control group (17/21) • Proportion with diabetes: treatment group (24); control group (21) • Exclusion criteria: not reported
Interventions	Treatment group

Hryszko 2013 *(Continued)*

	• Low concentration of heparin solution: 2500 IU/mL Control group • UFH: 5000 IU/mL
Outcomes	• The occurrence of bleeding within 24 h after catheter placement • The effects of clinical and laboratory data on bleeding events (prolongation of activated partial thromboplastin time)
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Toss coin method
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data; ITT was not reported.
Selective reporting (reporting bias)	High risk	Bleeding was not reported clearly
Other bias	Low risk	Insufficient information to permit judgement

Kaneko 2004

Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Country: Japan • Setting: single centre • Adult HD patients dialysing with double lumen CVC • Number: treatment group (26): control group (22) • Mean age, range (years): treatment group (69.9, 65.0 to 74.9); control group (66.7, 60.5 to 72.9) • Sex (M/F): treatment group (13/13); control group (11/11) • Proportion with diabetes: treatment group (19.2%); control group (27.3%) • Exclusion criteria: coagulation disorders; haemorrhagic diseases; Indication of abdominal or orthopaedic surgery; patients taking anticoagulant drugs

Kaneko 2004 *(Continued)*

Interventions	Treatment group • 20 mL normal saline flush into each lumen only Control group • 20 mL normal saline flush followed by 2 mL of heparin lock (1000 U/mL) Other information • The flushing procedure was conducted after each HD therapy 3 days/wk and once a day on the other days of the week
Outcomes	• Incidence of thrombotic occlusion, probability of catheter survival, and the adverse period during which the catheter's patency was maintained, until either the catheter was removed after substitutive blood access became available or at least one of the catheter's lumens was occluded with thrombus and in-flow blood flow was < 140 mL/min. Definitions: * Inability to remove the locking solution, but ability to push it into the blood circulation * Mean blood flow throughout the session < 250 mL/min for more than 2 consecutive sessions (alteplase would then be used as a lock at the end of the second session) or reverse use of the catheter for two consecutive sessions • Difference of haematological and coagulation markers between the 2 groups
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No reported
Allocation concealment (selection bias)	High risk	No
Blinding of participants and personnel (performance bias) All outcomes	High risk	No
Blinding of outcome assessment (detection bias) All outcomes	High risk	No
Incomplete outcome data (attrition bias) All outcomes	High risk	Nil catheter-related bacteraemia was reported; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Lustig 2011

Methods	• Study design: parallel RCT • Duration of study: not reported

Lustig 2011 *(Continued)*

	• Duration of follow-up: not reported
Participants	• Country: Israel • Setting: single centre • Adult HD patients dialysing with CVC • Number: 140 catheters inserted in 100 patients • Mean age ± SD (years): not reported • Sex (M/F): not reported • Proportion with diabetes: not reported • Exclusion criteria: not reported
Interventions	Treatment group • TSCEM lock (trisodium citrate, ethanol, methylene blue); invented by hospital pharmacists and approved for clinical trial evaluation Control group • Heparin lock
Outcomes	• Catheter-related bacteraemia • Exit site infections • Catheter removal • Adverse events
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

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

Malo 2010

Methods	• Study design: cross-over RCT • Study duration: 1 December 2004 to 1 April 2005 • Duration of follow-up: 14 weeks
Participants	• Country: Canada • Setting: single centre • Patients ≥ 18 years with ESKD who had been receiving HD for 1 month were eligible if they had been using a tunnelled CVC for 3 weeks • Number: 42 • Mean age ± SD: 66.5 ± 12.7 years • Sex (M/F): 20/22 • Proportion with diabetes: 50% • Exclusion criteria: received alteplase for catheter dysfunction within 2 weeks before randomisation; receiving chronic anticoagulation therapy (warfarin 1 mg/d); previously known liver disease or haematological conditions associated with bleeding or thrombotic complications
Interventions	Treatment group • Tinzaparin: 2000 U (0.2 mL of a 10,000 U/mL solution)/catheter line; the final concentration in the catheters ranged from 909 to 1,176 U/mL Control group • UFH: 5000 U (0.5 mL of a 10,000 U/mL solution); the final concentration in the catheters ranged from 2,273 to 2,941 U/mL Other information • The preparation and dispensation of single-dose UFH and tinzaparin syringes were carried out by the Pharmacy Department • Patients were randomised to 7 weeks of treatment or control and then crossed over

Outcomes	• The need for thrombolytic catheter lock use defined with the HD Unit alteplase protocol. Definitions:
	  * Inability to remove the locking solution, but ability to push it into the blood circulation
	  * Mean blood flow throughout the session < 250 mL/min for more than 2 consecutive sessions (alteplase would then be used as a lock at the end of the second session) or reverse use of the catheter for 2 consecutive sessions
	• The reasons for using alteplase, reverse use of the catheter
	• Mean blood flow during dialysis
	• On-line mean Kt/V
	• Mean pressure of the venous and arterial catheter lines, removal of the catheter
	• Reasons for removing the catheter

Notes	• Funding: "Supported by Leo Pharma, Denmark (EX 0405 CA, to L.S.)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Group assignment sequence was determined a priori from a computer generated table of random numbers and recorded on a master sheet that was accessible only to the main investigators
Allocation concealment (selection bias)	Unclear risk	Not reported

Malo 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No
Blinding of outcome assessment (detection bias) All outcomes	High risk	No
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	High risk	Supported by Leo Pharma, Denmark

Mokrzycki 2001

Methods	• Study design: parallel RCT • Study duration: May 1997 to September 1999 • Duration of follow-up: 1 year
Participants	• Country: USA • Setting: multicentre (3; after initiation of HD in the hospital-based unit, all patients received in chronic HD in one of four free-standing units) • Adult HD patients dialysing with tunnelled cuffed, dual-lumen CVC • Number: treatment group (41): control group (44) • Mean age ± SD (years): treatment group (58.9 ± 2.3); control group (57.8 ± 2.6) • Sex (males): treatment group (56%); control group (64%) • Proportion with DKD: treatment group (49%); control group (55%) • Exclusion criteria: receiving systemic anticoagulation; existing contraindication to warfarin therapy; refused to consent
Interventions	Treatment group • Coumadin (warfarin): 1 mg provided by DuPont Pharmaceuticals (Wilmington, DE, USA) Control group • Placebo

Outcomes	• Days of thrombosis-free TCC survival until TCC failure and removal because of late malfunction. Definitions
	  * Incipient thrombosis (defined as difficulty aspirating blood from the TCC lumen or a mean TCC blood flow < 200 mL/min during HD for two consecutive treatments despite repositioning of the patient
	  * Late TCC malfunction (defined as the presence of an inadequate TCC blood flow, without evidence of a mechanical malfunction by chest radiograph and/or venography, after a previously successful period of TCC function (> 2 weeks)
	• Days to first intervention with urokinase for incipient thrombosis
	• Rate of urokinase dosing
	• Haemorrhage

Mokrzycki 2001 *(Continued)*

Notes	• Funding: "We wish to acknowledge the Quinton Instrument Company and DuPont Pharmaceuticals for generously sponsoring this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Yes; the Jacobi Medical centre pharmacy repackaged the active drug and provided similar placebo capsules to facilitate a double-blinded study design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	Low risk	Bleeding reported
Other bias	High risk	Study sponsored by Quinton Instrument Company and DuPont Pharmaceuticals

Moran 2012

Methods	• Study design: parallel RCT • Study duration: September 2003 to May 2008 • Duration of follow-up: 2 years
Participants	• Country: USA • Setting: multicentre (16) • All adult patients with either newly placed or existing TCC for HD • Number: treatment group (155): control group (148) • Mean age ± SD (years): treatment group (63.4 ± 15.6); control group (62.8 ± 16.8) • Sex (males): treatment group (49%); control group (54.7%) • Proportion with diabetes: treatment group (54.8%); control group (58.1%) • Exclusion criteria: an active exit-site or tunnel infection or other systemic or localized infection that was unresponsive to antibiotic therapy and/or was life-threatening; any infection associated with one or more positive blood culture results were not eligible until 14 days after blood culture results had become negative and clinical resolution of the episode had occurred; known allergy to heparin or gentamicin; known intravenous drug use
Interventions	Treatment group • Gentamicin 320 mg/mL in 4% sodium citrate

Moran 2012 *(Continued)*

	Control group • 1,000 U/mL of heparin
Outcomes	• CRBSI: defined as the occurrence of symptoms consistent with bacteraemia together with positive blood culture results in the absence of another obvious source of infection • Catheter clotting • Definition: measured as the rate of thrombolytic agent use required to maintain adequate blood flow
Notes	• Funding: "This study was entirely funded by Satellite Healthcare, the study sponsor. Dr Moran, Ms Khababa, Ms Sun, Ms Doss, and Dr Schiller were employees of Satellite Healthcare at the time the study was conducted."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using central randomisation system, 1:1 with participants assigned within centres in blocks of 2 and 4
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients were blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	No
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Low risk	Funding undertaken by healthcare provider

Mozafar 2013

Methods	• Study design: parallel RCT • Study duration: June 2009 to June 2010 • Duration of follow-up: not reported
Participants	• Country: Iran • Setting: single centre • Patients with ESKD receiving intermittent haemodialysis via perm-cath • Number: treatment group (90); control group (90) • Mean age ± SD (years): treatment group (60 ± 1); control group (6 ± 1.3) • Sex (M/F): treatment group (55/35); control group (53/37) • Proportion with diabetes: treatment group (77.8%); control group (75.6%)

Mozafar 2013 *(Continued)*

	• Exclusion criteria: poor catheter flow immediately following perm-cath insertion during dialysis; absolute contraindication for aspirin
Interventions	Treatment group • Aspirin 80 mg/d on the first day following perm-cath insertion treatment Control group • Placebo
Outcomes	• Catheter malfunction: perm-cath survival • Aspirin induced complications such as GI bleed
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Bleeding was reported
Other bias	Unclear risk	Insufficient information to permit judgement

Nori 2006

Methods	• Study design: parallel, open-label RCT • Study duration: 4 October 2003 to 30 April 2004 • Duration of follow-up: unclear
Participants	• Country: USA • Setting: multicentre (3) • Adult HD patients with either tunnelled or non-tunnelled (only if placed in the internal jugular vein) catheters as their primary vascular access • Number: treatment group1 (20); treatment group 2 (21); control group (20) • Mean age ± SE (years): treatment group 1 (58 ± 3); treatment group 2 (58 ± 3); control group (59 ± 4)

Nori 2006 *(Continued)*

- Sex (M/F): treatment group 1 (11/9); treatment group 2 (13/8); control group (10/10)
- Proportion with diabetes: treatment group 1 (70%); treatment group 2 (62%); control group (60%)
- Exclusion criteria:< 18 years or required a surrogate decision maker; antibiotic treatment within 2 weeks before the date of enrolment; catheters with blood flow rates < 300 mL/min, or required frequent thrombolytic solution dwells in the catheter lumen for malfunction; admitted to an outside hospital for any illness or required thrombolytics for catheter thromboses on more than 3 occasions

Interventions	Treatment group 1 • Antibiotic lock solution of gentamicin/citrate (4 mg/mL and 3.13%, respectively, freshly prepared solutions stored for 7 days) Treatment group 2 • Minocycline/EDTA (3 mg/mL and 30 mg/mL, respectively) Control group • UFH: 5000 U/mL
Outcomes	• Catheter-related bacteraemia: occurrence of symptoms consistent with bacteraemia together with positive blood culture results in the absence of another obvious source of infection • Thrombosis: inability to use the catheter at a blood flow of ≥ 200 mL/min that did not respond to repositioning of the catheter or intraluminal thrombolytic agents)
Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The orange color of the minocycline solution precluded blinding of either patients or medical staff without masking the solutions."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Low risk	No funding received; no other potential sources of bias observed

Pervez 2002

Methods	• Study design: parallel RCT • Study duration: January 1999 to April 2000 • Duration of follow-up: 12 months
Participants	• Country: USA • Setting: single centre • Adult HD patients dialysing with double lumen TCC • Number: treatment group (14): control group 1 (19): control group 2 (22) • Mean age ± SD (years): treatment group (53.7 ± 4.0); control group 1(47.6 ±3.2); control group 2 (47.6 ±3.3) • Sex (males): treatment group (71%); control group 1 (42%); control group 2 (45%) • Proportion with diabetes: treatment group (57%); control group 1 (31%); control group 2 (32%) • Exclusion criteria: not reported
Interventions	Treatment group • Antibiotic tricitrasol: trisodium citrate 46.7% (Cytosol laboratories, MA, USA), gentamicin (40 mg/mL, Fujisawa, IL, USA) and normal saline in a ratio of 1:5:5, with final concentration of TSC of 4.6% Control group 1 • UFH: 1000 U/mL Control group 2 • Heparin lock and sterile bag
Outcomes	• Catheter-related bacteraemia: presence of fever or chills in the absence of an alternate source of infection • Catheter thrombosis: inability to use the catheter at a blood flow ≥ 200 mL/min that did not respond to repositioning of the catheter or intraluminal thrombolytic agents
Notes	• Funding: "This study was supported by Dialysis Clinic Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated number list
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported

Pervez 2002 *(Continued)*

Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Low risk	Funding provided by healthcare provider

Power 2009

Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Duration of follow-up: 6 months
Participants	• Country: UK • Setting: single centre • All patients who had been on dialysis therapy for longer than 90 days with tunnelled CVC • Number: treatment group (132): control group (100) • Mean age ± SD (years): treatment group (63 ± 14); control group (62 ± 13) • Sex (M/F): treatment group (73/59); control group (59/41) • Proportion with diabetes: treatment group (42%); control group (44%) • Exclusion criteria: patients with a bleeding diathesis, an intervention, or pathological state within 3 months of entry that would heighten the risk of bleeding and those with hypocalcaemia were excluded from the study
Interventions	Treatment group • 46.7% sodium citrate Control group • UFH: 5000 U/mL
Outcomes	• catheter-related bacteraemia: dialysis patients with pyrexia, defined as a tympanic temperature of 38°C or greater with or without a systemic inflammatory response were investigated for a catheter-related source of infection by means of exit-site swabs and multiple blood cultures before starting antibiotic therapy • Exit–site infection: exit-site swabs were used if there were exudates or crust, redness, or induration at the exit site • Tunnelled infection: defined as pain, redness, or induration along the subcutaneous course of the catheter with or without exudates at the exit site • Catheter thrombosis: defined as the use of urokinase lock and infusion; suboptimal blood flow < 250 mL/min and/or decreasing dialysis adequacy was used as a marker for TC dysfunction • New catheter insertion • Catheter-related admission • Blood transfusions, parenteral iron, and erythropoietin requirements. • Bleeding complications • Adverse events
Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Using single random-number allocation. Systematic error was produced by-having uneven numbers in 2 groups

Power 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT reported
Selective reporting (reporting bias)	Low risk	Bleeding reported
Other bias	Low risk	No funding received; no other potential sources of bias observed

PreCLOT Study 2006

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 180 days
Participants	• Country: Canada • Setting: multicentre (11) • Adults undergoing HD in whom a tunnelled catheter had been newly inserted into the upper central venous system were eligible to be included in the study if they were being treated with HD 3 times a week and were expected to continue undergoing HD with the use of a CVC for 6 months; patients with known catheter-related bacteraemia could be eligible for the study once the infection had been treated and the patient had not received antibiotics for a period covering three HD sessions • Number: treatment group (110): control group (115) • Mean age ± SD (years): treatment group (61.6 ± 16.6); control group (64.8 ± 15.2) • Sex (males): treatment group (64.5%); control group (57.4%) • Proportion with diabetes: treatment group (54.5%); control group (55.7%) • Exclusion criteria: long-term receipt of systemic anticoagulant therapy; CVC inserted by means of guidewire exchange; current use of antibiotics for catheter-related bacteraemia; major haemorrhage or intracranial bleeding in the previous 4 weeks; intracranial or intraspinal neoplasm; pregnancy or breast-feeding; pericarditis
Interventions	Treatment group • rt-PA (1 mg in each lumen) once a week, at the midweek session, with UFH (5000 U/mL, full luminal volume) used as a locking solution for the other two dialysis sessions that week The rt-PA was administered in each lumen initially (1 mg/mL), with saline added to fill the lock to the full luminal volume Control group • UFH: 5000 U/mL (full luminal volume) after each dialysis session
Outcomes	• Catheter malfunctions (defined as the first occurrence of any of the following, after attempts to re-establish patency had been undertaken: peak blood flow ≤ 200 mL/min for 30 minutes during a dialysis

PreCLOT Study 2006 *(Continued)*

	treatment, mean blood flow ≤ 250 mL/min during two consecutive dialysis treatments, or inability to initiate dialysis owing to inadequate blood flow) • catheter-related bacteraemia (defined according to published criteria,16, 20 with both "definite" and "probable" infections included in the outcome) • Bleeding complications (classified as fatal bleeding, major bleeding (bleeding at a critical site or overt bleeding with a fall in the Hb level ≥ 20 g/L or requiring transfusion ≥ 2 units of packed red cells), clinically important non major bleeding (overt bleeding requiring admission to the hospital or a visit to a medical facility or overt bleeding leading to an intervention such as suturing), or minor bleeding (all other episodes of bleeding) • Adverse events
Notes	• Funding: "Hoffmann–La Roche funded the trial. The funding body had no role in the design or conduct of the study, in any aspect of data management or analysis, in the reporting of the study results, in the writing of the manuscript, or in the decision to submit the manuscript for publication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generalised list of random numbers with use of a permuted block design stratified according to centre and catheter status
Allocation concealment (selection bias)	Low risk	"The pharmacy departments at each study site will receive the randomization number and treatment allocation via e-mail, and will prepare and dispense the drug accordingly"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study drug (rT-PA or heparin) was prepared and dispensed by the pharmacy in such a way that concealment of the treatment assignments was ensured"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...blinding of patients, health care providers, and all study staff and outcome assessors"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT not reported
Selective reporting (reporting bias)	Low risk	Bleeding reported
Other bias	Low risk	Funder had no role in reporting of study results

Solomon 2010

Methods	• Study design: parallel RCT • Study duration: November 2006 and May 2008 • Duration of follow-up: not reported
Participants	• Country: UK • Setting: multicentre (13) • Adult patients aged 18 years receiving tunnelled intravascular catheters for HD and able to give informed consent • Number: treatment group (53): control group (54)

Solomon 2010 *(Continued)*

- Mean age ± SD (years): treatment group (59.8 ± 14.7); control group (56.7 ± 17.4)
- Sex (males): treatment group (41.3%); control group (75.9%)
- Proportion with DKD: treatment group (13.2%); control group (9.3%)
- Exclusion criteria: not reported

Interventions	Treatment group • Taurolidine-citrate (Taurolock): 1.35% taurolidine and 4% citrate (Tauropharm AG, www.tauropharm.de) at catheter insertion and after every dialysis treatment until a study end point Control group • UFH: 5000 U/mL (porcine heparin sodium (European Pharmacopoeia)) with 1% benzylic acid as preservative (B. Braun AG, www.bbraun.com)) at catheter insertion and after every dialysis treatment until a study end point
Outcomes	• Time to first use of thrombolytic therapy: blood pump speed < 250 mL/min or the use of tissue plasminogen activator • Time to first bacteraemia episode from any cause; not specific for catheter-related bacteraemia • Exit–site infection: diagnosed on the basis of discharge, erythema, swelling, tenderness, and isolation of a pathogenic organism from a swab) • Total number of bacteraemia and gram-positive and gram-negative infections
Notes	• Funding: "This work was supported in part by a grant from the Preston branch of the North West Kidney Research Association and a grant from the Liverpool Regional Dialysis Unit Fund."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent pharmacists undertook randomisation on a 1:1 basis using computer-generated randomised permuted blocks of 10 patients, which were stratified among the 3 main centres
Allocation concealment (selection bias)	Low risk	Yes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All study personnel and participants were blinded to treatment assignment throughout the study until the database was complete"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All study personnel and participants were blinded to treatment assignment throughout the study until the database was complete"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Low risk	Funding provided by Preston branch of the North West Kidney Research Association and a grant from the Liverpool Regional Dialysis Unit Fund

Traynor 2001

Methods	• Study design: parallel RCT • Study duration: patients enrolled over a 2 year period • Duration of follow-up: not reported
Participants	• Country: UK • Setting: single centre • Adult HD patients dialysing with tunnelled or non-tunnelled catheters • Number: treatment group (10): control group (8) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Warfarin: 1 mg daily Control group • No treatment
Outcomes	• Catheter failure: inability to provide adequate blood flow rate for HD (>250mL/min) despite • Death • Transplantation or withdrawal of warfarin
Notes	• Short report only • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Catheter malfunction was not clearly stated and no catheter-related bacteraemia was reported; ITT not reported
Selective reporting (reporting bias)	High risk	Bleeding not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Wilkieson 2011

Methods	• Study design: parallel RCT • Study duration: January 1999 to January 2007 • Duration of follow-up: patients assigned to warfarin were followed for median 4.8 months, IQR 8.8
Participants	• Country: Canada • Setting: multicentre (3) • Adult HD dependent or to start HD, with double-lumen tunnelled or untunnelled CVC, subclavian or jugular position, within 72 hours (up to 2 weeks for well-functioning catheters at the discretion of the site investigator) of initial placement or of guidewire exchange • Number: treatment group (87): control group (87) • Mean age ± SD (years): treatment group (62.4 ± 14.3); control group (60.7 ± 16.7) • Sex (males): treatment group (55.2%); control group (57.5%) • Proportion with diabetes: treatment group (55.2%); control group (40.0%) • Exclusion criteria: major bleeding in the previous 3 months (bleeding requiring transfusion, bleeding in a critical site [retroperitoneal or intracranial], bleeding associated with hypovolaemia or requiring admission to hospital, and bleeding resulting in greater than a 20 g/L drop in haemoglobin concentration); persistent thrombocytopenia (platelet count < 50 x 10^9/L) or coagulopathy (e.g. known severe liver disease, haemophilia, or baseline INR 1.5); active peptic ulcer disease; need for further invasive investigation or intervention; warfarin anticoagulation for another indication; allergy or intolerance to warfarin; pregnancy and women of child-bearing age not using (or prepared to use) a form of effective contraception; inability to take oral medications; catheters with anticipated duration of use less than 2 weeks; previous participation in this study; known aortic aneurysms (6 cm); lack of agreement of clinical nephrologist; and inability to give or lack of informed consent
Interventions	Treatment group • Low density monitored dose of warfarin with target INR 1.5 to 1.9 Control group • Placebo Other information • Heparin was used for catheter locking according to local institutional practice at concentrations between 1000 and 10,000 U/mL
Outcomes	• Time to first mechanical-catheter failure: inability to establish a circuit or blood flow less than 200 mL/min) not caused by kinking or extrusion • Time to first guidewire exchange or catheter removal for mechanical failure • Time to catheter removal for mechanical failure • Time to catheter removal for any cause • Time to catheter removal foe mechanical failure • Use of thrombolytic agents or other interventions to restore catheter patency • Episodes of bacteraemia: positive blood culture • Exit-site infection (clinically identified and treated exit-site infection) • Major and minor bleeding * Major bleeding: bleeding requiring transfusion, bleeding in a critical site (retroperitoneal or intracranial), bleeding associated with hypovolaemia or requiring admission to hospital, and bleeding resulting in greater than a 20 g/L drop in haemoglobin concentration • Dialysis flow rates • Urea reduction ratio
Notes	• Funding: "The study was funded by the Canadian Institutes of Health Research."

Wilkieson 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in a 1:1 ratio in blocks of 4
Allocation concealment (selection bias)	Low risk	A central research pharmacy ensured concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants, clinical staff, outcome assessors, investigators, research coordinators, and data managers were blinded throughout"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants, clinical staff, outcome assessors, investigators, research coordinators, and data managers were blinded throughout"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data; ITT reported
Selective reporting (reporting bias)	Low risk	Bleeding reported
Other bias	Low risk	Funded by the Canadian Institutes of Health Research

BP - blood pressure; CFU - colony-forming units; CKD - chronic kidney disease; CRBSI - catheter-related blood stream infection; CRI - catheter-related infection; CVC - central venous catheter; DBP - diastolic BP; ESKD - end-stage kidney disease; GI - gastrointestinal; HD - haemodialysis; INR - international normalized ratio; IQR - interquartile range; ITT - intention-to-treat; IV - intravenous; LMWH - low molecular weight heparin; M/F - male/female; NSAID - nonsteroidal anti-inflammatory drug; rt-PA - recombinant tissue plasminogen; SBP - systolic blood pressure; SD - standard deviation; SE - standard error; TCC - tunnelled cuffed catheter; UFH - unfractionated heparin

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

Study	Reason for exclusion
Aslam 2008	Not RCT
Betjes 2006	Not relevant population
Caruana 1991	Not relevant population / not using CVC for dialysis
Gittins 2007	Paediatric patients
Hu 2011	Included patients with AKI
Huraib 1994	Arteriovenous fistulas were involved
Lange 2007	Included patients with AKI
Meeus 2005	Cross-over study with no extractable data
Oguzhan 2012	Included patients with AKI

Study	Reason for exclusion
Oran 2008	Wrong intervention
Ota 1996	Not RCT
Plamondon 2005	Included patients with AKI
Saxena 2012	Wrong intervention
Schenk 2000	Cross-over study with no extractable data
Thomson 2011	Included patients with AKI
Weijmer 2005	Included patients with AKI

AKI - acute kidney injury; CVC - central venous catheter; RCT - randomised controlled trial

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

Bonkain 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Clement 1998

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract-only publication; not enough data to analyse

Freudiger 1990

Methods	
Participants	
Interventions	

Freudiger 1990 *(Continued)*

Outcomes	
Notes	Abstract-only publication; not enough data to analyse

Geron 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract-only publication; not enough data to analyse

Hemmelder 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract-only publication; not enough data to analyse

ISRCTN27307877

Methods	RCT
Participants	Any patient who require a new tunnelled catheter for HD. Patients fall into three groups: 1. Patients who present to the Kidney unit of the UHNS with kidney failure needing maintenance HD 2. Patients who have to switch from PD to HD because of problems with their peritoneal dialysis 3. Existing HD patients who need tunnelled catheters because their arteriovenous fistulas or tunnelled catheters have failed The decision to place a tunnelled dialysis catheter is made by one of the renal consultants entirely on the basis of clinical need. Patients will be invited to take part prior to insertion of the tunnelled dialysis catheter. Randomisation will be by sealed envelopes. The only differences in dialysis care that patients will have is the locking agent, otherwise patients will have the same treatment whether they are dialysing in our main renal unit in Stoke or our two satellite units at Stafford and Leighton. They will be followed up and all dialysis related issues will be documented as per current practice.
Interventions	Trisodium citrate versus heparin for locking tunnelled haemodialysis catheters.
Outcomes	Primary outcomes: Catheter blood flow of < 250 mL/min and/or venous pressure > 260 mm Hg, persisting for 1 hour/session, in 2 consecutive sessions.

ISRCTN27307877 *(Continued)*

Notes	No data published as at 6/1/2016

Ray 1999

Methods	
Participants	
Interventions	
Outcomes	
Notes	To be assessed in a future update

Shi 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract-only publication; not enough data to analyse

Sishir 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract-only publication

HD - haemodialysis; PD - peritoneal dialysis; RCT - randomised controlled trial

DATA AND ANALYSES

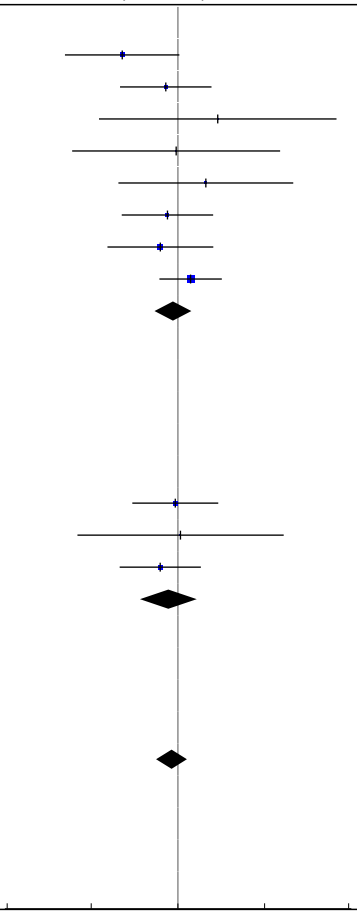
Comparison 1. Secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	11	1828	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.56, 1.27]
1.1 Alternative anticoagulant locking solutions	8	1425	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.54, 1.43]
1.2 Warfarin	3	403	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.65]
2 Subgroup analysis of all-cause mortality in alternative anticoagulant locking solutions	8	1425	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.54, 1.43]
2.1 Citrate	6	1151	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.52, 1.51]
2.2 rt-PA	1	225	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.15, 2.56]
2.3 Ethanol	1	49	Risk Ratio (M-H, Random, 95% CI)	2.88 [0.12, 67.53]
3 Total bleeding events	7	849	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.61, 1.25]
3.1 Alternative anticoagulant locking solutions	3	335	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.47, 1.01]
3.2 Systemic agents	3	439	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.93, 1.83]
3.3 Low/no dose heparin	1	75	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.21, 0.96]
4 Subgroup analysis of total bleeding events in alternative anticoagulant locking solutions	7	1074	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.65, 1.19]
4.1 Citrates	2	286	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.47, 1.02]
4.2 Ethanol	1	49	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.50]
4.3 Warfarin	2	259	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.86, 2.39]
4.4 Aspirin	1	180	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.77, 1.90]
4.5 rt-PA	1	225	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.43, 1.68]

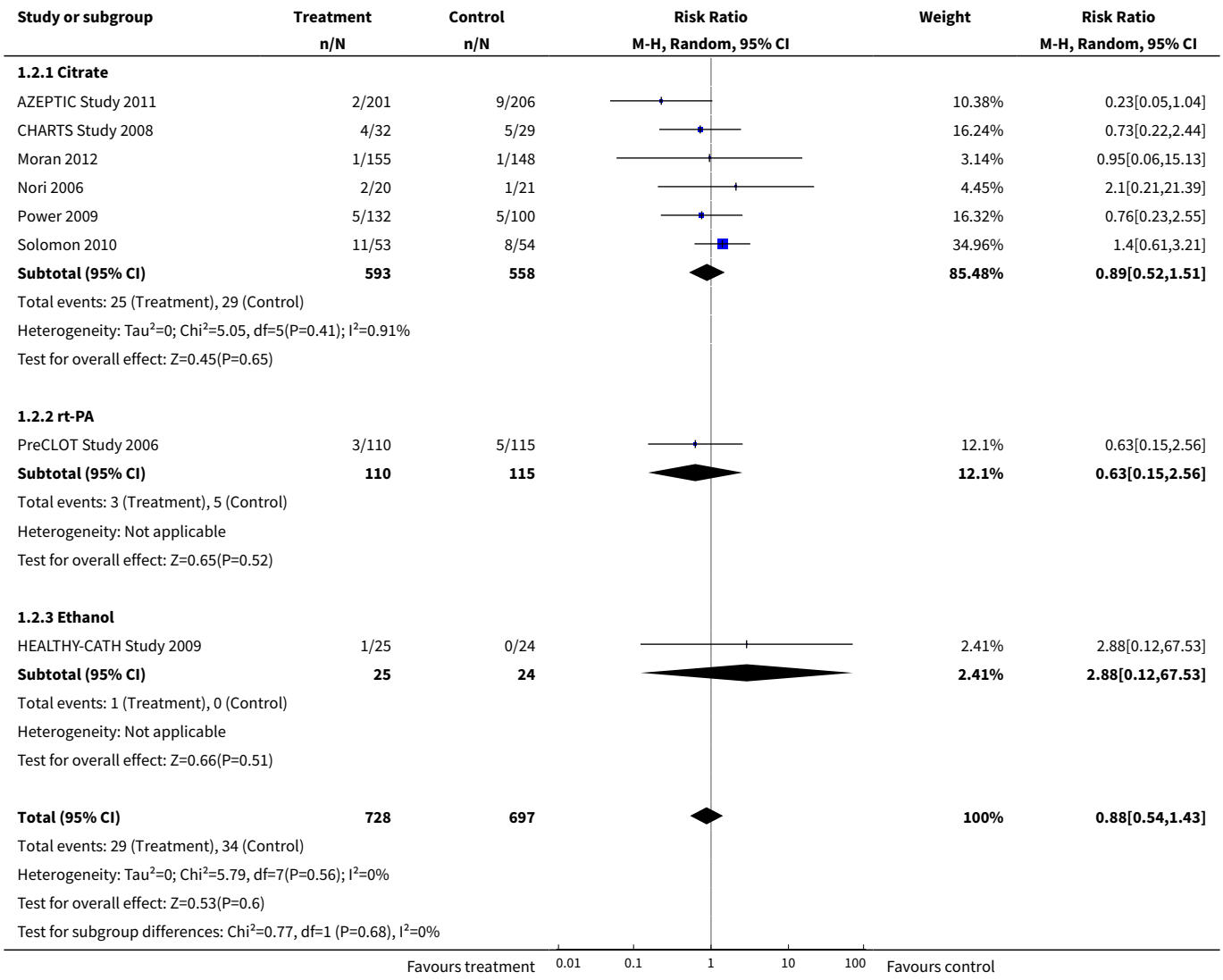
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.6 Low/no dose heparin	1	75	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.21, 0.96]
5 Incidence of major bleeding	2	286	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.32, 1.04]
6 Incidence of minor bleeding	2	286	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.44, 1.50]

Analysis 1.1. Comparison 1 Secondary outcomes, Outcome 1 All-cause mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Alternative anticoagulant locking solutions					
AZEPTIC Study 2011	2/201	9/206		7.29%	0.23[0.05,1.04]
CHARTS Study 2008	4/32	5/29		11.41%	0.73[0.22,2.44]
HEALTHY-CATH Study 2009	1/25	0/24		1.69%	2.88[0.12,67.53]
Moran 2012	1/155	1/148		2.21%	0.95[0.06,15.13]
Nori 2006	2/20	1/21		3.13%	2.1[0.21,21.39]
Power 2009	5/132	5/100		11.47%	0.76[0.23,2.55]
PreCLOT Study 2006	3/110	5/115		8.51%	0.63[0.15,2.56]
Solomon 2010	11/53	8/54		24.57%	1.4[0.61,3.21]
Subtotal (95% CI)	**728**	**697**		**70.28%**	**0.88[0.54,1.43]**
Total events: 29 (Treatment), 34 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.79, df=7(P=0.56); I^2=0%					
Test for overall effect: Z=0.53(P=0.6)					
1.1.2 Warfarin					
Coli 2006	6/81	5/63		12.96%	0.93[0.3,2.92]
Mokrzycki 2001	1/41	1/44		2.25%	1.07[0.07,16.6]
Wilkieson 2011	5/87	8/87		14.52%	0.63[0.21,1.84]
Subtotal (95% CI)	**209**	**194**		**29.72%**	**0.78[0.37,1.65]**
Total events: 12 (Treatment), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=2(P=0.86); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**937**	**891**		**100%**	**0.84[0.56,1.27]**
Total events: 41 (Treatment), 48 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.15, df=10(P=0.8); I^2=0%					
Test for overall effect: Z=0.81(P=0.42)					
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.79), I^2=0%					

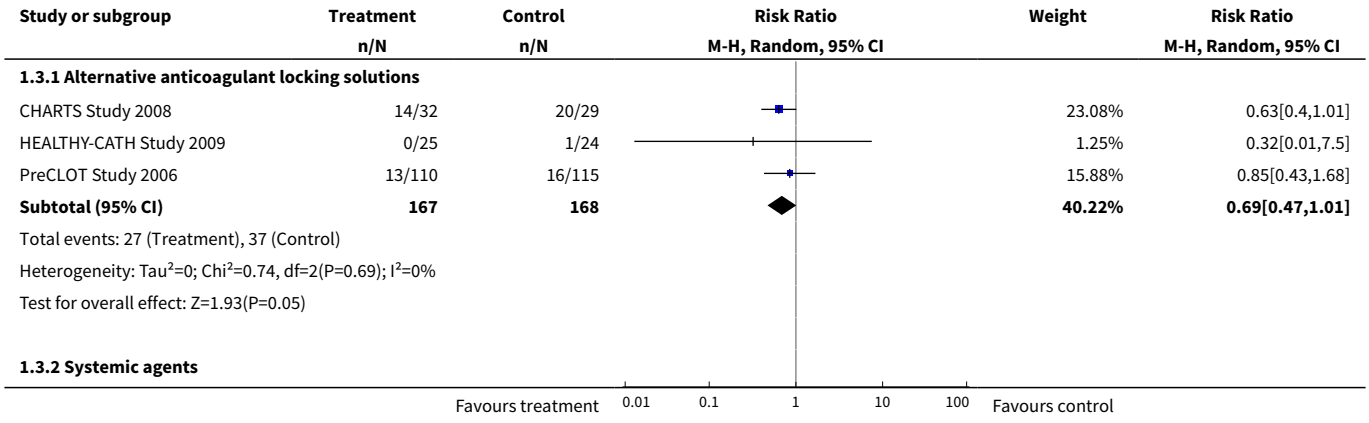


Analysis 1.2. Comparison 1 Secondary outcomes, Outcome 2 Subgroup analysis of all-cause mortality in alternative anticoagulant locking solutions.

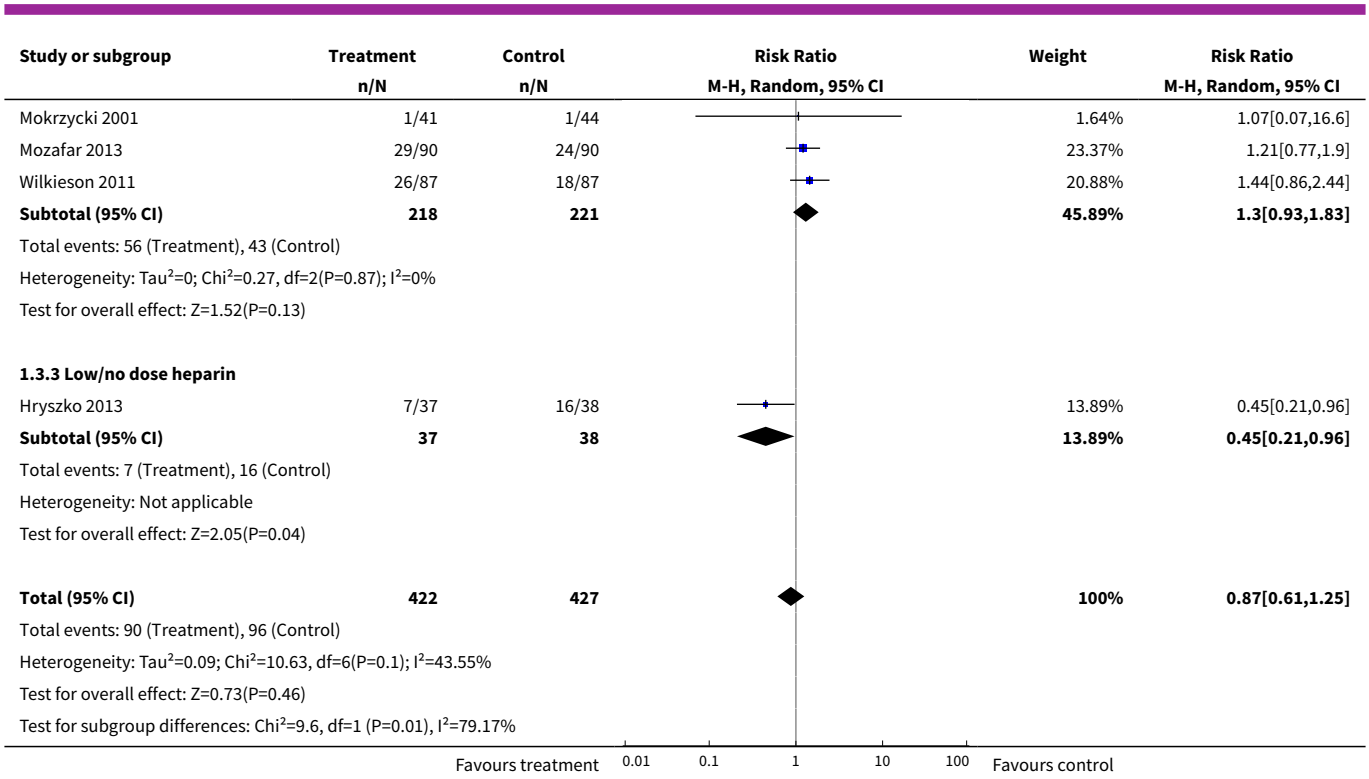


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Citrate					
AZEPTIC Study 2011	2/201	9/206		10.38%	0.23[0.05,1.04]
CHARTS Study 2008	4/32	5/29		16.24%	0.73[0.22,2.44]
Moran 2012	1/155	1/148		3.14%	0.95[0.06,15.13]
Nori 2006	2/20	1/21		4.45%	2.1[0.21,21.39]
Power 2009	5/132	5/100		16.32%	0.76[0.23,2.55]
Solomon 2010	11/53	8/54		34.96%	1.4[0.61,3.21]
Subtotal (95% CI)	**593**	**558**		**85.48%**	**0.89[0.52,1.51]**
Total events: 25 (Treatment), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.05, df=5(P=0.41); I^2=0.91%					
Test for overall effect: Z=0.45(P=0.65)					
1.2.2 rt-PA					
PreCLOT Study 2006	3/110	5/115		12.1%	0.63[0.15,2.56]
Subtotal (95% CI)	**110**	**115**		**12.1%**	**0.63[0.15,2.56]**
Total events: 3 (Treatment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					
1.2.3 Ethanol					
HEALTHY-CATH Study 2009	1/25	0/24		2.41%	2.88[0.12,67.53]
Subtotal (95% CI)	**25**	**24**		**2.41%**	**2.88[0.12,67.53]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**728**	**697**		**100%**	**0.88[0.54,1.43]**
Total events: 29 (Treatment), 34 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.79, df=7(P=0.56); I^2=0%					
Test for overall effect: Z=0.53(P=0.6)					
Test for subgroup differences: Chi^2=0.77, df=1 (P=0.68), I^2=0%					

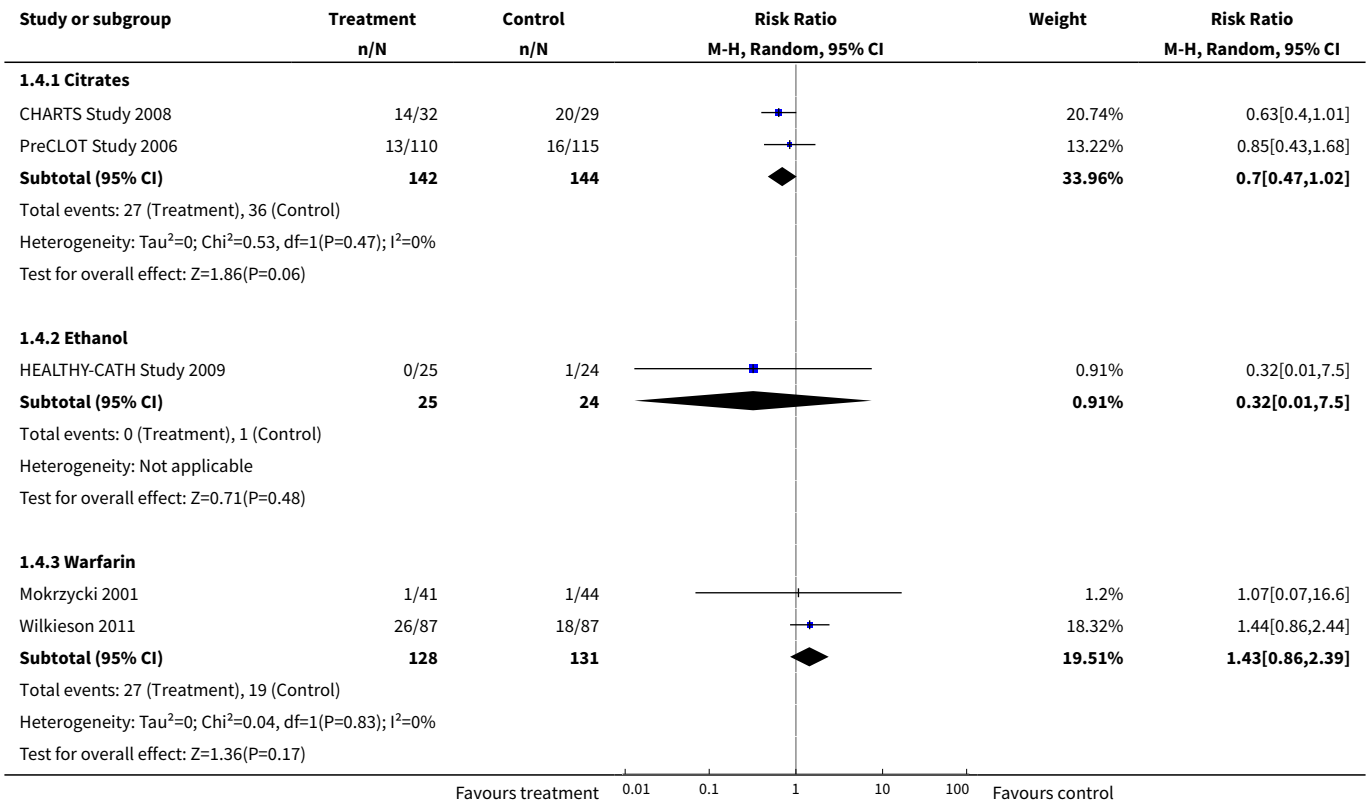
Analysis 1.3. Comparison 1 Secondary outcomes, Outcome 3 Total bleeding events.

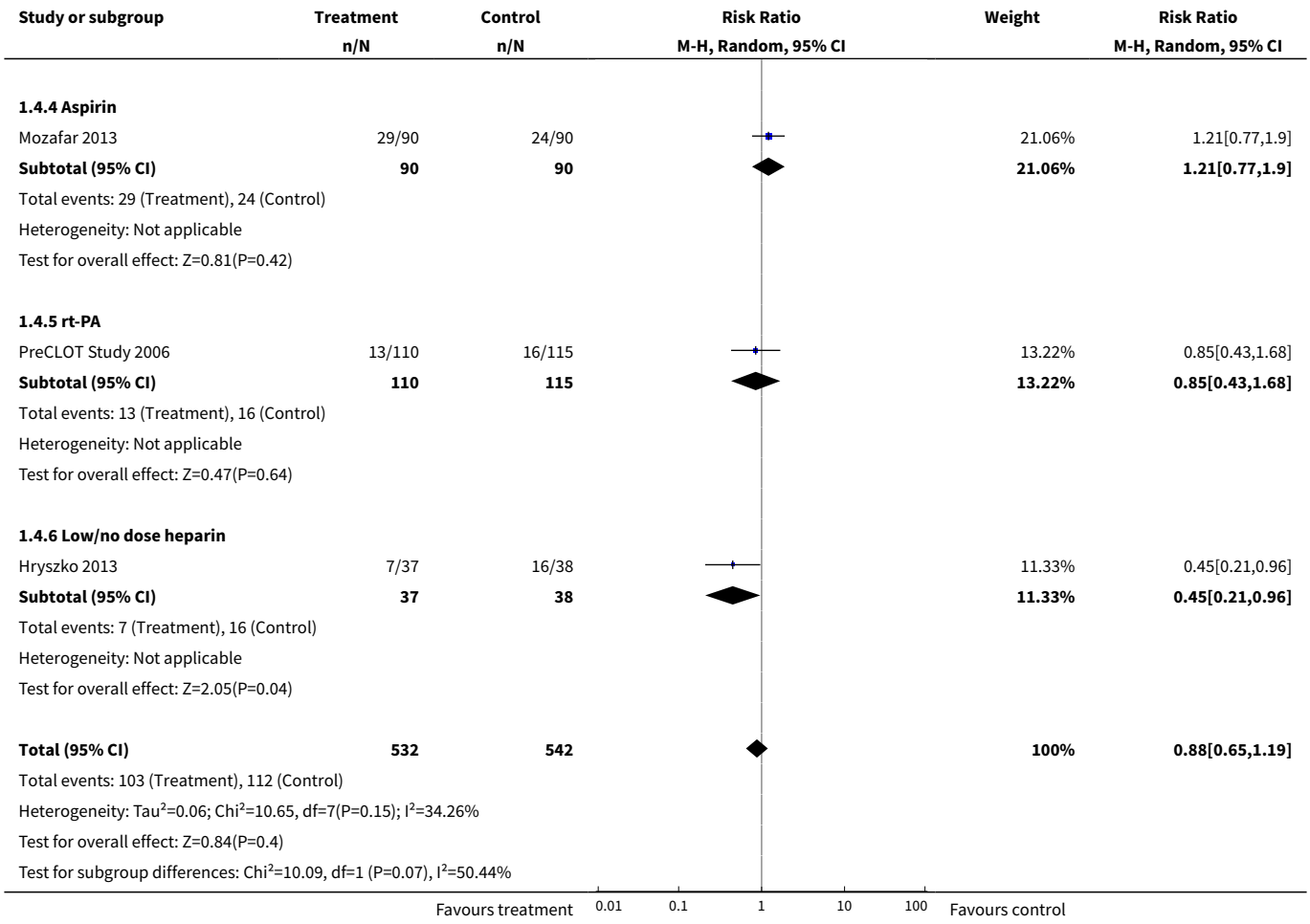


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Alternative anticoagulant locking solutions					
CHARTS Study 2008	14/32	20/29		23.08%	0.63[0.4,1.01]
HEALTHY-CATH Study 2009	0/25	1/24		1.25%	0.32[0.01,7.5]
PreCLOT Study 2006	13/110	16/115		15.88%	0.85[0.43,1.68]
Subtotal (95% CI)	**167**	**168**		**40.22%**	**0.69[0.47,1.01]**
Total events: 27 (Treatment), 37 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.74, df=2(P=0.69); I^2=0%					
Test for overall effect: Z=1.93(P=0.05)					
1.3.2 Systemic agents					

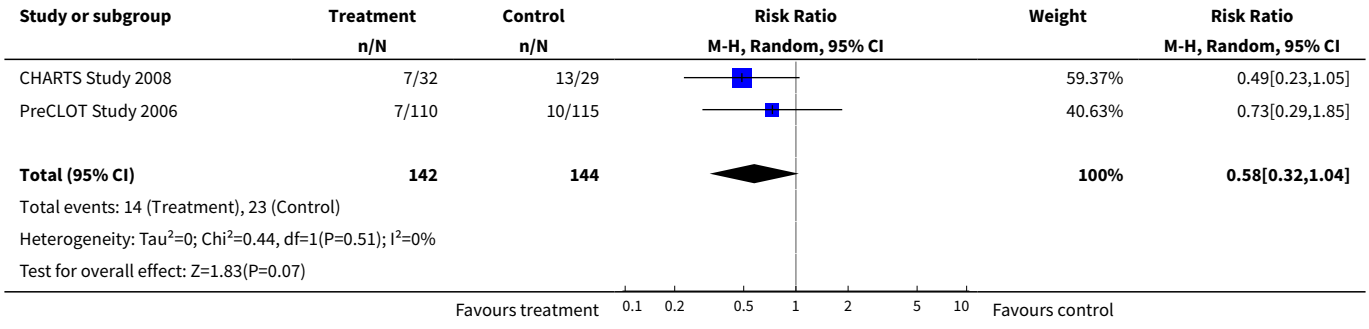


Analysis 1.4. Comparison 1 Secondary outcomes, Outcome 4 Subgroup analysis of total bleeding events in alternative anticoagulant locking solutions.

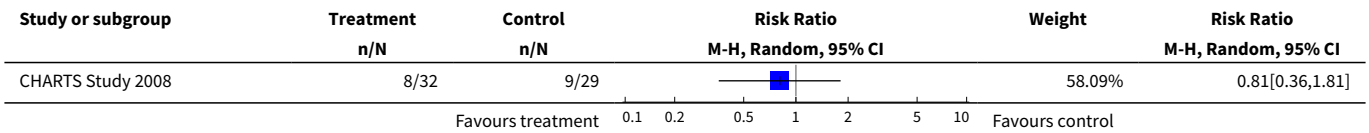


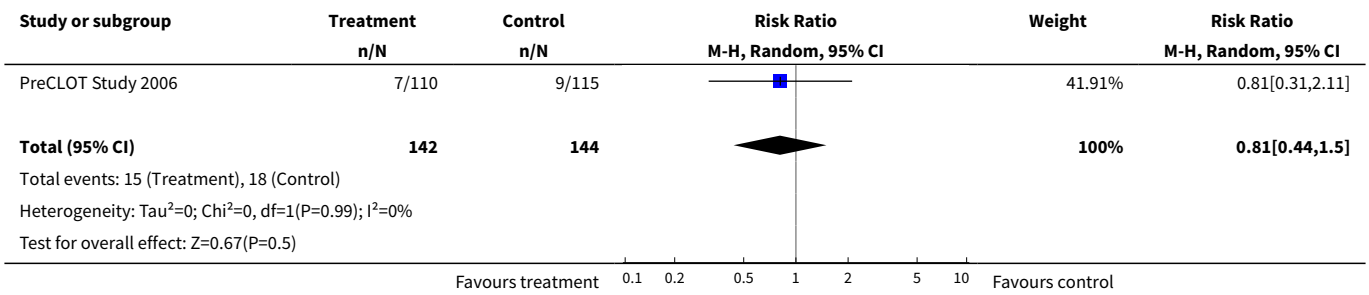


Analysis 1.5. Comparison 1 Secondary outcomes, Outcome 5 Incidence of major bleeding.



Analysis 1.6. Comparison 1 Secondary outcomes, Outcome 6 Incidence of minor bleeding.





ADDITIONAL TABLES

Table 1. Catheter malfunction events reported by study authors

Study Definition of malfunction	Overall malfunction	Sub-classification of catheter malfunction events			
		Loss due to malfunction	Catheter duration	Interventions to maintain catheter function	Venous occlusion
Alternative anticoagulant locking solutions					
Campos 2011 BFR < 200 mL/min for non-tunnelled and 250 mL/min for tunnelled	Int: 20/92 Cont: 14/95	Int: 20/92 Cont: 14/95	Not reported	Not reported	Not reported
CHARTS Study 2008 BFR < 250 mL/min	Int: 13/32 Cont: 12/39	Int: 25% Cont: 17.2%	Int: 55 days Cont: 90 days	Not reported	Not reported
Dogra 2002 BFR < 200 mL/min	Int: 13/42 Cont: 16/37	Not reported	Not reported	Not reported	Not reported
Filiopoulos 2011 BFR < 250 mL/min	Int: 9/59 Cont: 11/60	Not reported	Not reported	Not reported	Not reported
HEALTHY-CATH Study 2009 Catheter removal due to flow difficulties	Not reported	Not reported	Not reported	Not reported	Not reported
Hendrickx 2001 BFR < 200 mL/min	Int: 5/10 Cont: 5/9	Not reported	Not reported	Not reported	Int: 105 non-occlusive clots Cont: 44 non-occlusive clots
Pervez 2002 BFR < 250 mL/min	Int: 4/14 Cont: 6/19	Not reported	Not reported	Not reported	Not reported
PreCLOT Study 2006	Int: 18/110	Not reported	Not reported	Int: 0/110	Not reported

Table 1. Catheter malfunction events reported by study authors *(Continued)*

BFR < 200 mL/min	Cont: 36/115			Cont: 1/115	
Solomon 2010 Catheter loss due to occlusion	Int: 8/53 Cont: 3/54	Int: 8/53 Cont: 3/54	Not reported	Not reported	Int: 8/53 Cont: 3/54
Systematic anticoagulants					
Abdul-Rahman 2007 Catheter thrombosis	Int: 4/20 Cont: 9/19	Not reported	Int: 75% survival at 12 months Cont: 36.8% survival at 12 months	Not reported	Int: 4/20 Cont: 9/19
Coli 2006 BFR < 300 mL/min	Int: 10/81 Cont: 33/63	Not reported	Not reported	Not reported	Not reported
Mokrzycki 2001 BFR < 300 mL/min	Int: 8/41 Cont: 8/44	Int: 8/41 Cont: 8/44	Not reported	Not reported	Nor reported
Traynor 2001 BFR < 250 mL/min	Int: 1/10 Cont: 1/8	Not reported	Int: 188 days Cont: 356 days	Not reported	Not reported
Wilkieson 2011 BFR < 150 mL/min	Int: 8/41 Cont: 8/44	Not reported	Not reported	Not reported	Not reported
No or low dose heparin locking solution					
Hryszko 2013 Catheter thrombosis	Int: 0/37 Cont: 0/38	Not reported	Not reported	Not reported	Int: 0/37 Cont: 0/38
Kaneko 2004 Catheter thrombosis or BFR < 140 mL/min	Int: 1/26 Cont: 1/22	Not reported	Not reported	Not reported	Int: 1/26 Cont: 1/22

BFR - blood flow rate; Cont - control; Int - intervention

Table 2. Warfarin dosage and target INR in systemic anticoagulant studies

Study	Number	Intervention arm	Control arm	Background care
Abdul-Rahman 2007	58	Variable dose warfarin Target INR 1.5 to 2	Placebo	Tinzaparin 40 to 50 IU/kg
Coli 2006	144	Variable dose warfarin Target INR 1.8 to 2.5	Warfarin after catheter malfunction	Ticlopidine 250 mg/d
Mokrzycki 2001	85	Fixed dose warfarin 1 mg/d	Placebo	Heparin 5000 U/mL

Table 2. Warfarin dosage and target INR in systemic anticoagulant studies *(Continued)*

Traynor 2001	18	Fixed dose warfarin 1 mg/d	Placebo	Not reported
Wilkieson 2011	174	Variable dose warfarin Target INR 1.5 to 1.9	Placebo	Heparin 1000 to 10,000 U/mL

INR - international normalised ratio

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. (haemodialysis or hemodialysis):ti,ab,kw 2. (haemofiltration or hemofiltration):ti,ab,kw 3. (haemodiafiltration or hemodiafiltration):ti,ab,kw 4. dialysis:ti,ab,kw 5. (#1 OR #2 OR #3 OR #4) 6. catheter*:ti,ab,kw 7. (central next line*):ti,ab,kw 8. (central next venous next line*):ti,ab,kw 9. (#6 OR #7 OR #8) 10.MeSH descriptor Anticoagulants explode all trees 11.(anticoagul* or anti-coagul*):ti,ab,kw 12.heparin*:ti,ab,kw 13.warfarin*:ti,ab,kw 14.MeSH descriptor Antithrombins explode all trees 15.(tissue next plasminogen next activator*).ti,ab,kw 16.enoxaparin:ti,ab,kw 17.LMWH:ti,ab 18.dalteparin:ti,ab,kw 19.ticlopidine:ti,ab,kw 20.clopidogrel:ti,ab,kw 21.citrate*:ti,ab,kw 22.citric acid*:ti,ab,kw 23.TSC:ti,ab,kw 24.(platelet next aggregation next inhibitor*):ti,ab,kw 25.UFH:ti,ab,kw 26.hirudin:ti,ab,kw 27.(#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) 28.(#5 AND #9 AND #27)
MEDLINE	1. Renal Dialysis/ 2. exp Hemofiltration/ 3. (haemodialysis or hemodialysis).tw. 4. (haemofiltration or hemofiltration).tw. 5. (haemodiafiltration or hemodiafiltration).tw.

(Continued)

	6. dialysis.tw. 7. or/1-6 8. Catheterization/ 9. Catheterization, Central Venous/ 10.Catheters, Indwelling/ 11.catheter$.tw. 12.central line$.tw. 13.central venous line$.tw. 14.or/8-13 15.exp Anticoagulants/ 16.Citrates/ 17.exp Platelet Aggregation Inhibitors/ 18.Tissue Plasminogen Activator/ 19.(anticoagul$ or anti-coagul$).tw. 20.(antithrombo$ or anti-thrombo$).tw. 21.citrate*.tw. 22.TSC.tw. 23.platelet aggregation inhibitor$.tw. 24.tissue plasminogen activator$.tw. 25.heparin$.tw. 26.UFH.tw. 27.warfarin$.tw. 28.hirudin.tw. 29.ticlopidine.tw. 30.enoxaparin.tw. 31.clopidogrel.tw. 32.or/15-31 33.and/7,14,32
EMBASE	1. Hemodialysis/ 2. Hemofiltration/ 3. Hemodiafiltration/ 4. (hemodialysis or haemodialysis).tw. 5. (hemofiltration or haemofiltration).tw. 6. (hemodialfiltration or haemodiafiltration).tw. 7. dialysis.tw. 8. or/1-7 9. Catheterization/ 10.Central Venous Catheterization/ 11.exp Central Venous Catheter/ 12.Catheter Thrombosis/ 13.catheter$.tw. 14.central venous line$.tw. 15.central line$.tw. 16.or/9-15 17.exp Anticoagulant Agent/ 18.Anticoagulant Therapy/ 19.Tissue Plasminogen Activator/ 20.Citric Acid/ 21.Citrate Trisodium/ 22.anticoagul$.tw. 23.tissue plasminogen activator$.tw.

(Continued)

24.citrate$.tw.
25.TSC.tw.
26.heparin$.tw.
27.UFH.tw.
28.hirudin.tw.
29.warfarin$.tw.
30.enoxaparin.tw.
31.ticlopidine.tw.
32.clopidogrel.tw.
33.platelet aggregation inhibit$.tw.
34.or/17-33
35.and/8,16,34

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement

(Continued)

Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

- Ying Wang: literature search, study selection, quality appraisal, data extraction, data analysis, data display, writing the review, updating the review
- Jessica Ivany: literature search, study selection, quality appraisal, data extraction, data analysis, data display
- Meg Jardine: data analysis, quality appraisal, data display, writing the review, updating the review
- Martin Gallagher: updating the review
- Vlado Perkovic: updating the review
- Mark Woodward: data analysis and updating the review

DECLARATIONS OF INTEREST

- Martin Gallagher has received funding competitive research funding from the Royal Australasian College of Physicians, the Australian National Health and Medical Research Council and the Commonwealth Fund in the last 36 months.
- Jessica Ivany: None known
- Meg Jardine is supported by a Career Development Fellowship from the National Health and Medical Research Council of Australia and the National Heart Foundation. She has received speakers' fees from Amgen and Roche, funding for a clinical trial from Gambro and serves on Steering Committees for trials funded by Janssen. Her employer conducts clinical trials funded by Servier, Janssen, Roche and Merck. This funding is unrelated to the conduct of this review.
- Vlado Perkovic is supported by a fellowship from the Heart Foundation of Australia and a various grants from the Australian National Health and Medical Research Council. He has received speakers' fees from Roche, Servier and Astra Zeneca, funding for a clinical trial from Baxter, and serves on Steering Committees for trials funded by Johnson and Johnson, Boehringer Ingelheim, Vitae and Abbott. His employer conducts clinical trials funded by Servier, Johnson and Johnson, Roche and Merck. This funding is unrelated to the conduct of this review.
- Ying Wang: None known
- Mark Woodward has a consultancy contract with Amgen and has had consultancy contracts with Novartis and Sanofi, has received lecturing fees from Servier and has served as an expert witness for Bernstein, Litowitz, Berger and Grossmann LLP. This support is unrelated to the conduct of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Our original protocol was designed to use a conventional random-effects model for data synthesis. However, we observed a variety of methods of outcome reporting including reporting by patient numbers experiencing an event and reporting by repeated events. The random-effects model weights individual studies by the confidence interval of the relative risk. As confidence intervals decrease in inverse proportion to increasing events, the use of repeated events measures will generally result in a smaller confidence interval than the use of patient numbers. The use of a pure random-effects model would thus mean that the weighting of individual studies in the meta-analysis would be determined in part by the decision on reporting measure. This appeared to introduce an arbitrary component into the analysis. We therefore developed a modified statistical analysis in which we derived the summary estimates of relative risks in a two-step process. Firstly random effects models were constructed pooling individual studies that reported by any particular method (by patient or by repeated event rate). Secondly the relative risks derived from step one were combined using a fixed effects model weighted by trial sample size.

We have added Prof Mark Woodward as an author in recognition of his contribution to the statistical analyses, particularly in finding a solution to the issues addressed above.

INDEX TERMS

Medical Subject Headings (MeSH)

*Catheter Obstruction; *Central Venous Catheters; Anticoagulants [*administration & dosage]; Bacteremia [prevention & control]; Catheter-Related Infections [prevention & control]; Heparin [administration & dosage]; Kidney Failure, Chronic [*therapy]; Platelet Aggregation Inhibitors [*administration & dosage]; Randomized Controlled Trials as Topic; Renal Dialysis [*instrumentation]

MeSH check words

Humans