## Original Article
# Anticoagulant therapies versus heparin for the prevention of hemodialysis catheter-related complications: systematic review and meta-analysis of prospective randomized controlled trials

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**Abstract:** Locking of central venous catheters with heparin is an accepted practice to maintain catheter patency between dialysis sessions. However, this practice may cause other adverse reactions. Although many studies suggest benefits of other catheter lock solutions over heparin on these grounds, no consensus has been reached for clinical practice. A systematic review and meta-analysis was performed of randomized controlled trials (RCT) that compared antimicrobial-containing or citrate-alone catheter lock solutions with heparin alone in patients undergoing hemodialysis with central venous catheters. Medline, Cochrane Central Register of Controlled Trials from EMBASE, and PubMed were searched for articles published through June 2014. The primary outcomes were catheter-related bacteremia (CRB) and catheter malfunction (CM). The secondary outcomes were bleeding, exit-site infection (ESI), clinical sepsis, and all-cause mortality. Seventeen RCTs met the inclusion criteria. The meta-analysis showed that antimicrobial-containing and citrate-alone lock solutions were superior to heparin for preventing CRB (both $P < 0.01$). Although antimicrobial-containing lock solutions significantly affected clinical sepsis ($P < 0.01$), they did not affect ESI, bleeding, or all-cause mortality. Incidence of CM episodes was lower in patients receiving antibiotics + heparin and gentamicin + citrate (both $P < 0.05$), while other antimicrobial-containing and citrate-alone lock solutions showed no difference. Only citrate-alone lock solutions significantly decreased bleeding and ESI episodes (both $P < 0.05$). Compared with heparin, antimicrobial-containing lock solutions more effectively prevent CRB and clinical sepsis. Antibiotics + heparin and gentamicin + citrate solutions showing better prevention of CM. Citrate-alone lock solutions result in fewer CRB, bleeding and ESI episodes.

**Keywords:** Catheter lock solutions, hemodialysis, heparin, meta-analysis

## Introduction

The use of central venous catheters (CVCs) for vascular access is becoming increasingly common in patients without permanent vascular access [1]. Unfortunately, 25-50% of CVCs fail within the first year of insertion [2]. Moreover, CVCs are associated with increased levels of antibiotic exposure, longer hospital stays, higher health care costs, and higher mortality rates [3]. The main causes of these increased risks are catheter malfunction (CM) and catheter-related infection, especially catheter-related bloodstream infection (CRBI). Therefore, an

accepted practice is to lock the CVC lumen with an anticoagulant solution to prevent thrombosis, maintain catheter patency, and avoid infections between dialysis sessions. A variety of anticoagulants are available in China. A significantly lower risk of catheter occlusion, CRBI, and catheter colonization has been observed in heparin bonded-catheters compared to non-heparin-bonded catheters because of the efficacy, favorable side effect profile, and cost-effectiveness of diluted heparin solution; this solution has thus been routinely used as a locking solution for many years [4, 5]. In recent years, however, many studies have found that

diluted heparin increases the danger of systemic anticoagulation if it inadvertently overfills the lumen [1]. Therefore, the need for alternative anticoagulant locking solutions is imperative. A review of the literature shows that the current guidelines propose the use of antithrombotic locking solutions to prevent CM in patients undergoing hemodialysis; however, it is difficult to identify specific agents or concentrations because of the lack of definitive evidence regarding individual regimens.

Newer approaches including antimicrobial-containing catheter lock solutions and citrate-alone catheter lock solutions have been investigated to seek improvements in catheter patency and reduce adverse events. For example, citrate lock solutions reduce the incidence of heparin-associated bleeding complications [6] and catheter-related bacteremia (CRB) rates (1.1 *vs* 4.1 per 1000 catheter-days) [7]. Antibiotic catheter lock solutions reduce CRBI and catheter removal rates in patients undergoing hemodialysis [8]. Hemmelgarn *et al*. [9] compared the use of once-weekly recombinant tissue plasminogen activator (rt-PA) with the use of heparin three times weekly as locking solutions and found that once-weekly rt-PA significantly reduced the incidence of CM and CRBI. However, these findings have not been confirmed in similar studies. Several meta-analyses on anticoagulant locking solutions versus heparin have been performed in recent years. Zhao et al. [1] suggested that antimicrobial-containing citrate locks are more effective than heparin locks in the prevention of CRBI, while citrate alone fails to show a similar advantage. However, no difference in the efficacy of maintaining catheter patency between citrate and heparin locks was found. In fact, no method that can simultaneously prevent CRBI and CM has been identified. Therefore, we performed a meta-analysis focused on lock solutions containing anticoagulants (heparin, citrate) with or without antimicrobials for prevention of CM, CRB, bleeding, all-cause mortality, exit-site infection (ESI), and clinical sepsis in patients undergoing maintenance hemodialysis with CVCs.

## Methods

### Study selection

Two reviewers executed a search of Medline, the Cochrane Central Register of Controlled Trials from EMBASE, and PubMed. The last search was conducted in June 2014. All spellings of hemodialysis, anticoagulants, and catheterization in the Medical Subject Headings (MeSH) were used alone and in combination. No language or date restrictions were applied. Only published prospective randomized controlled trials (RCTs) involving humans were included.

### Study selection and outcomes

The inclusion criteria were as follows: the study was a prospective RCT, patients in the control arm received a heparin lock solution alone and the experimental groups received either heparin with antimicrobials, heparin with other anticoagulants, or other anticoagulants with or without antimicrobials. Sufficient data were present to allow for calculation of the risk ratio (RR) with 95% confidence interval (95% CI), and the follow-up period was > 30 days. The exclusion criteria were as follows: the CVCs were not used for hemodialysis, the study was retrospective, and the study did not involve humans.

The primary outcomes were CRB (defined as a positive bacterial blood culture drawn from the dialysis catheter) and CM (poor blood flow or the need for thrombolytic treatment). The secondary outcomes were any bleeding, ESI, clinical sepsis, and all-cause mortality.

### Data extraction and quality assessment

Two investigators independently evaluated each study and recorded the eligibility, quality, and outcomes according to the inclusion and exclusion criteria. Data were extracted on baseline patient characteristics, interventions, number of patients, number of catheter-days, follow-up duration, and additional prophylactic measures used that may have affected the outcomes. Missing data were requested from the authors. The Cochrane quality criteria were used to conduct the quality assessment [10]. Disputes were resolved by consultation between the investigators.

### Statistical analysis

Dichotomous and continuous variables in the treatment and control groups were expressed as the RR and weighted mean difference with 95% CI, respectively. Considering the inherent heterogeneity among the studies, we assumed
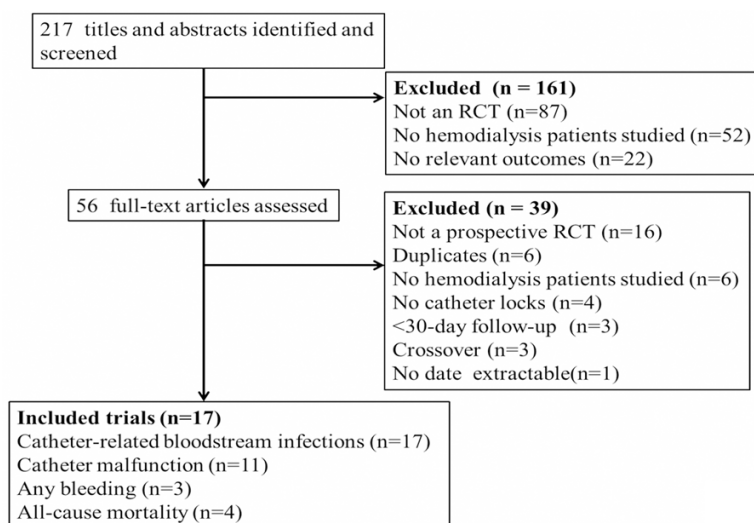
**Figure 1.** Flow diagram of study selection. RCT, randomized controlled trial.

the presence of statistical heterogeneity and used only a random-effects model (DerSimonian-Laird approach) before pooling the data. Heterogeneity of the results was measured using Cochran's $Q$ test, and $I^2$ was used to quantify the heterogeneity [10]. Subgroup analysis was performed to explore the sources of heterogeneity and assess the sensitivity of the results. Sensitivity tests were performed according to the Cochrane method. A $P$ value of < 0.05 was considered statistically significant for all analyses.

A funnel plot was used to detect publication bias. Data analysis was performed with Review Manager, version 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

**Results**

*Eligible studies*

The literature search yielded 217 potentially relevant records, 161 of which were irrelevant. Fifty-six articles were further evaluated by full-text reading, and 39 articles were excluded (**Figure 1**). Thus, 17 RCTs conducted from 1998 through 2012 were included in this systematic review and meta-analysis [7, 9, 11-27] (**Table 1**).

The interventions in the RCTs included antimicrobial-containing lock solutions (13 trials, 1405 patients) [9, 12, 14-18, 20-22, 24-27] or citrate-alone catheter lock solutions (4 trials, 604 patients) [7, 11, 13, 19]. All trials compared the intervention with a heparin catheter lock solution alone. The studies reported the rates of CRB (17 trials), CM (12 trials), ESI (10 trials), bleeding (3 trials), clinical sepsis (2 trials), and all-cause mortality at the end of follow-up (4 trials).

Although all included studies were identified as randomized, only seven trials [9, 11, 17, 19, 23, 27] described the method used to generate the random allocation sequence, and only two [17, 22] adequately described the allocation concealment. Nine trials were double-blind [7, 9, 12, 17, 18, 22, 23, 27], one trial was patient-blinded [24], two trials were unclear [13, 20, 26], and all others were open-label [11, 14-16, 19, 21, 25]. The quality assessment of the included studies is shown in Figure S1.

*CRB*

All trials reported on CRB. The incidence of CRB was significantly lower in association with anti-microbial-containing lock solutions than with heparin alone (RR 0.32, 95% CI: 0.25-0.41; $P <$ 0.001) (**Figure 2**). There was evidence that the incidence of CRB events was lower in association with citrate-alone locking solutions than with heparin (RR 0.43, 95% CI: 0.27-0.69; $P <$ 0.001), with no significant heterogeneity among studies. However, a subgroup analysis was performed based on different catheter types, yielding an $I^2$ of 55%. Interestingly, there was no heterogeneity among studies using non-tunneled cuffed catheters (NTCC; $I^2 = 0$%), whereas there was heterogeneity among those using tunneled cuffed catheters (TCC; $I^2 = 65$%) (**Figure 3**). This indicates that the catheter type was a likely source of heterogeneity among studies.

*CM*

Of the 12 RCTs (1803 patients) that reported on CM, 8 RCTs (889 patients) focused on anti-microbial-containing lock solutions, and 4 RCTs

**Table 1.** Characteristics of studies and patients fulfilling inclusion criterion

| Ref. | Treatment | Control (U/mL H) | Patients (n) | Mean age (y) | DM (%) | CT | CD |
|---|---|---|---|---|---|---|---|
| Buturovic *et al.* 1998 [13] | 4% citrate | 5000 | 20 | ------ | ----- | NTCC | 740 |
| Dogra *et al.* 2002 [17] | 40 mg/mL CN + 3.13% citrate | 5000 | 79 | 57.5 | 35 | TCC | 5923 |
| Pervez *et al.* 2002 [9] | 4 mg/mL CN + 4.67% citrate | 1000 | 36 | 50.7 | 41.6 | TCC | 2924 |
| Betjes *et al.* 2004 [16] | 1.35% TD + 4% citrate | 5000 | 58 | 54.3 | 27.5 | TCC/NTCC | 3404 |
| McIntyre *et al.* 2004 [14] | 5 mg/mL CN + 5000 U/mL H | 5000 | 50 | 60.7 | 26 | TCC | 5722 |
| Weijmer *et al.* 2005 [7] | 30% citrate | 5000 | 291 | 61.3 | 29.5 | NTCC/TCC | 16541 |
| Nori *et al.* 2006 [25] | 3 mg/mL MI + 30 mg/mL EDTA and 4 mg/mL CN + 3.13% citrate | 5000 | 62 | 58.5 | ---- | TCC | 6189 |
| Saxena *et al.* 2006 [12] | 10 mg/mL CTX + 5000 U/mL H | 5000 | 113 | 76.8 | 37.1 | TCC | 43435 |
| Kim *et al.* 2006 [18] | 10 mg/mL cefazolin + 5 mg/mL CN + 1000 U/mL H | 1000 | 120 | 54.9 | 52.5 | UC | 4503 |
| MacRae *et al.* 2008 [11] | 4% citrate | 5000 | 61 | 66 | 52.3 | TCC | 4091 |
| Al-Hwiesh 2008 [20] | 25 mg/mL VA + 40 mg/mL CN + 5000 U/mL H | 5000 | 69 | 46.4 | 23.2 | TCC | 8854 |
| Power *et al.* 2009 [19] | 46.7% citrate | 5000 | 232 | 64.5 | 27 | TCC | 36108 |
| Zhang *et al.* 2009 [23] | 4 mg/mL CN + 5500 U/mL H | 5500 | 140 | 52.1 | 13.6 | TCC | 34080 |
| Solomon *et al.* 2010 [22] | 1.35% TD + 4% citrate | 5000 | 107 | 58.2 | ----- | TCC | 17771 |
| Campos *et al.* 2011 [15] | 3 mg/mL MI + 30 mg/mL EDTA | 5000 | 133 | 55 | 38 | TCC/NTCC | 8747 |
| Sofroniadou *et al.* 2012 [27] | 5 mg/mL VA + 2000 U/mL H and 2 mg/mL linezolid + 2000 U/mL H | 2000 | 135 | 70.5 | 33.63 | TCC/NTCC | 5158 |
| Moran *et al.* 2012 [24] | 320 µg/mL CN + 4% citrate | 1000 | 303 | 63.1 | 56.5 | TCC | 72760 |

CD, catheter-days; CN, gentamicin; CT, catheter type; CTX, cefotaxime; DM, diabetes mellitus; H, heparin; MI, minocycline; NTCC, non-tunneled cuffed catheter; TCC, tunneled cuffed catheter; TD, taurolidine; VA, vancomycin.

**Figure 2.** Catheter-related bloodstream infections per catheter-day. Analysis of studies comparing antimicrobial-containing lock solutions (treatment) and heparin alone (control). Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
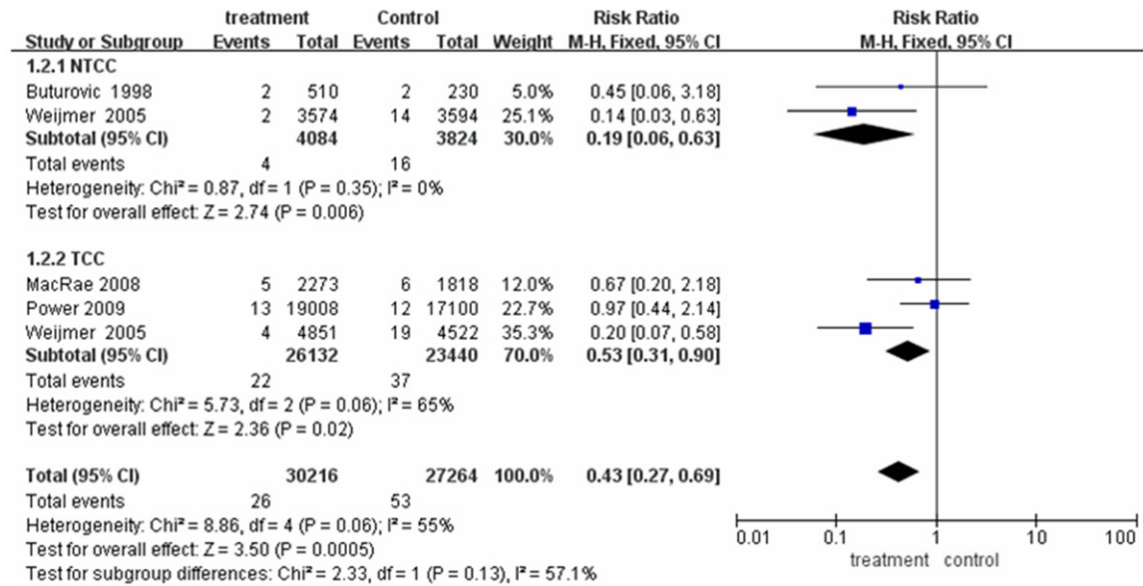


**Figure 3.** Catheter-related bloodstream infections per catheter-day. Analysis of studies comparing citrate-alone lock solutions (treatment) and heparin alone (control). The analysis is subcategorized by the different concentrations of citrate. Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; NTCC, non-tunneled cuffed catheter; TCC, tunneled cuffed catheter.

(604 patients) focused on citrate-alone lock solutions. A subgroup analysis was performed focusing on different anticoagulants in the RCTs that evaluated antimicrobial-containing lock solutions. The subgroup analysis using a random-effects model suggested that antibiotics + heparin and gentamicin + citrate lock solutions more effectively prevented CM than did heparin alone (RR 0.58, *P* = 0.030; and RR 0.67, *P* = 0.003, respectively). Lock solutions containing antibiotics + EDTA failed to significantly decrease CM events in comparison to heparin alone (**Figure 4**). Although there was an increase in CM events with taurolidine + citrate, this was based on the result of only one trial. This indicates that the heterogeneity in this

| Study or Subgroup | Treatment Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.1.1 antibiotics+heparin vs heparin** | | | | | | | |
| Saxena 2006 | 9 | 21535 | 22 | 21900 | 12.4% | 0.42 [0.19, 0.90] | |
| Sofroniadou 2012 | 9 | 1652 | 11 | 1642 | 11.3% | 0.81 [0.34, 1.96] | |
| Sofroniadou 2012 | 8 | 1864 | 11 | 1642 | 11.0% | 0.64 [0.26, 1.59] | |
| Subtotal (95% CI) | | 25051 | | 25184 | 34.6% | 0.58 [0.36, 0.95] | |
| Total events | 26 | | 44 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 2 (P = 0.52); I² = 0% | | | | | | | |
| Test for overall effect: Z = 2.18 (P = 0.03) | | | | | | | |
| | | | | | | | |
| **2.1.2 gentamicin+citrate vs heparin** | | | | | | | |
| Moran 2012 | 78 | 32933 | 136 | 39827 | 17.8% | 0.69 [0.53, 0.92] | |
| Nori 2006 | 4 | 2002 | 10 | 1734 | 8.7% | 0.35 [0.11, 1.10] | |
| Pervez 2002 | 4 | 1613 | 5 | 1311 | 7.5% | 0.65 [0.17, 2.42] | |
| Subtotal (95% CI) | | 36548 | | 42872 | 34.0% | 0.67 [0.51, 0.87] | |
| Total events | 86 | | 151 | | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 2 (P = 0.52); I² = 0% | | | | | | | |
| Test for overall effect: Z = 3.00 (P = 0.003) | | | | | | | |
| | | | | | | | |
| **2.1.3 taurolidine+citrate vs heparin** | | | | | | | |
| Solomon 2010 | 28 | 8119 | 14 | 9642 | 13.9% | 2.38 [1.25, 4.51] | |
| Subtotal (95% CI) | | 8119 | | 9642 | 13.9% | 2.38 [1.25, 4.51] | |
| Total events | 28 | | 14 | | | | |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z = 2.65 (P = 0.008) | | | | | | | |
| | | | | | | | |
| **2.1.4 antibiotics+EDTA vs heparin** | | | | | | | |
| Campos 2011 | 20 | 4374 | 14 | 4376 | 13.5% | 1.43 [0.72, 2.83] | |
| Nori 2006 | 1 | 2453 | 10 | 1734 | 4.0% | 0.07 [0.01, 0.55] | |
| Subtotal (95% CI) | | 6827 | | 6110 | 17.5% | 0.37 [0.02, 7.88] | |
| Total events | 21 | | 24 | | | | |
| Heterogeneity: Tau² = 4.32; Chi² = 8.08, df = 1 (P = 0.004); I² = 88% | | | | | | | |
| Test for overall effect: Z = 0.64 (P = 0.52) | | | | | | | |
| | | | | | | | |
| Total (95% CI) | | 76545 | | 83808 | 100.0% | 0.73 [0.46, 1.17] | |
| Total events | 161 | | 233 | | | | |
| Heterogeneity: Tau² = 0.29; Chi² = 25.28, df = 8 (P = 0.001); I² = 68% | | | | | | | |
| Test for overall effect: Z = 1.30 (P = 0.19) | | | | | | | |
| Test for subgroup differences: Chi² = 14.43, df = 3 (P = 0.002), I² = 79.2% | | | | | | | |

0.01  0.1  1  10  100
Favours [experimental]  Favours [control]

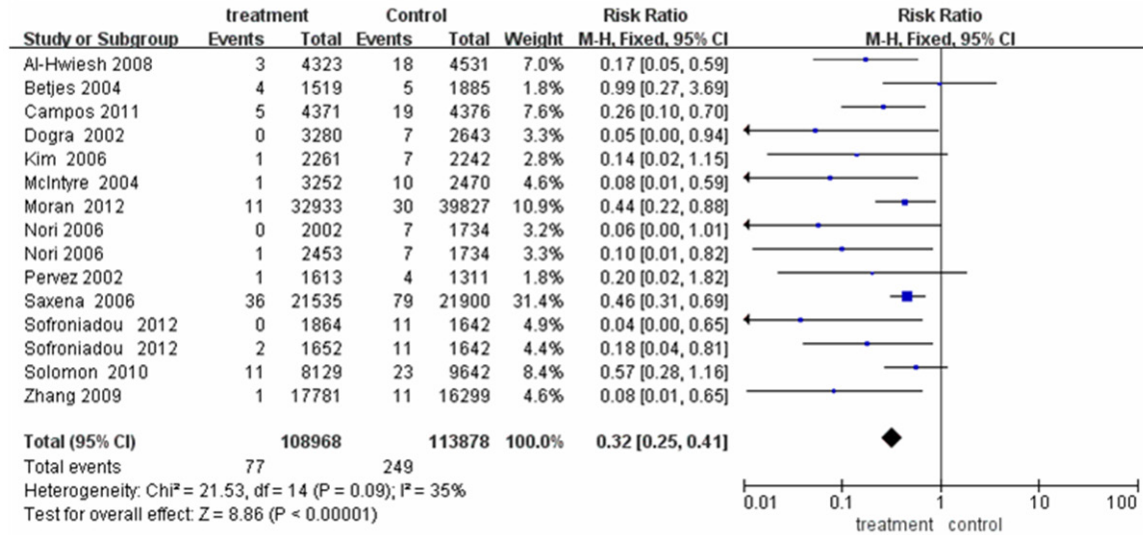**Figure 4.** Catheter malfunctions per catheter-day. Analysis of studies comparing antimicrobial-containing lock solutions (treatment) and heparin alone (control). Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
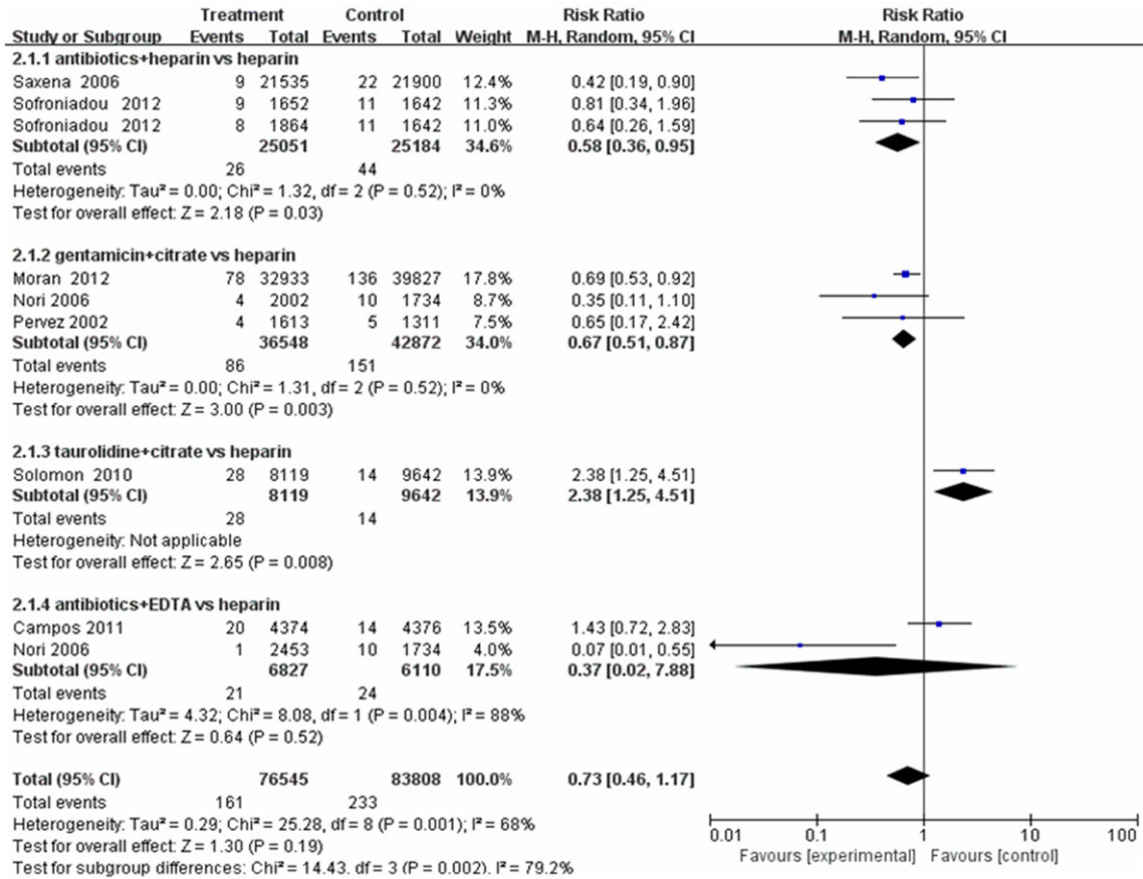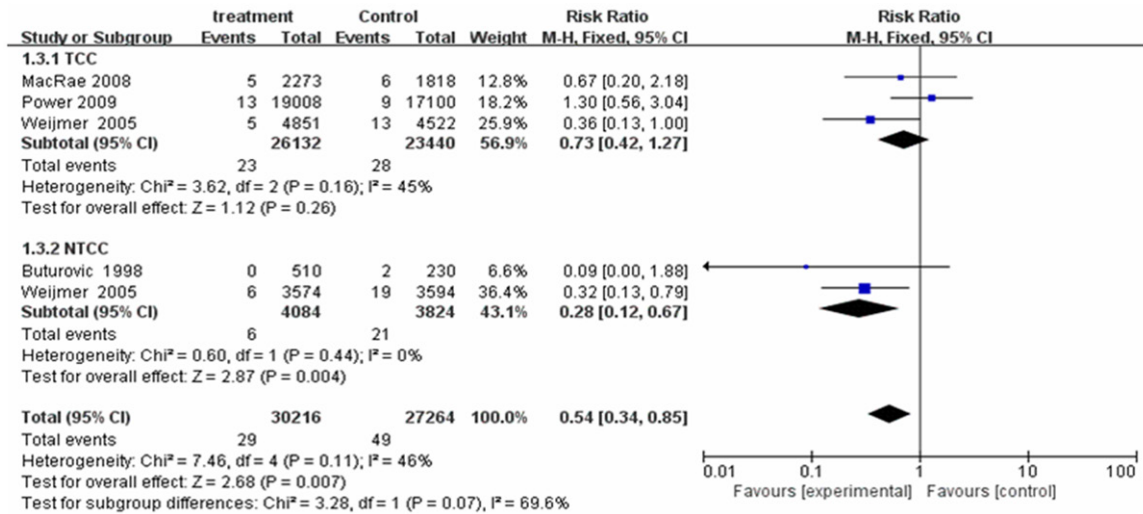
| Study or Subgroup | treatment Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.3.1 TCC** | | | | | | | |
| MacRae 2008 | 5 | 2273 | 6 | 1818 | 12.8% | 0.67 [0.20, 2.18] | |
| Power 2009 | 13 | 19008 | 9 | 17100 | 18.2% | 1.30 [0.56, 3.04] | |
| Weijmer 2005 | 5 | 4851 | 13 | 4522 | 25.9% | 0.36 [0.13, 1.00] | |
| Subtotal (95% CI) | | 26132 | | 23440 | 56.9% | 0.73 [0.42, 1.27] | |
| Total events | 23 | | 28 | | | | |
| Heterogeneity: Chi² = 3.62, df = 2 (P = 0.16); I² = 45% | | | | | | | |
| Test for overall effect: Z = 1.12 (P = 0.26) | | | | | | | |
| | | | | | | | |
| **1.3.2 NTCC** | | | | | | | |
| Buturovic 1998 | 0 | 510 | 2 | 230 | 6.6% | 0.09 [0.00, 1.88] | |
| Weijmer 2005 | 6 | 3574 | 19 | 3594 | 36.4% | 0.32 [0.13, 0.79] | |
| Subtotal (95% CI) | | 4084 | | 3824 | 43.1% | 0.28 [0.12, 0.67] | |
| Total events | 6 | | 21 | | | | |
| Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0% | | | | | | | |
| Test for overall effect: Z = 2.87 (P = 0.004) | | | | | | | |
| | | | | | | | |
| Total (95% CI) | | 30216 | | 27264 | 100.0% | 0.54 [0.34, 0.85] | |
| Total events | 29 | | 49 | | | | |
| Heterogeneity: Chi² = 7.46, df = 4 (P = 0.11); I² = 46% | | | | | | | |
| Test for overall effect: Z = 2.68 (P = 0.007) | | | | | | | |
| Test for subgroup differences: Chi² = 3.28, df = 1 (P = 0.07), I² = 69.6% | | | | | | | |

0.01  0.1  1  10  100
Favours [experimental]  Favours [control]

**Figure 5.** Exit-site infections per catheter-day. Analysis of studies comparing citrate-alone lock solutions (treatment) and heparin alone (control). Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; NTCC, non-tunneled cuffed catheter; TCC, tunneled cuffed catheter.
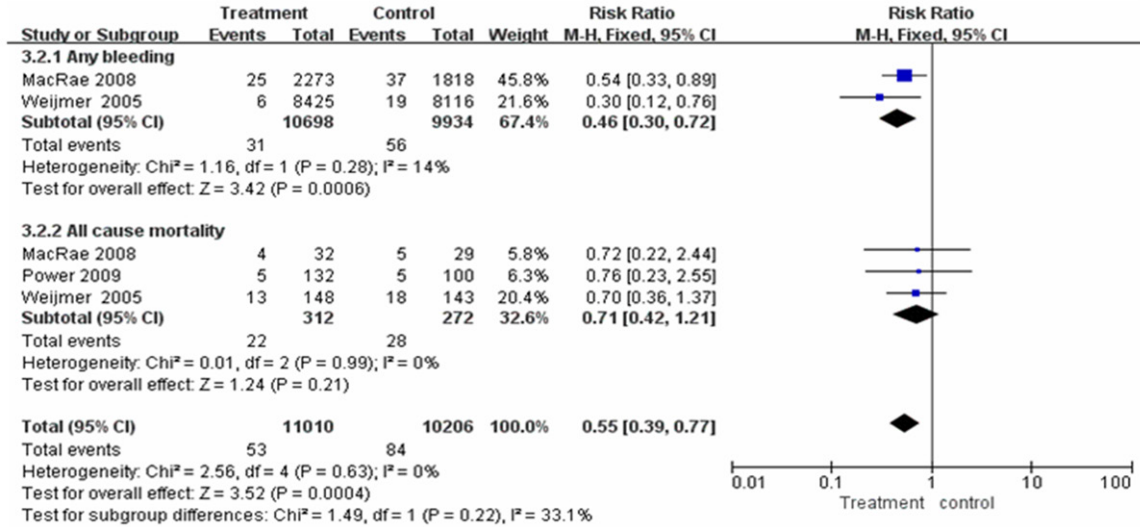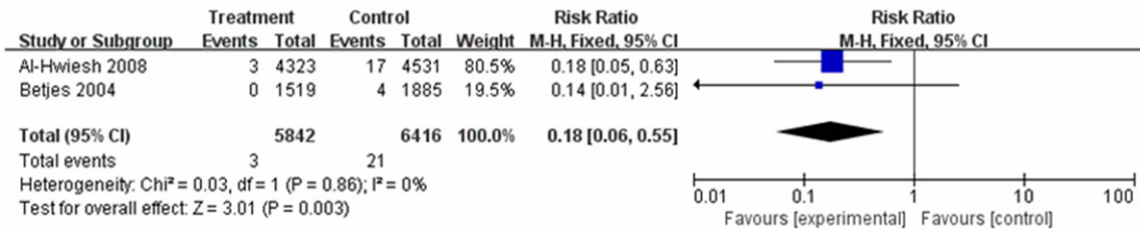
**Figure 6.** Secondary outcomes per catheter-day. Analysis of studies comparing citrate-alone lock solutions (treatment) and heparin alone (control). Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.



**Figure 7.** Clinical sepsis per catheter-day. Analysis of studies comparing antimicrobial-containing lock solutions (treatment) and heparin alone (control). Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

analysis (overall, $I^2$ = 68%; $P$ = 0.001) was likely due to the different catheter lock solutions. In the evaluation of citrate-alone lock solutions at different concentrations, two RCTs used a low-concentration, and two used a high-concentration group; the incidence of CM was similar between these two subgroups (Figure S2).

*Secondary outcomes*

Three RCTs (487 patients) evaluated the rate of bleeding events, and four RCTs (646 patients) compared all-cause mortality between two kinds of lock solutions. The rate of any type of bleeding per catheter-day was significantly lower in association with citrate-alone lock solutions than with heparin alone (RR 0.46, 95% CI: 0.30-0.72; $P$ < 0.001) (**Figure 5**), with no heterogeneity among studies; however, there was no evidence that antimicrobial-con-

taining lock solutions reduced the rates of any bleeding episodes (Figure S3).

A total of 10 RCTs (1185 patients) described ESIs. Compared with heparin lock solutions, the overall summary RR using the fixed-effects model was 0.54 (95% CI: 0.34-0.85; $P$ = 0.007). Further subgroup analysis was performed according to catheter types. Although the RR of NTCC subgroups had statistical significance (RR 0.28, 95% CI: 0.12-0.67; $P$ = 0.004), no difference was identified in the TCC subgroups (RR 0.73, 95% CI: 0.42-1.27) (**Figure 5**). This indicates that catheter type was the likely source of heterogeneity among studies. The ESI incidence was similar between antimicrobial-containing lock solutions and heparin locks when used alone (RR 0.83, 95% CI: 0.57-1.21) (Figure S4).

Another secondary outcome was all-cause mortality, and no difference was found between any of the three types of interventions and the control groups, with no heterogeneity among studies (**Figure 6**; Figure S3). Meta-analysis using the fixed-effects model showed that antimicrobial-containing lock solutions are a better choice than heparin to avoid clinical sepsis (RR 0.18, 95% CI: 0.06-0.55; *P* = 0.003), with no heterogeneity among studies (**Figure 7**). A funnel plot analysis for the included trials revealed no evidence of publication bias (Figure S5).

## Discussion

Although CVCs are considered inferior to arteriovenous fistulas and grafts in all nephrology guidelines, they are being increasingly used for hemodialysis vascular access [28]. However, a complication of long-term use of CVCs for hemodialysis is the high rate of infection and thrombus-related dysfunction [29]. More effective strategies to protect patients from these adverse events during hemodialysis are urgently needed. The use of heparin solutions to lock the CVC lumen has become a conventional method with which to avoid thrombosis between hemodialysis sessions [19]. In recent years, increasingly more experts have stated that heparin should be abandoned because it can induce rapid biofilm development and introduce a risk of bleeding secondary to overspill of heparin into the bloodstream [30]. Therefore, many new lock solutions have been developed, such as antimicrobial lock solutions, which are associated with lower rates of CRB and catheter removal than heparin in patients undergoing hemodialysis [8, 31]. However, such studies have not focused on avoiding poor flow, the thrombolytic treatment of catheters, or reduction of the rates of any bleeding events and all-cause mortality.

The results of the present meta-analysis indicate that antimicrobial-containing lock solutions (antibiotics + heparin, antibiotics + citrate, and antibiotics + EDTA) are associated with fewer CRB events than with citrate-alone lock solutions (low or high concentrations), which is consistent with some previous meta-analyses [3, 31, 34]. In addition, further analyses revealed that antimicrobial-containing lock solutions reduced the rate of clinical sepsis compared to heparin locks, but not ESI, bleed-

ing, or all-cause mortality. These results should be interpreted with caution until the results of more large-scale trials are available. Further studies should assess whether antibiotics increase the risk of bleeding.

rt-PA has primarily been used to treat catheter thrombosis [32]. Only one double-blind, randomized study of 23449 catheter-days in 225 patients compared heparin with rt-PA-heparin as catheter-lock solutions. The results of that study indicated that use of rt-PA once weekly instead of heparin may significantly reduce the incidence of CM, with rates of 1.76 cases per 100 catheter-days compared to 3.65 cases per 100 catheter-days in the heparin group [32]. However, additional RCTs are warranted to verify this result. The present study is the first meta-analysis to our knowledge that confirms the benefit of lock solutions containing antibiotics + heparin or gentamycin + citrate with regard to CMs.

Unlike heparin, citrate is rapidly metabolized to bicarbonate without causing systemic bleeding [1] and exhibits an antimicrobial effect [33]. Thus, citrate has drawn much interest in the medical field. Several studies have demonstrated the superiority of citrate in combination with other antimicrobials over heparin in avoiding CRB [17, 21, 24]. The present study shows that the use of citrate-alone lock solutions is associated with a significant reduction in the rate of CRB. In contrast, Zhao *et al*. [1] failed to find a benefit of citrate-alone solutions, but demonstrated that antimicrobial-containing citrate locks were superior to heparin locks in the prevention of CRB. The prevention of CRB with citrate-alone lock solutions has been controversial. Of four studies on CRB, only one RCT identified a difference between citrate and heparin lock solutions (RR, 0.26; 95% CI, 0.13-0.55) [7]. Thus, further high-quality randomized trials are needed to clarify the benefits of citrate alone for prevention of CRB.

With regard to ESI, only four studies met the criteria for inclusion in the meta-analysis, including one RCT that identified a significant reduction with citrate-only locks [7]. However, pooling of their results in a subgroup analysis by catheter type (NTCC and TCC) revealed a remarkable protective effect against ESI, which differed from the findings of a previous meta-

analysis [1]. This benefit was primarily due to NTCC-type catheters.

Bleeding rates appeared to be reduced by citrate-alone solutions. Although this result was based on two trials, it is consistent with previous literature [35]. Nevertheless, this finding should be interpreted with caution. In addition, Grudzinski *et al.* [6] reported that a high (46.7%) citrate concentration can induce fatal cardiac arrest, and thus the US Food and Drug Administration stated that it should not be used as a catheter-locking solution. Therefore, although it was determined that citrate alone cannot be used to reduce the risk of CRB, whether it can be used to avoid bleeding still requires additional large-scale RCTs.

Several limitations of our study should be addressed. First, because of the limited number of RCTs included in this meta-analysis, subgroup analyses based on parameters that could potentially contribute to heterogeneity, such as the age of patients, race, clinical complications, and catheter site were not possible. Second, there was insufficient data available to allow for analyses of side effects and disadvantages associated with the use of various solutions, such as length of hospital stay, health care costs, thrombolytic treatment, and catheter removal. Third, because the duration of each study varied, and the endpoints of different follow-up periods could modify the absolute risk, and thus affect the overall RR. Fourth, drug resistance associated with long-term use of antibiotics was not assessed in these trials. Finally, only the results of published trials were included in the data analysis; therefore, we cannot rule out publication bias. Regardless of these limitations, bias was minimized throughout the study via the study methods, data selection, quality evaluation, and funnel plot analysis. These procedures should enhance the stability and accuracy of this study.

In conclusion, this meta-analysis provides further evidence that antimicrobial-containing and citrate-alone lock solutions are superior to heparin in preventing CRB. Antimicrobial-containing lock solutions might also decrease clinical sepsis in hemodialysis patients. Solutions containing antibiotics + heparin or gentamycin + citrate may effectively reduce the incidence of CM. Citrate-alone lock solutions are associated with a lower incidence of bleeding episodes and ESI

compared to heparin. Additional prospective, long-term RCTs on other types of catheter lock solutions versus heparin are required to confirm these findings.

## Disclosure of conflict of interest

None.

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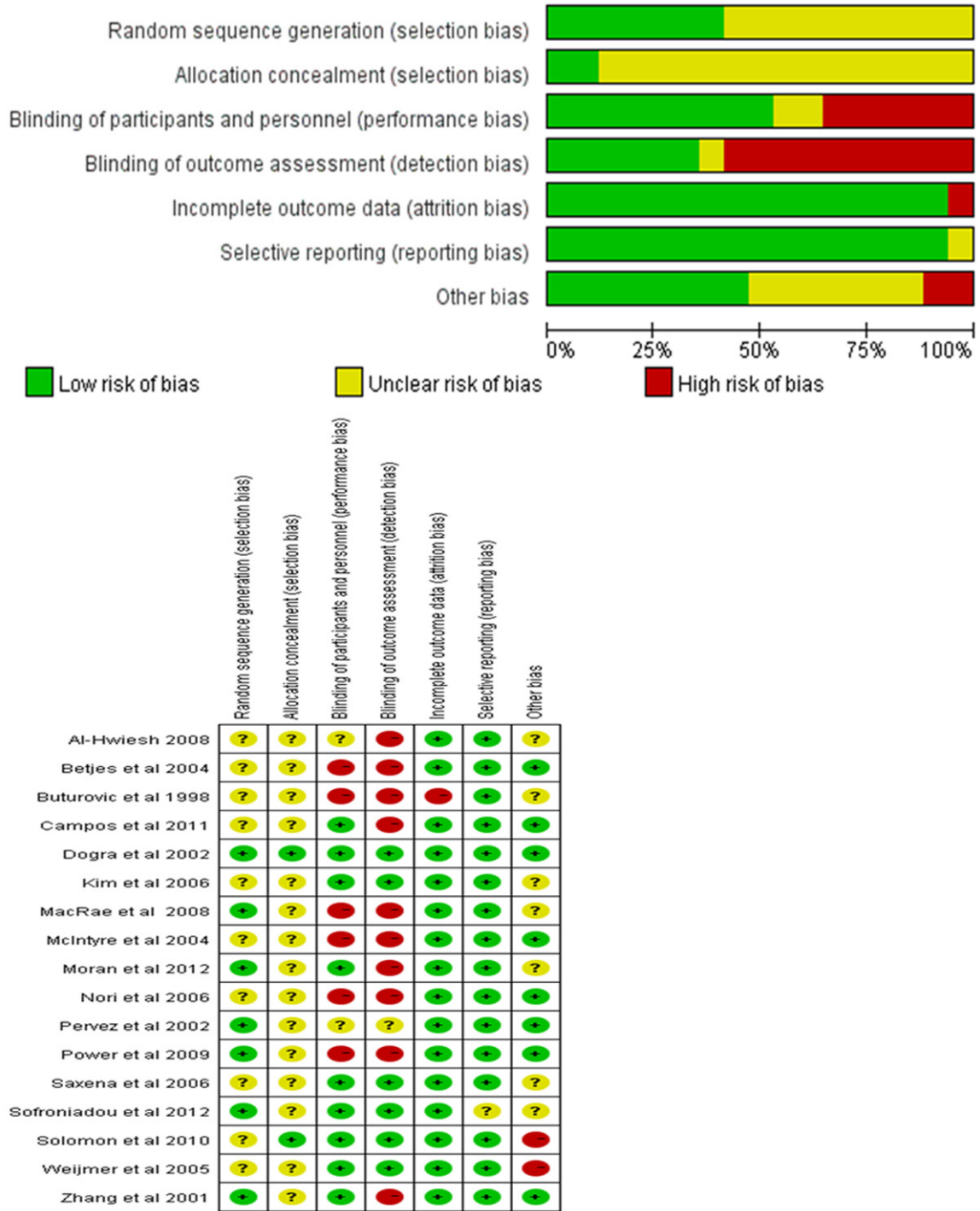# Catheter lock solutions for hemodialysis



**Figure S1.** Quality assessment of included studies.

| Study or Subgroup | Treatment Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.2.1 low concentration** | | | | | | |
| Buturovic 1998 | 1 | 510 | 1 | 230 | 2.7% | 0.45 [0.03, 7.18] |
| MacRae 2008 | 13 | 2273 | 13 | 1818 | 20.6% | 0.80 [0.37, 1.72] |
| Subtotal (95% CI) | | 2783 | | 2048 | 23.4% | 0.77 [0.37, 1.61] |
| Total events | 14 | | 14 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.70 (P = 0.48) | | | | | | |
| | | | | | | |
| **2.2.2 high concentration** | | | | | | |
| Power 2009 | 152 | 19008 | 74 | 17100 | 39.6% | 1.85 [1.40, 2.44] |
| Weijmer 2005 | 69 | 8425 | 63 | 8116 | 37.0% | 1.06 [0.75, 1.48] |
| Subtotal (95% CI) | | 27433 | | 25216 | 76.6% | 1.41 [0.81, 2.44] |
| Total events | 221 | | 137 | | | |
| Heterogeneity: Tau² = 0.13; Chi² = 6.27, df = 1 (P = 0.01); I² = 84% | | | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | | |
| | | | | | | |
| Total (95% CI) | | 30216 | | 27264 | 100.0% | 1.22 [0.76, 1.94] |
| Total events | 235 | | 151 | | | |
| Heterogeneity: Tau² = 0.12; Chi² = 9.21, df = 3 (P = 0.03); I² = 67% | | | | | | |
| Test for overall effect: Z = 0.82 (P = 0.41) | | | | | | |
| Test for subgroup differences: Chi² = 1.67, df = 1 (P = 0.20), I² = 40.2% | | | | | | |

0.01   0.1   1   10   100
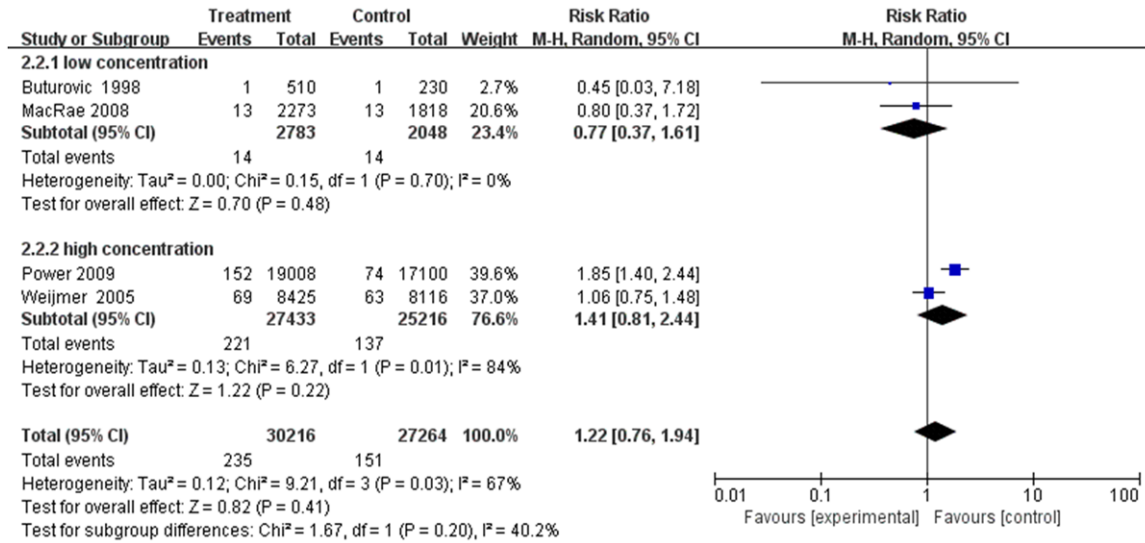Favours [experimental]   Favours [control]

**Figure S2.** Catheter malfunctions per catheter-day. Analysis of studies comparing citrate-alone lock solutions (treatment) and heparin alone (control). The analysis is subcategorized by the different concentrations of citrate. Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
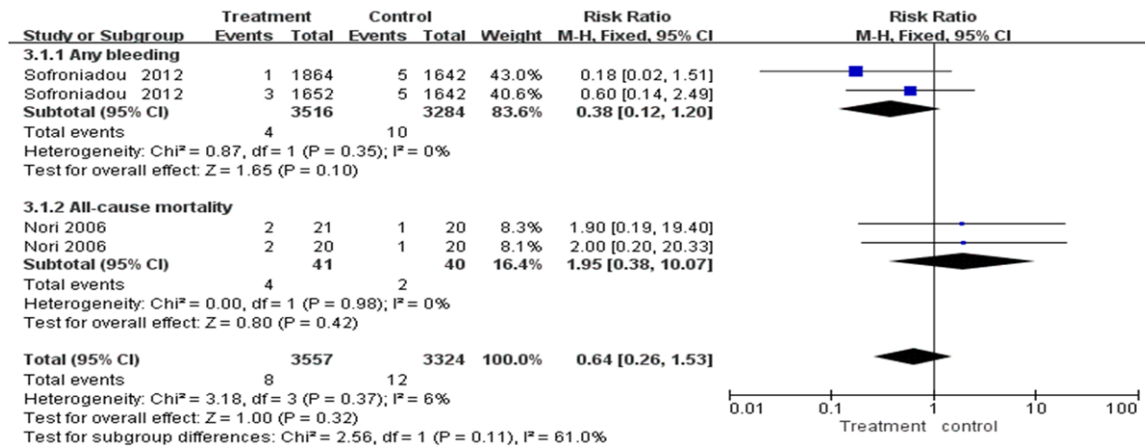
| Study or Subgroup | Treatment Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.1.1 Any bleeding** | | | | | | |
| Sofroniadou 2012 | 1 | 1864 | 5 | 1642 | 43.0% | 0.18 [0.02, 1.51] |
| Sofroniadou 2012 | 3 | 1652 | 5 | 1642 | 40.6% | 0.60 [0.14, 2.49] |
| Subtotal (95% CI) | | 3516 | | 3284 | 83.6% | 0.38 [0.12, 1.20] |
| Total events | 4 | | 10 | | | |
| Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.65 (P = 0.10) | | | | | | |
| | | | | | | |
| **3.1.2 All-cause mortality** | | | | | | |
| Nori 2006 | 2 | 21 | 1 | 20 | 8.3% | 1.90 [0.19, 19.40] |
| Nori 2006 | 2 | 20 | 1 | 20 | 8.1% | 2.00 [0.20, 20.33] |
| Subtotal (95% CI) | | 41 | | 40 | 16.4% | 1.95 [0.38, 10.07] |
| Total events | 4 | | 2 | | | |
| Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.80 (P = 0.42) | | | | | | |
| | | | | | | |
| Total (95% CI) | | 3557 | | 3324 | 100.0% | 0.64 [0.26, 1.53] |
| Total events | 8 | | 12 | | | |
| Heterogeneity: Chi² = 3.18, df = 3 (P = 0.37); I² = 6% | | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | | |
| Test for subgroup differences: Chi² = 2.56, df = 1 (P = 0.11), I² = 61.0% | | | | | | |

0.01   0.1   1   10   100
Treatment   control

**Figure S3.** Secondary outcomes per catheter-day. Analysis of studies comparing antimicrobial-containing lock solutions (treatment) and heparin alone (control). Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

| Study or Subgroup | treatment Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Al-Hwiesh 2008 | 13 | 4323 | 18 | 4531 | 30.0% | 0.76 [0.37, 1.54] |
| Betjes 2004 | 2 | 1519 | 4 | 1885 | 6.1% | 0.62 [0.11, 3.38] |
| Campos 2011 | 8 | 4371 | 9 | 4376 | 15.3% | 0.89 [0.34, 2.30] |
| Dogra 2002 | 1 | 3280 | 4 | 2643 | 7.6% | 0.20 [0.02, 1.80] |
| Sofroniadou 2012 | 10 | 1652 | 9 | 1642 | 15.4% | 1.10 [0.45, 2.71] |
| Sofroniadou 2012 | 7 | 1864 | 9 | 1642 | 16.3% | 0.69 [0.26, 1.84] |
| Solomon 2010 | 7 | 8129 | 6 | 9642 | 9.4% | 1.38 [0.47, 4.12] |
| | | | | | | |
| Total (95% CI) | | 25138 | | 26361 | 100.0% | 0.83 [0.57, 1.21] |
| Total events | 48 | | 59 | | | |
| Heterogeneity: Chi² = 3.18, df = 6 (P = 0.79); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.98 (P = 0.33) | | | | | | |

0.01   0.1   1   10   100
treatment   control

**Figure S4.** Exit-site infections per catheter-day. Analysis of studies comparing antimicrobial-containing lock solutions (treatment) and heparin alone (control). Risk ratio of < 1.0 favors treatment. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
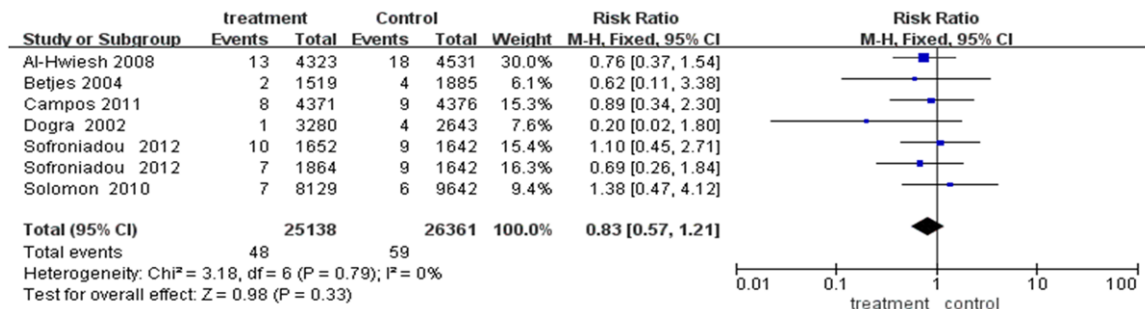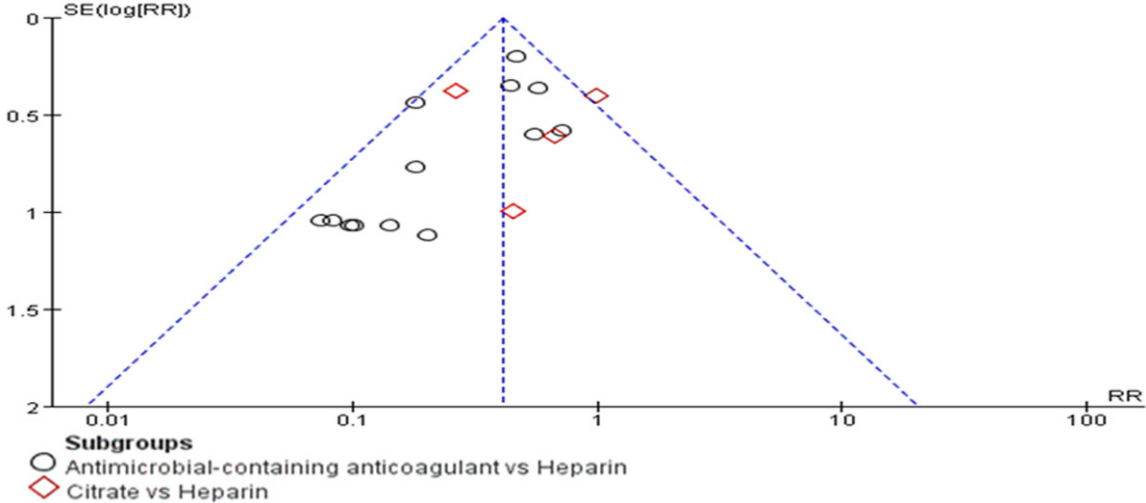
# Catheter lock solutions for hemodialysis



**Figure S5.** Funnel plot of 19 trials on the effect of different catheter anticoagulation treatments on catheter-related bloodstream infections per catheter-day in patients undergoing hemodialysis.