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Original Investigation

Citrate Versus Heparin Lock for Hemodialysis Catheters: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Citrate solution has been suggested as an effective and safe catheter lock in hemodialysis. However, whether a citrate lock is superior to a heparin lock in preventing catheter-related infections and maintaining catheter patency is inconclusive.

Study Design: A systematic review and meta-analysis was performed by searching in PubMed, EMBASE, Ovid, the Cochrane Library, and Web of Science databases and major nephrology journals.

Setting & Population: Patients receiving hemodialysis with central venous catheters.

Selection Criteria for Studies: Randomized controlled trials comparing citrate locks with heparin locks in hemodialysis patients with central venous catheters.

Intervention: Locking central venous catheters with citrate locks.

Outcomes: Primary outcomes include catheter-related bloodstream infection (CRBSI), exit-site infection, catheter removal for poor flow, and thrombolytic treatment.

Results: 13 randomized controlled trials (1,770 patients, 221,064 catheter-days) met the inclusion criteria. Pooled analyses found that citrate locks could significantly reduce the incidence of CRBSI (risk ratio [RR], 0.39; 95% CI, 0.27-0.56; $P < 0.001$). Subgroup analysis showed that antimicrobial-containing citrate locks (citrate + gentamicin, citrate + taurolidine, and citrate + methylene blue + methylparaben + propylparaben) were superior to heparin locks in the prevention of CRBSI ($P < 0.001$, $P = 0.003$, and $P = 0.008$, respectively), whereas citrate alone failed to show a similar advantage ($P = 0.2$). Low- (1.04%-4%) to moderate-concentration (4.6%-7%) citrate locks were associated with decreased CRBSI incidence ($P < 0.001$ and $P = 0.003$, respectively), but patients receiving high-concentration (30%-46.7%) citrate and heparin locks had similar incidences ($P = 0.3$). The incidence of bleeding episodes (RR, 0.48; 95% CI, 0.30-0.76; $P = 0.002$) was significantly lower in patients receiving citrate locks, whereas both groups were similar in terms of exit-site infection ($P = 0.2$), catheter removal for poor flow ($P = 0.9$), thrombolytic treatment ($P = 0.8$), all-cause death ($P = 0.3$), catheter thrombosis ($P = 0.9$), mean catheter duration ($P = 0.2$), CRBSI-free catheter survival ($P = 0.2$), and catheter-related readmission ($P = 0.5$).

Limitations: All studies used in the meta-analysis were performed in Western countries. The applicability of our findings to other regions remains to be clarified.

Conclusions: An antimicrobial-containing citrate lock is better than a heparin lock in the prevention of catheter-related infection, while citrate alone fails to show a similar advantage. Citrate locks of low to moderate concentrations, rather than high concentration, were superior to heparin locks in preventing CRBSI. Citrate locks also might decrease bleeding episodes. No difference has been identified in the efficacy to prevent exit-site infection or preserve catheter patency between citrate and heparin locks.
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INDEX WORDS: Hemodialysis; lock solution; citrate; heparin; catheter-related bacteremia; antimicrobial solution; catheter lock; renal replacement therapy; exit-site infection; vascular access.

Central venous catheters (CVCs) are widely used in hemodialysis patients who have no permanent vascular access.[1] However, CVCs are prone to catheter malfunction and catheter-related infection (CRI), which includes catheter-related bloodstream infection (CRBSI) and exit-site infection. It is accepted practice to lock the CVC lumen with a heparin solution to prevent thrombosis and maintain catheter patency between dialysis sessions,[2] but heparin could increase the risk of systemic anticoagulation in case of inadvertent overfills of the lumen.[3]

Citrate is an anticoagulant that blocks the blood coagulation cascade by binding to calcium ions.

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If citrate leaves the catheter lumen, it would be metabolized rapidly into bicarbonates without causing systemic bleeding. The anticoagulation activity of citrate therefore is confined to the catheter, which potentially reduces the risk of bleeding episodes. Furthermore, citrate itself shows an antimicrobial effect,[4] and there is renewed interest in citrate lock solution for the prevention of CRIs.[5] At the same time, there have been concerns about citrate toxicity and arrhythmia in case of overfills, especially at high concentrations. A previous study found that 30% citrate solution was as effective as heparin in maintaining catheter patency by comparing premature catheter removals, and it was superior to heparin in preventing CRIs.[6] In contrast, citrate failed to show an advantage over heparin locks in 2 other randomized controlled trials (RCTs) in terms of CRI.[2,5] Results from studies comparing citrate with heparin locks remain inconclusive.

We performed a systematic review and meta-analysis to assess whether citrate locks are superior to heparin locks in the maintenance of catheter patency and the prevention of CRIs in patients receiving hemodialysis.

METHODS

Search Strategy

Two independent reviewers (Y.Z. and Z.L.) conducted a search in PubMed, EMBASE, Ovid, the Cochrane Library, Web of Science, and major nephrology journals. No language or date restrictions were imposed. We performed the last updated search on March 10, 2013. Search terms were as follows: "lock or filling solution" and "hemodialysis or dialysis or blood purification or renal replacement therapy." The exact search strategy used in the PubMed database is provided as an example in Item S1 (available as online supplementary material). Reference lists of identified articles were searched for relevant studies.

Study Selection and Data Abstraction

The inclusion criteria were as follows: (1) RCTs, (2) experimental arms receiving a citrate lock (with or without other antimicrobials) and control arms receiving a heparin lock alone, (3) reporting on CRI and/or catheter patency, and (4) sufficient data available to calculate a risk ratio (RR) or weighted mean difference with 95% confidence interval (95% CI). The following exclusion criteria were used: (1) studies focusing on lock solutions for dialysis vascular accesses other than CVCs, (2) studies dealing with the treatment of CRI and catheter malfunction rather than with prophylaxis, and (3) nonhuman studies. For studies with the same or overlapping data by the same authors, the most suitable studies with the largest number of cases or latest publication dates were selected.

Two investigators (Y.Z. and Z.L.) examined each study independently and recorded eligibility, quality, and outcomes, with disagreements resolved by discussion. We extracted the following study features: first author, publication year, country, intervention, mean age of patients, percentage of tunneled catheters, number of patients, number of catheter-days, intention-to-treat analysis, blinding, randomization method, and allocation concealment method. Missing data were requested from the authors.

Study Outcomes

The primary outcomes were: (1) CRBSI, defined as bacteremia without obvious sources other than the hemodialysis catheter; (2) exit-site infection, defined as the development of a purulent exudate or redness around the site not resulting from residual stitches; (3) catheter removal for poor flow; and (4) the need for thrombolytic treatments. Secondary outcomes included bleeding episodes, all-cause death, catheter thrombosis, CRBSI-free catheter survival, mean catheter duration, and catheter-related readmission. Incidence was presented as the number of episodes per catheter-day or per patient. Outcomes were extracted preferentially by intention to treat at the end of follow-up.

Quantitative Data Synthesis

For dichotomous variables such as CRBSI, rates of the experimental (citrate) and control (heparin) groups were expressed as RR and 95% CI. For the continuous variable (mean catheter duration), the pooled effects were expressed as weighted mean difference and 95% CI, which was calculated by multiplying the standard error to a coefficient $t_{0.05}$ associated with the degrees of freedom under t-distribution. Considering the inherited heterogeneity between these studies, we assumed the presence of statistical heterogeneity and used only a random-effects model (DerSimonian-Laird) before pooling the data. By using higher estimated variances and wider CIs, the random-effects model provided a more conservative estimate of an effect than a fixed-effects model. In the pooled-analysis, $P < 0.05$ was considered statistically significant.

We performed meta-regression analyses to assess the potential sources of heterogeneity. The small number of studies precluded the use of multivariable meta-regression. Selected characteristics were type of citrate lock solution, citrate concentration, blinding, and intention-to-treat analysis. A stratified analysis then was conducted according to results of metaregression analyses, as well as study characteristics considered to be clinically important.

For publication bias, Egger test was carried out for statistical assessment. Sensitivity analysis was conducted by sequentially deleting a single study each time in an attempt to identify the potential influence of the individual study. Data analysis was performed using Review Manager, version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration), and Stata, version 10.0 (StataCorp LP).

RESULTS

Eligible Studies

The literature search yielded 347 potentially relevant records. By screening the abstracts, we removed 290 irrelevant studies. Then 57 articles were assessed further by full-text reading, of which 44 were excluded (Fig 1). Thus, 13 RCTs comparing citrate with heparin locks for hemodialysis CVCs were included in this systematic review and meta-analysis.[2,3,5-15]

The eligible studies were conducted from 1998 through 2012, with a total of 1,770 patients and 221,064 catheter-days involved. Five studies compared citrate alone with heparin locks, whereas 8 studies challenged mixtures of citrate and other antimicrobials (gentamicin, taurolidine, methylparaben, methylene blue, and propylparaben) against heparin locks. Studies were from North America, Europe, and Australia. Nine studies focused on tunneled catheters, and 2 studies, on nontunneled catheters, whereas

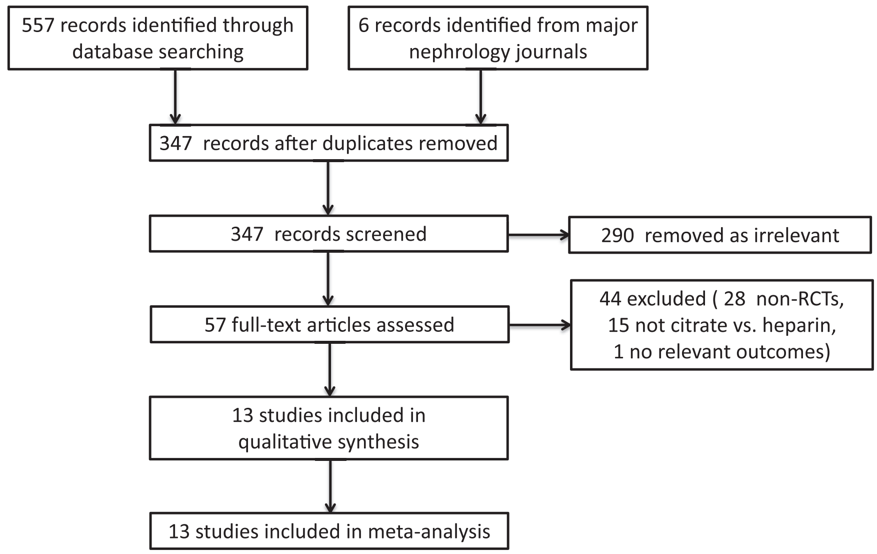

Figure 1. Flow chart of selection of studies. Abbreviation: RCT, randomized controlled trial.

another 2 studies included both types. A variety of end points were used in these studies. Most studies reported on CRBSI (11 studies[2,3,5,6,9-15]), followed by exit-site infection (8 studies[2,3,5,6,8,9,11,13]), all-cause death (7 studies[2,3,5,6,12,13,15]), catheter removal for poor flow (7 studies[3,5-7,11,13,15]), thrombolytic treatment (6 studies[2,3,6,8,12,13]), CRBSI-free catheter survival (3 studies[2,12,14]), mean catheter duration

Table 1. Characteristics of Studies Fulfilling the Inclusion Criteria

Study	Experimental vs Control	Country	N	Mean Age (y)	No. of Catheter-Days	Tunneled Catheter	ITT Analysis	Allocation Generation	Concealment	Blinding
Buturovic[7] (1998)	4% citrate vs 1,666 U/mL heparin	SI	20	63	740	0%	No	U	U	OL
Hendrickx[8] (2001)	5% citrate vs 5,000 U/mL heparin	BE	19	70	3,196	100%	No	U	U	OL
Dogra[9] (2002)	26.7 mg/mL gentamicin + 1.04% citrate vs 5,000 U/mL heparin	AU	79	58	5,923	100%	Yes	A	A	DB
Pervez[10] (2002)	18.2 mg/mL gentamicin + 4.6% citrate vs 1,000 U/mL heparin	USA	36	50	2,924	100%	No	U	U	OL
Betjes[11] (2004)	1.35% taurolidine + 4% citrate vs 5,000 U/mL heparin	NL	58	54	3,404	23.7%	No	A	U	OL
Weijmer[6] (2005)	30% citrate vs 5,000 U/mL heparin	NL	291	61	16,547	33.7%	Yes	A	A	DB
Nori[12] (2006)	4 mg/mL gentamicin + 3.13% citrate vs 5,000 U/mL heparin	USA	40	58	3,736	100%	No	A	U	OL
MacRae[5] (2008)	4% citrate vs 5,000 U/mL heparin	CA	61	66	4,091	100%	No	I	U	OL
Power[2] (2009)	46.7% citrate vs 5% heparin	UK	232	62	36,108	100%	Yes	A	U	OL
Solomon[13] (2010)	1.35% taurolidine + 4% citrate vs 5,000 U/mL heparin	UK	107	58	17,771	100%	Yes	A	A	DB
Filiopoulos[14] (2011)	1.35% taurolidine + 4% citrate vs 5,000 U/mL heparin	GR	117	74	4,195	0%	Yes	U	U	OL
Maki[15] (2011)	7.0% citrate + 0.15% methylene blue + 0.15% methylparaben + 0.015% propylparaben vs 5,000 U/mL heparin	USA	407	62	49,669	100%	Yes	A	U	OL
Moran[3] (2012)	320 μg/mL gentamicin + 4% citrate vs 1,000 U/mL heparin	USA	303	63	72,760	100%	No	A	A	PB

Abbreviations: A, adequate; AU, Australia; BE, Belgium; CA, Canada; DB, double-blind; I, inadequate; GR, Greece. ITT, intention-to-treat; NL, the Netherlands; OL, open-label; PB, patient-blind; SI, Slovenia; U, unclear; UK, United Kingdom; USA, United States of America.

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Citrate alone vs. Heparin							
Weijmer 2005	9	8431	33	8116	15.0%	0.26 [0.13, 0.55]	2005
Macrae 2008	5	2273	6	1818	7.7%	0.67 [0.20, 2.18]	2008
Power 2009	13	19008	12	17100	13.9%	0.97 [0.44, 2.14]	2009
Subtotal (95% CI)		**29712**		**27034**	**36.5%**	**0.54 [0.22, 1.30]**	
Total events	27		51				
Heterogeneity: Tau² = 0.40; Chi² = 5.99, df = 2 (P = 0.05); I² = 67%							
Test for overall effect: Z = 1.37 (P = 0.17)							
1.2.2 Citrate + gentamicin vs. Heparin							
Pervez 2002	1	1613	4	1311	2.7%	0.20 [0.02, 1.82]	2002
Dogra 2002	0	3280	7	2643	1.6%	0.05 [0.00, 0.94]	2002
Nori 2006	0	2002	7	1734	1.6%	0.06 [0.00, 1.01]	2006
Moran 2012	11	39827	30	32933	16.1%	0.30 [0.15, 0.60]	2012
Subtotal (95% CI)		**46722**		**38621**	**22.0%**	**0.25 [0.13, 0.47]**	
Total events	12		48				
Heterogeneity: Tau² = 0.00; Chi² = 2.61, df = 3 (P = 0.46); I² = 0%							
Test for overall effect: Z = 4.34 (P < 0.0001)							
1.2.3 Citrate + taurolidine vs. Heparin							
Betjes 2004	0	1519	4	1885	1.5%	0.14 [0.01, 2.56]	2004
Solomon 2010	11	8129	23	9642	15.4%	0.57 [0.28, 1.16]	2010
Filiopoulos 2011	8	2179	20	2016	13.2%	0.37 [0.16, 0.84]	2011
Subtotal (95% CI)		**11827**		**13543**	**30.1%**	**0.45 [0.27, 0.77]**	
Total events	19		47				
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 2 (P = 0.53); I² = 0%							
Test for overall effect: Z = 2.93 (P = 0.003)							
1.2.4 Citrate + methylene blue + methylparaben + propylparaben vs. Heparin							
Maki 2011	6	25274	20	24395	11.4%	0.29 [0.12, 0.72]	2011
Subtotal (95% CI)		**25274**		**24395**	**11.4%**	**0.29 [0.12, 0.72]**	
Total events	6		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.66 (P = 0.008)							
Total (95% CI)		**113535**		**103593**	**100.0%**	**0.39 [0.27, 0.56]**	
Total events	64		166				
Heterogeneity: Tau² = 0.10; Chi² = 13.73, df = 10 (P = 0.19); I² = 27%							
Test for overall effect: Z = 5.03 (P < 0.00001)							

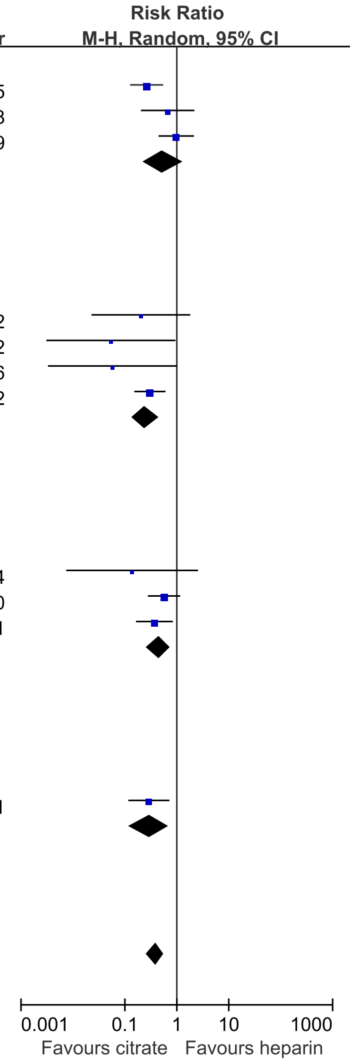

Figure 2. Catheter-related bloodstream infection per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

(3 studies[5,7,13]), bleeding episodes (2 studies[5,6]), catheter thrombosis (2 studies[10,14]), and catheter-related readmission (2 studies[2,6]). Characteristics of RCTs fulfilling the inclusion criteria are listed in Table 1.

Although all included studies were identified as randomized, only 8 described the method used to generate the random allocation sequence. Of note, in one study, patients were randomly assigned according to the initial letter of their last name; thus, it could be regarded as half-randomized only. Allocation concealment was well described in 4 studies. Three trials were double blinded and one study was patient blinded, whereas all others were open label. Six studies used intention-to-treat analysis (Table 1).

Catheter-Related Bloodstream Infection

Eleven studies (1,731 patients; 217,128 catheter-days) reported on CRBSI. The incidence of CRBSI was significantly lower with citrate locks compared with heparin locks alone (RR, 0.39; 95% CI, 0.27-0.56; $P < 0.001$). We examined possible sources of underlying heterogeneity across studies by using metaregression (Table S1). Results suggested that heterogeneity may be explained in part by type of citrate lock ($P = 0.02$). In addition, we also performed subgroup analysis basing on different citrate concentrations, which was considered to be of clinical importance. According to the subgroup analysis by type of citrate lock, citrate alone is similar to heparin in the prevention of CRBSI (RR, 0.54; 95% CI, 0.22-1.30; $P = 0.2$), whereas citrate plus gentamicin ($P < 0.001$), citrate plus taurolidine ($P = 0.003$), and citrate plus methylene blue plus methylparaben plus propylparaben ($P = 0.008$) were all superior to heparin (Fig 2). In subgroup analysis by citrate concentration, it was interesting to find that low (1.04%-4%) and moderate (4.6%-7%) concentrations of citrate lock solution were both

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 High concentration						
Power 2009	13	19008	12	17100	13.9%	0.97 [0.44, 2.14]
Weijmer 2005	9	8431	33	8116	15.0%	0.26 [0.13, 0.55]
Subtotal (95% CI)		**27439**		**25216**	**28.8%**	**0.50 [0.14, 1.83]**
Total events	22		45			
Heterogeneity: Tau² = 0.72; Chi² = 5.76, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 1.05 (P = 0.30)						
1.3.2 Moderate concentration						
Maki 2011	6	25274	20	24395	11.4%	0.29 [0.12, 0.72]
Pervez 2002	1	1613	4	1311	2.7%	0.20 [0.02, 1.82]
Subtotal (95% CI)		**26887**		**25706**	**14.0%**	**0.27 [0.12, 0.64]**
Total events	7		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						
1.3.3 Low concentration						
Betjes 2004	0	1519	4	1885	1.5%	0.14 [0.01, 2.56]
Dogra 2002	0	3280	7	2643	1.6%	0.05 [0.00, 0.94]
Filiopoulos 2011	8	2179	20	2016	13.2%	0.37 [0.16, 0.84]
Macrae 2008	5	2273	6	1818	7.7%	0.67 [0.20, 2.18]
Moran 2012	11	39827	30	32933	16.1%	0.30 [0.15, 0.60]
Nori 2006	0	2002	7	1734	1.6%	0.06 [0.00, 1.01]
Solomon 2010	11	8129	23	9642	15.4%	0.57 [0.28, 1.16]
Subtotal (95% CI)		**59209**		**52671**	**57.1%**	**0.38 [0.25, 0.58]**
Total events	35		97			
Heterogeneity: Tau² = 0.03; Chi² = 6.63, df = 6 (P = 0.36); I² = 10%						
Test for overall effect: Z = 4.43 (P < 0.00001)						
Total (95% CI)		**113535**		**103593**	**100.0%**	**0.39 [0.27, 0.56]**
Total events	64		166			
Heterogeneity: Tau² = 0.10; Chi² = 13.73, df = 10 (P = 0.19); I² = 27%						
Test for overall effect: Z = 5.03 (P < 0.00001)						

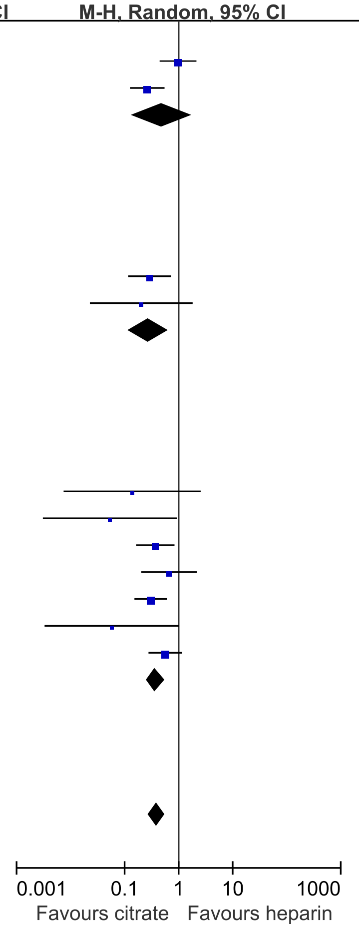

Figure 3. Catheter-related bloodstream infection per catheter-day. The analysis was stratified by citrate concentration. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

advantageous to heparin in terms of CRBSI ($P < 0.001$ and $P = 0.003$, respectively), but high-concentration (30%-46.7%) citrate was no better than heparin ($P = 0.3$; Fig 3).

Exit-Site Infection

A total of 8 RCTs (1,150 patients, 159,800 catheter-days) described exit-site infection. As shown in Fig 4, z test in a random-effects model seemed to show a decreased exit-site infection rate under citrate lock in comparison to heparin, but the difference was not statistically significant (RR, 0.73; 95% CI, 0.46-1.16; $P = 0.2$). In 4 studies, citrate alone was tested against heparin. Their results, when pooled, suggested the similarity in exit-site infection incidence of citrate and heparin locks when used alone (RR, 0.73; 95% CI, 0.35-1.53; $P = 0.4$). There are 2 studies that focused on citrate plus gentamicin, and 2 others, on citrate plus taurolidine. Both combinations failed to show an advantage over heparin in preventing exit-site infection ($P = 0.3$ and $P = 0.9$, respectively). When stratified by citrate concentration, subgroups of different citrate dosages were all similar in both arms regarding the incidence of exit-site infection ($P = 0.5$, $P = 0.7$, and $P = 0.4$; Fig 5).

Catheter Removal for Poor Flow

Seven studies (1,247 patients, 164,982 catheter-days) reported catheters being removed for poor blood flow. As shown in Fig 6, no difference was identified between patients receiving citrate locks and heparin locks regarding the number of catheters drawn for flow problems (RR, 1.00; 95% CI, 0.73-1.36; $P = 0.9$). Neither citrate alone ($P = 0.8$) nor in combination with other antimicrobials ($P = 0.9$) could reduce catheter removal for poor flow in comparison to heparin. As to citrate locks of different concentrations (Fig 7), 5 RCTs were categorized into the low-concentration group, whereas there was only one study each for moderate and high concentrations. Premature removal of catheters locked with citrate and heparin solution was similar in these subgroups ($P = 0.6$, $P = 0.1$, and $P = 0.7$, respectively).

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.2.1 Citrate alone vs. Heparin							
Hendrickx 2001	7	1703	5	1493	11.8%	1.23 [0.39, 3.86]	2001
Weijmer 2005	11	8431	32	8116	21.6%	0.33 [0.17, 0.66]	2005
Macrae 2008	5	2273	6	1818	11.2%	0.67 [0.20, 2.18]	2008
Power 2009	13	19008	9	17100	17.3%	1.30 [0.56, 3.04]	2009
Subtotal (95% CI)		**31415**		**28527**	**61.8%**	**0.73 [0.35, 1.53]**	
Total events	36		52				
Heterogeneity: Tau² = 0.34; Chi² = 7.50, df = 3 (P = 0.06); I² = 60%							
Test for overall effect: Z = 0.83 (P = 0.41)							
2.2.2 Citrate + gentamicin vs. Heparin							
Dogra 2002	1	3280	4	2643	4.1%	0.20 [0.02, 1.80]	2002
Moran 2012	8	39827	9	32933	15.1%	0.74 [0.28, 1.90]	2012
Subtotal (95% CI)		**43107**		**35576**	**19.2%**	**0.57 [0.20, 1.57]**	
Total events	9		13				
Heterogeneity: Tau² = 0.10; Chi² = 1.14, df = 1 (P = 0.29); I² = 12%							
Test for overall effect: Z = 1.09 (P = 0.28)							
2.2.3 Citrate + taurolidine vs. Heparin							
Betjes 2004	2	1519	4	1885	6.4%	0.62 [0.11, 3.38]	2004
Solomon 2010	7	8129	6	9642	12.6%	1.38 [0.47, 4.12]	2010
Subtotal (95% CI)		**9648**		**11527**	**19.0%**	**1.09 [0.44, 2.74]**	
Total events	9		10				
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0%							
Test for overall effect: Z = 0.19 (P = 0.85)							
Total (95% CI)		**84170**		**75630**	**100.0%**	**0.73 [0.46, 1.16]**	
Total events	54		75				
Heterogeneity: Tau² = 0.14; Chi² = 10.38, df = 7 (P = 0.17); I² = 33%							
Test for overall effect: Z = 1.33 (P = 0.19)							

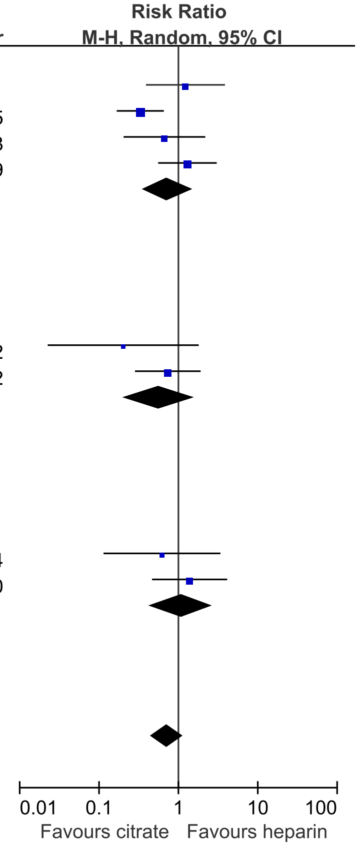

Figure 4. Exit-site infection per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Thrombolytic Treatment

There were 6 RCTs (992 patients, 150,118 catheter-days) included in the analysis of thrombolytic treatment. The overall summary RR using the random-effects model was 1.08 (95% CI, 0.65-1.80; $P = 0.8$), indicating a similar need for thrombolytic treatment between patients randomly assigned to receive citrate and heparin locks (Fig 8). Subgroup analysis was performed further, stratifying the 6 RCTs into 3 subgroups: citrate alone (3 studies), citrate plus gentamicin (2 studies), and citrate plus taurolidine (1 study). A borderline statistically significant difference was identified regarding the need for thrombolytic treatment between the citrate plus gentamicin and heparin groups ($P = 0.05$). There was no difference found between the 2 arms in subgroup analysis by citrate concentration ($P = 0.2$, $P = 0.4$, and $P = 0.9$, respectively; Fig 9).

Secondary Outcomes

There were 2 RCTs (352 patients, 20,638 catheter-days) comparing bleeding episodes between 2 kinds of lock solutions. Meta-analysis in the random-effects model suggested citrate lock as a better choice than heparin to avoid bleeding (RR, 0.48; 95% CI, 0.30-0.76; $P = 0.002$). Other secondary outcomes analyzed in the meta-analysis included all-cause death, catheter thrombosis, CRBSI-free catheter survival, mean catheter duration, and catheter-related readmission. However, no difference was detected in these fields between the experimental and control groups. Results of pooled-analysis of each secondary outcome are shown in Table 2.

Publication Bias

Publication bias was evaluated using Egger test for CRBSI, which indicated a lack of publication bias ($t = -0.98$; $P = 0.4$) in the meta-analysis.

Sensitivity Analysis

In order to assess the stability of the results of the present meta-analysis, we performed a one-study–removed sensitivity analysis for CRBSI incidence. Statistically similar results were obtained after omitting each of the studies (Table 3), indicating the stability of this meta-analysis.

DISCUSSION

This systematic review and meta-analysis of 13 RCTs provides insights into the comparison of citrate locks and heparin locks regarding CRI and catheter patency.

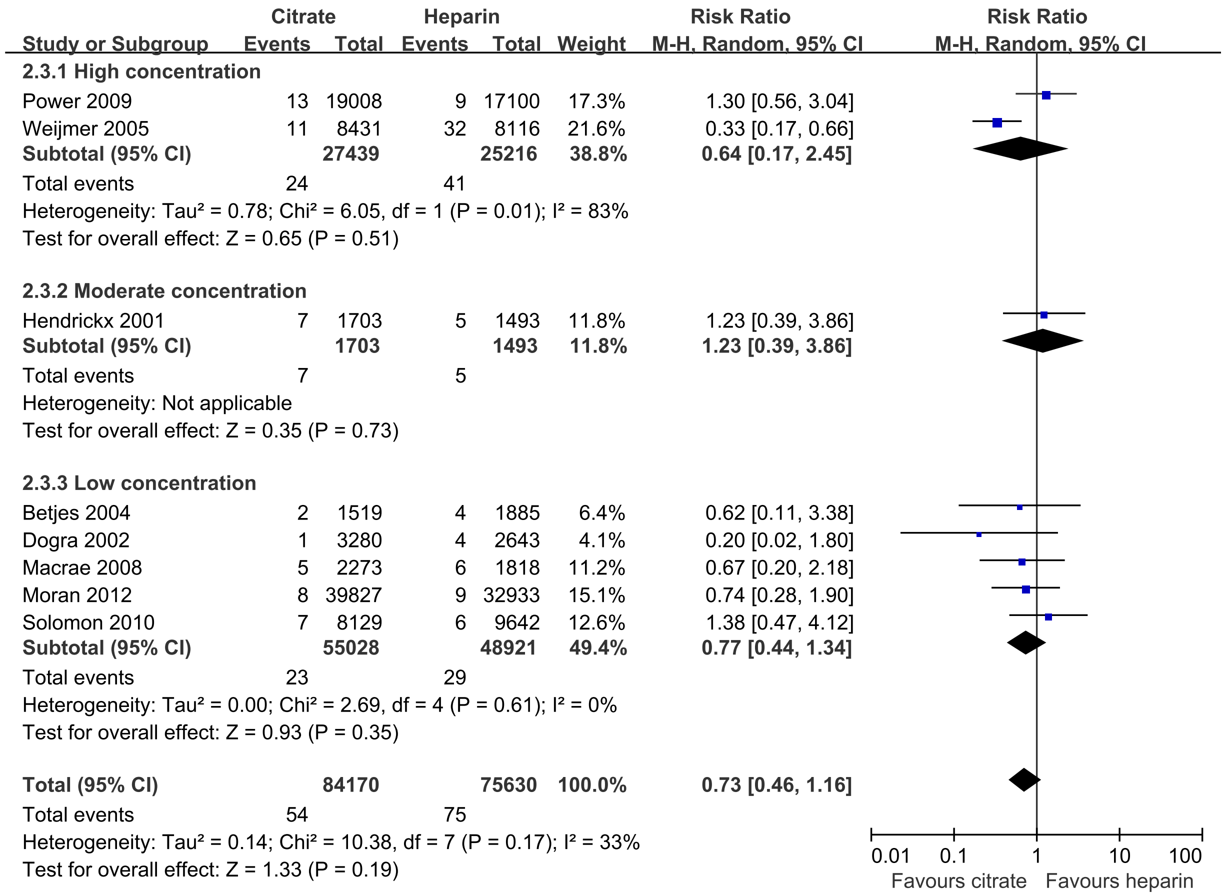

Figure 5. Exit-site infection per catheter-day. The analysis was stratified by citrate concentration. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Our study demonstrated that citrate in combination with other antimicrobials results in a reduction in CRBSIs, whereas no difference between citrate and heparin locks was identified in preserving catheter patency.

Although efforts have been made to minimize the use of catheters for maintenance hemodialysis, the proportion of patients dialyzed through CVCs has not yet declined.[16] More effective strategies to protect hemodialysis patients from CRIs and catheter malfunction are urgently needed.[15] Locking the CVC lumen with heparin solutions has become an accepted practice to avoid thrombosis between dialysis sessions,[2] but heparin locks might cause unintentional systemic anticoagulation and bleeding episodes,[17] as well as heparin-induced thrombocytopenia. A variety of new lock solutions therefore have been developed, of which citrate has drawn much interest.

Three previous meta-analyses have shown that antimicrobial and antibiotic lock solutions could effectively reduce the frequency of CRBSI without significant side effects,[18-20] but they did not focus on comparing citrate with heparin. In the present study, we identified the superiority of citrate locks in preventing CRBSIs, which was consistent with a previous systematic review by Yahav et al.[20] Subgroup analyses by type of citrate lock revealed that citrate in combination with other antimicrobials (gentamicin, taurolidine, methylparaben, etc) was associated with a lower incidence of CRBSI, but citrate alone did not show a similar advantage over heparin. Bosma et al[21] further demonstrated that using a 30% citrate solution for catheter locking reduced the formation of microbial biofilm in hemodialysis catheters and culture-positive colonization, explaining the observed prevention of CRBSI by citrate locking. A stratified analysis of different citrate concentrations confirmed the superiority of low- and moderate-concentration citrate over heparin; for citrate locks of high concentration, interestingly, the incidence of CRBSI in both arms was similar. As early as 2000, the US Food and Drug Administration warned that concentrated trisodium citrate (46.7%) should not be used as a catheter-locking solution because of a reported death from cardiac arrest after a mistaken bolus injection of 46.7% citrate systemically[22]; highly concentrated citrate then became unavailable in the United States. Apart from arrhythmias, the

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Citrate alone vs. Heparin						
Buturovic 1998	1	510	1	230	1.3%	0.45 [0.03, 7.18]
Macrae 2008	8	2273	5	1818	7.7%	1.28 [0.42, 3.91]
Weijmer 2005	27	8431	29	8116	35.0%	0.90 [0.53, 1.51]
Subtotal (95% CI)		**11214**		**10164**	**44.0%**	**0.94 [0.59, 1.49]**
Total events	36		35			
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
4.3.2 Citrate+antimicrobials vs. Heparin						
Betjes 2004	1	1519	2	1885	1.7%	0.62 [0.06, 6.84]
Maki 2011	0	25274	4	24395	1.1%	0.11 [0.01, 1.99]
Moran 2012	42	39827	35	32933	47.7%	0.99 [0.63, 1.55]
Solomon 2010	8	8129	3	9642	5.5%	3.16 [0.84, 11.92]
Subtotal (95% CI)		**74749**		**68855**	**56.0%**	**1.06 [0.41, 2.69]**
Total events	51		44			
Heterogeneity: Tau² = 0.38; Chi² = 5.26, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**85963**		**79019**	**100.0%**	**1.00 [0.73, 1.36]**
Total events	87		79			
Heterogeneity: Tau² = 0.00; Chi² = 5.97, df = 6 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						

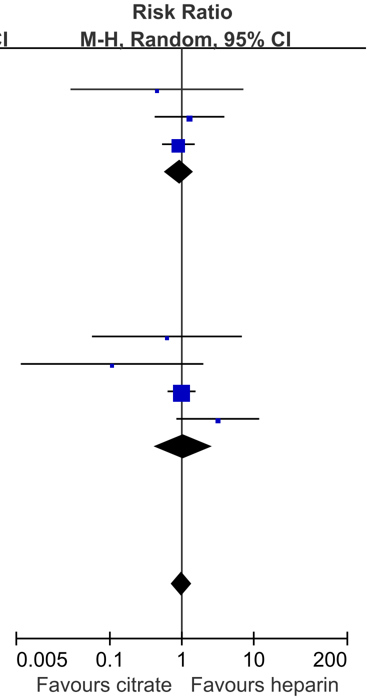

Figure 6. Catheter removal for poor flow per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 High concentration						
Weijmer 2005	27	8431	29	8116	35.0%	0.90 [0.53, 1.51]
Subtotal (95% CI)		**8431**		**8116**	**35.0%**	**0.90 [0.53, 1.51]**
Total events	27		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
4.4.2 Moderate concentration						
Maki 2011	0	25274	4	24395	1.1%	0.11 [0.01, 1.99]
Subtotal (95% CI)		**25274**		**24395**	**1.1%**	**0.11 [0.01, 1.99]**
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
4.4.3 Low concentration						
Betjes 2004	1	1519	2	1885	1.7%	0.62 [0.06, 6.84]
Buturovic 1998	1	510	1	230	1.3%	0.45 [0.03, 7.18]
Macrae 2008	8	2273	5	1818	7.7%	1.28 [0.42, 3.91]
Moran 2012	42	39827	35	32933	47.7%	0.99 [0.63, 1.55]
Solomon 2010	8	8129	3	9642	5.5%	3.16 [0.84, 11.92]
Subtotal (95% CI)		**52258**		**46508**	**63.8%**	**1.10 [0.75, 1.62]**
Total events	60		46			
Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 4 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**85963**		**79019**	**100.0%**	**1.00 [0.73, 1.36]**
Total events	87		79			
Heterogeneity: Tau² = 0.00; Chi² = 5.97, df = 6 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						

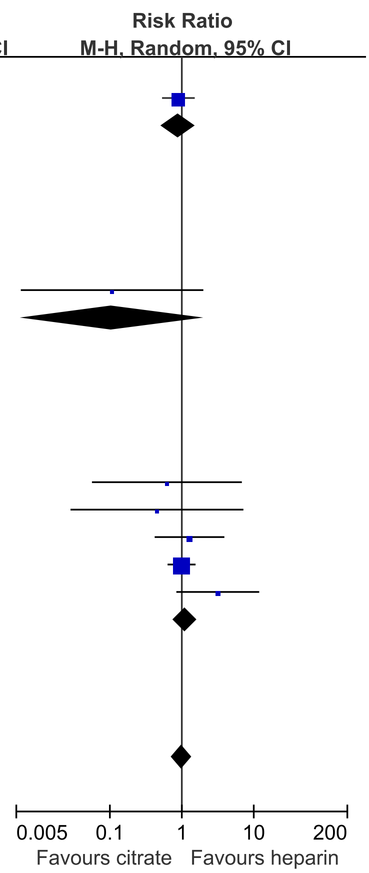

Figure 7. Catheter removal for poor flow per catheter-day. The analysis was stratified by citrate concentration. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
3.2.1 Citrate alone vs. Heparin							
Hendrickx 2001	6	1703	8	1493	11.2%	0.66 [0.23, 1.89]	2001
Weijmer 2005	69	8431	63	8116	19.5%	1.05 [0.75, 1.48]	2005
Power 2009	153	19008	74	17100	20.1%	1.86 [1.41, 2.45]	2009
Subtotal (95% CI)		**29142**		**26709**	**50.7%**	**1.25 [0.74, 2.11]**	
Total events	228		145				
Heterogeneity: Tau² = 0.15; Chi² = 8.63, df = 2 (P = 0.01); I² = 77%							
Test for overall effect: Z = 0.82 (P = 0.41)							
3.2.2 Citrate + gentamicin vs. Heparin							
Nori 2006	4	2002	10	1734	10.2%	0.35 [0.11, 1.10]	2006
Moran 2012	94	39827	113	32933	20.1%	0.69 [0.52, 0.90]	2012
Subtotal (95% CI)		**41829**		**34667**	**30.3%**	**0.62 [0.38, 1.00]**	
Total events	98		123				
Heterogeneity: Tau² = 0.05; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%							
Test for overall effect: Z = 1.95 (P = 0.05)							
3.2.3 Citrate + taurolidine vs. Heparin							
Solomon 2010	79	8129	38	9642	19.0%	2.47 [1.68, 3.63]	2010
Subtotal (95% CI)		**8129**		**9642**	**19.0%**	**2.47 [1.68, 3.63]**	
Total events	79		38				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.59 (P < 0.00001)							
Total (95% CI)		**79100**		**71018**	**100.0%**	**1.08 [0.65, 1.80]**	
Total events	405		306				
Heterogeneity: Tau² = 0.32; Chi² = 45.18, df = 5 (P < 0.00001); I² = 89%							
Test for overall effect: Z = 0.29 (P = 0.77)							

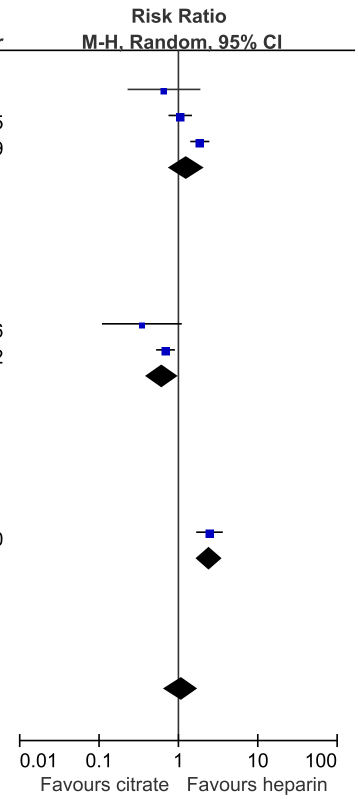

Figure 8. Thrombolytic treatment per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

application of high-concentration citrate locks also is hampered by potential toxicity and allergic reactions. The American Society of Diagnostic and Interventional Nephrology (ASDIN) and European Renal Best Practice (ERBP) both proposed to use 4% rather than a high concentration of citrate as a catheter lock,[23,24] which is supported by the findings of the present meta-analysis.

Eight trials assessed the difference in exit-site infection rates between the experimental and control groups. Only one RCT identified a statistically significant reduction in exit-site infection incidence in the citrate lock group,[6] whereas other studies had negative findings. When their results were pooled in an overall analysis, no remarkable protective effect against exit-site infection was found for citrate locks. After categorization, neither citrate alone nor citrate lock solutions containing antimicrobials differed from heparin locks in terms of exit-site infection. Citrate locks of different concentrations were all similar to heparin regarding exit-site infection rates. In 2 studies, patients received additional antibiotic ointments at the exit site during dressing changes,[3,6] which possibly could have added to interstudy variation. However, because the experimental and control arms within a study underwent the same aseptic procedure, a marked bias in overall results seems unlikely.

In a previous meta-analysis, citrate locks reduced catheter removals from all causes per catheter-day.[20] However, in the present study, we chose only catheter removal for poor flow as an end point for the preservation of catheter patency, excluding confounding reasons such as CRI and discontinuation of hemodialysis therapy. We pooled results of 7 eligible RCTs, only to detect a lack of difference in the number of catheters removed for unsatisfactory patency between both arms. This incongruity might be attributed to the fact that: (1) we focused on a narrower spectrum of catheter removal, and (2) our study is likely to be better powered by including several recent large-scale RCTs.[3,13,15] In accordance with the literature,[20,25] thrombolytic treatments and thrombosis episodes were similar between citrate and heparin locks.

In terms of other secondary end points, including all-cause death, CRBSI-free catheter survival, mean catheter duration, and catheter-related readmission, similar outcomes also were seen. Interestingly, the CRBSI rate was much lower with citrate, but CRBSI-free catheter survival was similar between the 2 groups. One possible explanation might be the limited studies and cases in the analysis of CRBSI-free catheter survival. There were 11 RCTs comparing the incidence of CRBSI between citrate and heparin, but only 3 of them reported CRBSI-free catheter survival during

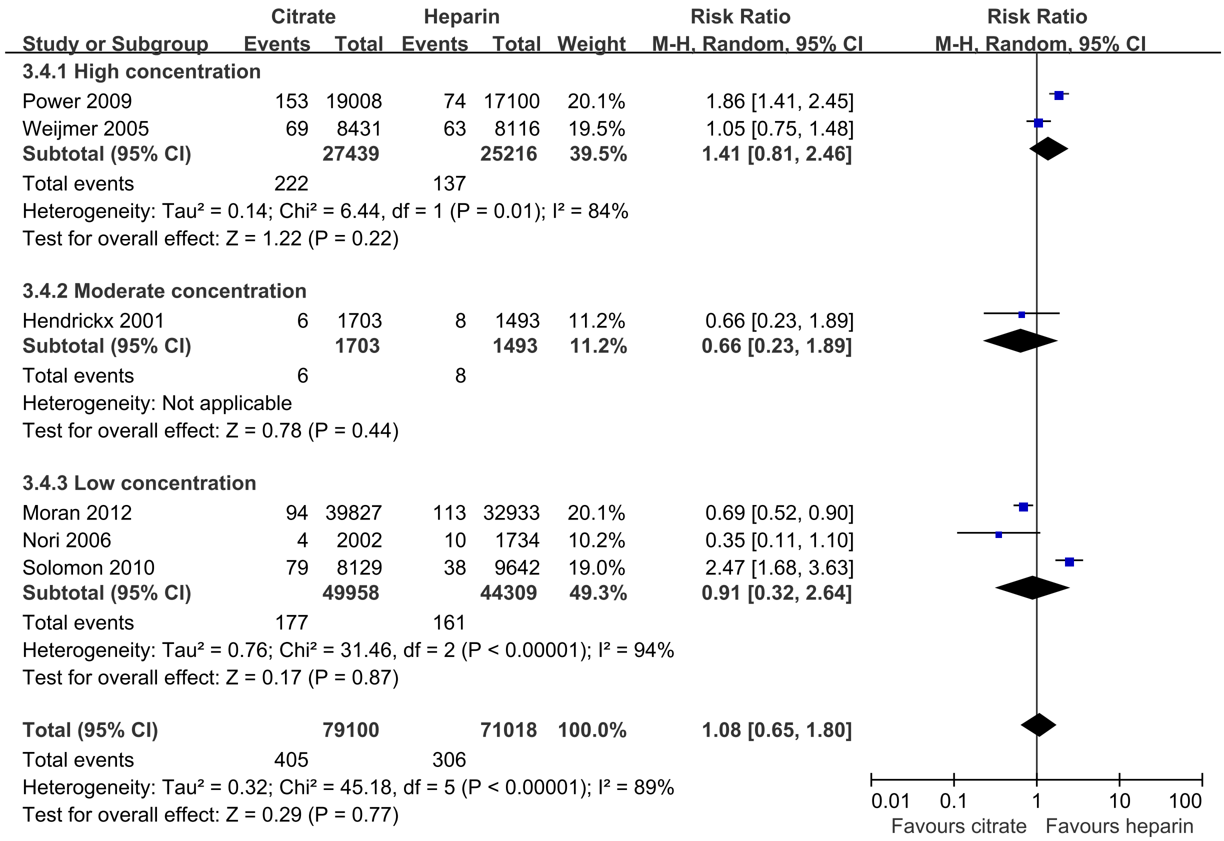

Figure 9. Thrombolytic treatment per catheter-day. The analysis was stratified by citrate concentration. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

follow-up. Taking this into consideration, the result regarding CRBSI-free catheter survival has to be interpreted within the context of limitations, and more RCTs are warranted to give a solid conclusion.

It is of interest that citrate locks were associated with fewer bleeding episodes, which, to our knowledge, for the first time is confirmed by a meta-analysis. Nevertheless, this finding is consistent with previous literature.[26] However, because only 2 RCTs with limited case numbers (352 patients, 20,638 catheter-days) met our inclusion criteria,[5,6] results should be interpreted with caution until more large-scale RCTs are available.

Some limitations of our study should be noted. First, despite a total of 13 RCTs being included in this meta-analysis, eligible studies comparing specific outcomes usually were limited. We therefore did not perform subgroup analysis based on parameters such as catheter type, heparin dosage, and other differences in individual unit practices, which possibly might have added to heterogeneity. Second, although we extracted data at the end of follow-up, the duration of each study varied. Even so, although end points of different follow-up periods could modify the absolute risk, it should not bias the overall RR. Third, all

Table 2. Pooled Analysis and Heterogeneity Analysis of Secondary Outcomes

Outcome	No. of Studies	RR or WMD[a] (95% CI)	*z* Score	*P*	Description
All-cause death	7	0.81 (0.53 to 1.23)	1.00	0.3	RR < 1; favors citrate
Bleeding episode	2	0.48 (0.30 to 0.76)	3.07	0.002	RR < 1; favors citrate
Catheter-related readmission	2	0.61 (0.13 to 2.74)	0.65	0.5	RR < 1; favors citrate
Catheter thrombosis	2	1.04 (0.46 to 2.34)	0.09	0.9	RR > 1; favors heparin
CRBSI-free catheter survival	3	1.74 (0.72 to 4.19)	1.23	0.2	RR > 1; favors citrate
Mean catheter duration	3	−32.81 (−82.91 to 17.29)	1.28	0.2	WMD < 0; favors heparin

Abbreviations: RR, risk ratio; CI, confidence interval; CRBSI, catheter-related bloodstream infection; WMD, weighted mean difference.

[a]Value shown is RR except for mean catheter duration, which is given as WMD.

Table 3. Sensitivity Analysis by Omitting Each Study In Random-Effects Model

Study Omitted	RR (95% CI)
Dogra[9] (2002)	0.40 (0.29-0.57)
Pervez[10] (2002)	0.39 (0.27-0.58)
Betjes[11] (2004)	0.39 (0.27-0.57)
Weijmer[6] (2005)	0.41 (0.27-0.62)
Nori[12] (2006)	0.40 (0.28-0.57)
MacRae[5] (2008)	0.37 (0.25-0.55)
Power[2] (2009)	0.34 (0.25-0.47)
Solomon[13] (2010)	0.36 (0.24-0.54)
Maki[15] (2011)	0.40 (0.26-0.60)
Filiopoulos[14] (2011)	0.38 (0.25-0.59)
Moran[3] (2012)	0.40 (0.26-0.61)

Note: RR $<$ 1 favors citrate. $P < 0.001$ for all.
Abbreviation: CI, confidence interval; RR, risk ratio.

studies used in the meta-analysis were performed in Western countries. The applicability of our findings to other regions and other populations remains to be clarified. Last but not least, only studies covered by the selected databases were included for data analysis. The unavailability of unreported outcomes in some theses possibly could result in reporting bias. Regardless of these limitations, we have minimized bias throughout the process by our methods of study identification, data selection, and statistical analysis, as well as in our control of publication bias and sensitivity. These steps should strengthen the stability and accuracy of the meta-analysis.

To conclude, this systematic review and meta-analysis demonstrated that locking CVCs with antimicrobial-containing citrate solutions could effectively reduce the incidence of CRBSIs. Low- to moderate-concentration, rather than high-concentration, citrate locks were superior to heparin in preventing CRBSI. Citrate also might decrease bleeding episodes in hemodialysis patients, although no difference was found between citrate and heparin locks in the prevention of exit-site infection or maintenance of catheter patency. More RCTs of either temporary or tunneled catheters are required to confirm our findings and assess the safety and optimal dosage of citrate lock.

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SUPPLEMENTARY MATERIAL

Table S1: Meta-regression of CRBSI.
Item S1: Search strategy in PubMed.
Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.08.016) is available at www.ajkd.org

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