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NEPHROLOGY - ORIGINAL PAPER

Citrate versus heparin lock for prevention of hemodialysis catheter-related complications: updated systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective To provide updated evidence, we conducted a systematic review and meta-analysis to compare citrate lock with heparin in the prevention of hemodialysis catheter-related complications.

Methods A systematic review and meta-analysis of randomized controlled trials were obtained by searching PubMed, EMBASE, Ovid, Cochrane library, and the Web of Science databases. Primary outcomes were catheter-related bloodstream infections (CRBI), exit-site infections, bleeding events, catheter removal for poor flow, and thrombolytic treatment. Secondary outcomes were thrombocytopenia, access-related admission, and all-cause mortality.

Results The meta-analysis showed that the citrate lock containing antimicrobials can reduce the risk of CRBI when compared with heparin lock (RR: 0.34, 95% CI 0.24–0.49; $I^2=0\%$; $P<0.00001$), and a tunneled cuffed catheter (TCC) was more beneficial for the prevention of CRBI (RR: 0.42, 95% CI 0.25–0.69; $I^2=40\%$; $P=0.0007$) when compared with non-tunneled cuffed catheters (NTCC). The microbiological correlation analysis suggests that the occurrence of CRBI is closely related to *S. aureus* in catheters locked by citrate ($P=0.015$) rather than by heparin ($P=0.868$). In the analysis of exit-site infection, citrate lock with NTCC was more effective in preventing exit-site infection than heparin (RR: 0.48, 95% CI 0.31–0.75; $I^2=0\%$; $P=0.001$). In addition, the risk of bleeding episodes was reduced in hemodialysis patients using citrate lock with TCC (RR: 0.53, 95% CI 0.32–0.86; $I^2=0\%$; $P=0.01$) and patients with citrate alone (RR: 0.51, 95% CI 0.30–0.85; $I^2=12\%$; $P=0.010$). The risk of catheter removal for poor flow ($P=0.91$), thrombolytic treatment ($P=0.76$), thrombocytopenia ($P=0.37$), access-related admission ($P=0.10$), and all-cause mortality ($P=0.62$) was not significantly different.

Conclusions Antimicrobial-containing citrate lock solutions could reduce the risk of CRBI in hemodialysis patients. The occurrence of CRBI is closely related to *S. aureus* in catheters locked by citrate rather than by heparin. Citrate lock was effective in reducing exit-site infection in NTCC and bleeding events in TCC.

Keywords Citrate lock · Heparin · Hemodialysis · Updated meta-analysis

Hongxia Mai and Yuliang Zhao have contributed equally to this work.

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Introduction

Despite arteriovenous fistulas being the preferred mean of vascular access in hemodialysis patients, central venous catheters (CVCs) are a commonly used alternative, particularly in patients susceptible to fistula failure. However, problems with catheter-related infection and catheter-related dysfunction greatly limit the application of indwelling catheter. Effective catheter lock during dialysis is of crucial importance in maintaining catheter patency. Heparin is currently the most widely used catheter lock solution. However, there have been many reports on the adverse reactions of long-term heparin lock such as infection, hemorrhage, and catheter dysfunction, warranting a better lock solution to reduce complications related to hemodialysis catheters. Citrate is a local anticoagulant that blocks the coagulation cascade reaction by complexing blood calcium ions and does not affect the system coagulation function [1]. Studies have also shown that citrate has certain antibacterial activity [2]. As a kind of safe and effective, and antibacterial lock, citrate has drawn more and more attention in recent years.

Although the comparisons between citrate and heparin lock for the prevention of hemodialysis catheter-related complications have been reported in previous systematic reviews, the results are not consistent. In one study, it was reported that citrate lock containing antimicrobial agents is more effective in preventing CRBI while citrate alone fails to show a similar advantage [1]. On the contrary, a meta-analysis showed that the use of citrate alone can reduce the occurrence of CRBI, hemorrhage, and exit-site infection [2]. New RCT studies have been published in recent years [3–5]. Since previous meta-analysis did not take into account catheter type, bacteria analysis, and other important considerations, an updated meta-analysis of lock solutions was needed to further clarify the advantages and disadvantages of citrate compared with heparin in preventing catheter-related infections, bleeding events, and catheter dysfunction in hemodialysis patients with CVCs.

Methods

Search strategy

Two independent reviewers (M.H. and Z.Y.) conducted literature search in PubMed, EMBASE, Ovid, Cochrane Library, and Web of Science. No language or date restrictions were imposed. The last search was conducted in September 2018. Search terms were as follows: "hemodialysis or dialysis or renal replacement therapy or blood purification" and "lock or filling solution" and "catheter." Only published human prospective randomized controlled trials (RCTs) were included.

Study selection, data extraction and quality assessment

The inclusion criteria were as follows: (1) the studies were prospective RCTs involving human subjects, (2) the experimental group received a citrate lock (with or without other antimicrobials) and the control group received a heparin lock alone, (3) there were reports on adverse events including catheter-related infection (CRI), exit-site infection, catheter removal for poor flow, thrombolytic treatment, bleeding events, readmission, and death, and (4) sufficient data were available to obtain a risk ratio (RR) or weighted mean difference with a 95% confidence interval (95% CI). The following exclusion criteria were used: (1) studies that focused on treatment, not prophylaxis, (3) nonhuman studies, (4) studies that were not prospective. In terms of duplicate reports, we selected those with the largest number of cases or the most recent updates, judging from the aspects of publication year, type and topic of articles, main authors, data source, experimental design and data integrity. Two investigators (M.H. and Z.Y.) reviewed each study independently and recorded eligibility, quality, and outcomes, with disagreements resolved by discussion. We extracted the study characteristics: first author, publication year, published journal, intervention, endpoint, number of patients, mean age of patients, percentage of tunneled catheters, number of catheter-days, dialysis vintage, duration of follow-up, intention-to-treat analysis, blinding, randomization method, and allocation concealment method. When the information is incomplete, we contacted the original author for missing data. If complete data was still not available, this article was excluded. In case of disagreement, the third researcher was invited to discuss and solve the problem.

Two authors (M.H. and Z.Y.) independently evaluated the methodological quality of the included studies for major potential sources of bias using the Cochrane Collaboration's risk of bias tool, which includes method of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (detection bias), selective reporting (detection bias) and other sources of bias. We evaluated the methodological quality of each study on each criterion as "low, high or unclear risk of bias.

Study outcomes

The primary outcomes were: catheter-related bloodstream infection (CRBI, defined as being positive for bacteremia obtained from the dialysis catheter), exit-site infection (defined as appearance of exudates, crust, redness, or induration at the exit site), catheter removal for poor flow, need for thrombolytic treatments, and bleeding events. Secondary outcomes included thrombocytopenia, catheter-related readmission and all-cause death.

Statistical analysis

Dichotomous variables were expressed in terms of RR and 95% CI, and pooled in a random-effects model, with differences considered statistically significant at a significance level of $\alpha = 0.05$. Heterogeneity of literature was evaluated by the Q test and I^2 statistic ($I^2 \geq 75\%$, $I^2 = 50–74\%$ and $I^2 = 25–49\%$ were considered as high, moderate, or low heterogeneity, respectively) [6, 7].

In addition, a subgroup analysis was performed to further assess the relationship between heparin or citrate lock solution and hemodialysis catheter-related complications. Subgroup analysis was performed according to the type of citrate lock and different catheter types. The main objective of the subgroup analysis was to confirm the generality of the results and to explore possible explanations for heterogeneity in pooled analysis.

A sensitivity analysis was performed by comparing the results of this investigation to the results obtained when excluding each study individually, to assess the impact of the individual studies on our overall results (CRBI). The publication bias was examined by Egger's test.

The statistical analysis was performed using the Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), and STATA 12.0 software (STATA Corp., College Station, Texas, USA).

Results

Eligible studies

A total of 1727 relevant articles were searched in the initial retrieval. Of these, 807 articles were excluded due to duplication and 904 articles were removed due to the reasons listed in Fig. 1. After screening titles and abstract, 20 trials conducted from 1998 to 2018 were considered based on full-text review. Four of these trials were excluded due to insufficient data, resulting in 16 trials included in this meta-analysis. See Fig. 1 for details.

The eligible studies identified consisted of 2489 patients and 244,916 catheter-days in total. Eight of these studies compared citrate alone to heparin, while the remaining eight compared a mixture of citrate and other antimicrobials to heparin. The studies reported the rates of CRBI (14 trials), bleeding (4 trials), exit-site infection (9 trials), catheter removal for poor flow (8 trials), thrombolytic treatment (9 trials), thrombocytopenia (4 trials), access-related readmission (4 trials), and all-cause mortality (8 trials) at the end of follow-up (Table 1).

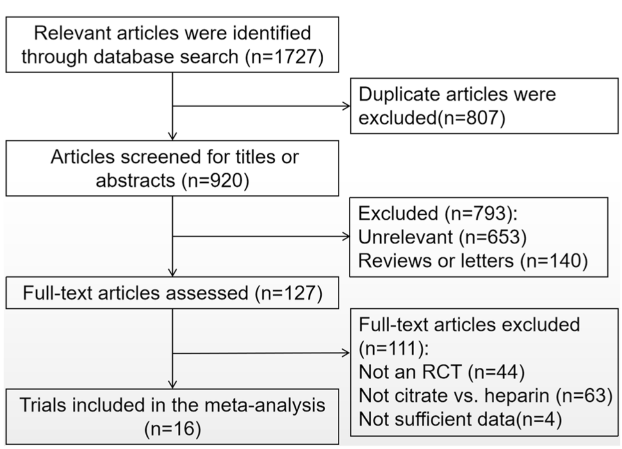

Fig. 1 Flow diagram of study selection. RCT, randomized controlled trial

Although the included studies were all RCT, only 11 studies provided detailed methods for generating random allocation sequences. One study was considered semi-random by allocating individuals according to the first letter of their last names. Seven studies state allocation concealment. Five trials were double blind, one was patient blind, and the remaining ten were open label. Seven studies carried out an intention-to-treat analysis (ITT analysis, Table 1). The methodological quality assessment of the included studies is shown in Table 2.

Catheter-related bloodstream infection

A total of 14 studies (2450 patients, 240,980 catheter-days) reported CRBI and concluded that the citrate lock containing antimicrobials can reduce the incidence of CRBI when compared with the heparin lock, without significant heterogeneity among studies (RR: 0.34, 95% CI 0.24–0.49; $I^2=0\%$; $P<0.00001$). Compared with heparin, citrate alone was not found to have a statistically significant reduction in risk, suggesting that citrate alone does not have much advantage in reducing the occurrence of CRBI (RR: 0.69, 95% CI 0.35–1.35; $I^2=72\%$; $P=0.28$). See Fig. 2 for details. In addition, a subgroup analysis was conducted based on different catheter types. The results of this analysis suggest that a tunneled cuffed catheter (TCC) was more beneficial when locked with citrate compared with heparin in terms of CRBI reduction (RR: 0.42, 95% CI 0.25–0.69; $I^2=40\%$; $P=0.0007$) (Fig. 3).

In the absence of citrate alone groups, we grouped citrate lock containing antimicrobials into those with non-tunneled cuffed catheters (NTCC) (0–33.7%) and those with tunneled cuffed catheters (TCC) (100%). There was a decline in RR from 0.52 to 0.34 and from 0.42 to 0.33, respectively; the heterogeneity significantly decreased from 75 to 0% and from 40 to 11%, respectively, indicating that the type of citrate lock and catheter was both likely the cause of heterogeneity among studies (Fig. 4).

Six studies (1071 patients, 153,722 catheter-days) reported the CRBI microbiology, as shown in Table 3. According to a correlation analysis of citrate group, the r value between *S. aureus* and CRBI is 0.850 ($P=0.015$), suggesting that the occurrence of CRBI is closely related to *S. aureus* in the citrate group. However, in the heparin group, no correlative factors were found in the occurrence of CRBI. The results highlighted the etiological importance of

Table 1 Characteristics of studies fulfilling the inclusion criteria

Refs.	Intervention (I)	Control (C)	Patients (I/C)	Mean age (years)	No. of catheter-days	Tunneled catheter (%)	Dialysis vintage (months; I/C)	Duration of follow-up (month)	ITT analysis	Allocation generation	Concealment	Blinding
Betjes et al. [8]	1.35% taurolidine + 4% citrate	5000 U/mL heparin	29/29	58.3/50.3	3404	23.70	–	–	No	A	U	OL
Buturovic et al. [9]	4% citrate	1666 U/mL heparin	10/10	63	740	0.00	–	–	No	U	U	OL
Dogra et al. [10]	26.7 mg/mL gentamicin + 1.04% citrate	5000 U/mL heparin	42/37	55.7/59.3	5923	100.00	–	–	Yes	A	A	DB
Filiopoulos et al. [11]	1.35% taurolidine + 4% citrate	5000 U/mL heparin	59/58	75/70	4195	0.00	34/41	3	Yes	U	U	OL
MacRae et al. [12]	4% citrate	5000 U/mL heparin	32/29	63/69	4091	100.00	10.5/9.0	2	No	I	U	OL
Maki et al. [13]	7.0% citrate + 0.15% methylene blue + 0.15% methylparaben + 0.015% propylparaben (C–MB–P)	5000 U/mL heparin	201/206	62.2/61.7	49669	100.00	–	6	Yes	A	U	OL
Moran et al. [14]	320 mg/mL gentamicin 1 + 4% citrate	1000 U/mL heparin	155/148	63.4/62.8	72,760	100.00	42.4/44.3	–	No	A	A	PB
Nori et al. [15]	4 mg/mL gentamicin + 3.13% citrate	5000 U/mL heparin	20/20	58/59	3736	100.00	–	6	No	A	U	OL
Pervez et al. [16]	18.2 mg/mL gentamicin 1 + 4.6% citrate	1000 U/mL heparin	14/22	53.7/47.6	2924	100.00	–	–	No	U	U	OL
Power et al. [17]	46.7% citrate	5% heparin	132/100	63/62	36,108	100.00	37/34	6	Yes	A	U	OL
Solomon et al. [18]	1.35% taurolidine + 4% citrate	5000 U/mL heparin	53/54	59.8/56.7	17,771	100.00	–	–	Yes	A	A	DB
Weijmer et al. [19]	30% citrate	5000 U/mL heparin	148/143	61.6/61.3	16,547	33.70	13.2/16.8	–	Yes	A	A	DB
Hendrickx et al. [20]	5% citrate	5000 U/mL heparin	10/9	74.6/71.4	3196	100.00	–	6	No	U	U	OL
Barcellos et al. [3]	30% citrate	5000 U/mL heparin	231/233	58.61/57.44	12,979	0.00	2.76/2.54	–	Yes	A	A	DB

Table 1 (continued)

Refs.	Intervention (I)	Control (C)	Patients (I/C)	Mean age (years)	No. of catheter-days	Tunneled catheter (%)	Dialysis vintage (months; I/C)	Duration of follow-up (month)	ITT analysis	Allocation generation	Concealment	Blinding
Luiz et al. [4]	30% citrate	1000 IU/mL heparin	22/23	53.5/53.2	2000/1957	0.00	–	4	No	A	A	DB
Abdel et al. [5]	4% citrate	5000μ/mL heparin	105/105	51.33/51.74	3628/3288	0.00	11.34/13.33	1	No	A	A	OL

A, adequate; I, inadequate; U, unclear; DB, double blind; PB, patient blind; OL, open label; ITT, intention to treat

S. aureus in CRBI hemodialysis patients locked with citrate solution rather than heparin.

Exit-site infection

Of the nine RCT studies reporting rates of exit-site infections (1360 patients, 166,716 catheter-days), five described citrate-alone lock on exit-site infection, and four reported citrate lock containing antimicrobials. A subgroup analysis was performed to evaluate the effects of citrate and heparin on exit-site infection. Using a random-effects model, it was shown that citrate lock with NTCC was more effective in preventing exit-site infection than heparin (RR: 0.48, 95% CI 0.31–0.75; $I^2=0\%$; $P=0.001$). The results showed that the risk of exit-site infection between citrate and heparin was similar with TCC (RR: 0.97, 95% CI, 0.62–1.51; $I^2=0\%$; $P=0.88$) (Fig. 5). Citrate lock containing antimicrobials did not significantly reduce the risk of exit-site infection compared to heparin without significant heterogeneity among studies (RR: 0.80, 95% CI 0.42–1.50; $I^2=0\%$; $P=0.48$) (Fig. 6).

Bleeding episodes

Four trials (969 patients, 77,223 catheter-days) reported on bleeding episodes. Bleeding events refer to a major bleeding episode immediately after catheter placement, such as gastrointestinal bleeding, exit-site bleeding, hematuria, or post-operative bleeding without persistent bleeding from the place of insertion after catheter placement. A subgroup analysis was again performed based on catheter types. The RR of the TCC subgroup was statistically significant (RR: 0.53, 95% CI 0.32–0.86; $I^2=0\%$; $P=0.01$), while the NTCC subgroup showed no difference (RR: 0.53, 95% CI 0.13–2.22; $I^2=52\%$; $P=0.38$), suggesting the types of catheter may lead to result heterogeneity (Fig. 7). As shown in Fig. 8, the risk of bleeding episodes in patients with citrate alone was lower than those with heparin, while the heterogeneity was 12% (RR: 0.51, 95% CI 0.30–0.85; $I^2=12\%$; $P=0.010$). Only one study for citrate lock containing antimicrobials reported bleeding episodes.

Catheter removal for poor flow

Eight studies (1457 patients, 171,898 catheter-days) reported catheter removal for poor flow. As shown in Fig. 9, neither citrate alone (RR: 0.99, 95% CI 0.66–1.49; $I^2=0\%$; $P=0.96$) nor the mixture of antimicrobial lock (RR: 1.06, 95% CI 0.41–2.69; $I^2=43\%$; $P=0.91$) reduced the risk of catheter removal for poor flow, compared to heparin lock. Similarly, no difference was identified in the NTCC (RR: 0.94, 95% CI 0.61–1.44; $I^2=0\%$; $P=0.77$) or TCC subgroups (RR: 1.18, 95% CI 0.57–2.44; $I^2=42\%$;

Table 2 Methodological quality of included studies

Refs.	Random sequence generation	Allocation conceal-ment	Blinding of participants and personnel	Blinding of outcome assess-ment	Incomplete outcome data	Selective reporting	Other sources of bias	Risk of bias
Betjes et al. [8]	–	?	+	?	–	?	–	+
Buturovic et al. [9]	?	?	?	?	?	?	–	?
Dogra et al. [10]	–	–	–	–	–	–	–	–
Filiopoulos et al. [11]	–	?	+	?	–	–	+	+
MacRae et al. [12]	+	+	+	+	–	–	+	+
Maki et al. [13]	–	?	–	–	–	–	–	?
Moran et al. [14]	–	–	–	–	–	–	–	–
Nori et al. [15]	–	?	?	?	–	–	–	?
Pervez et al. [16]	–	?	?	?	?	?	–	?
Power et al. [17]	–	–	?	?	–	+	–	+
Solomon et al. [18]	–	?	–	–	–	–	–	?
Weijmer et al. [19]	–	–	–	–	–	–	–	–
Hendrickx et al. [20]	?	?	+	?	–	?	–	+
Barcellos et al. [3]	–	–	–	–	–	–	–	–
Luiz et al. [4]	–	–	–	–	–	–	–	–
Abdel et al. [5]	–	–	+	?	–	–	+	+

Explanations: "+" means high risk of bias, "–" means low risk of bias, "?" means unclear risk of bias

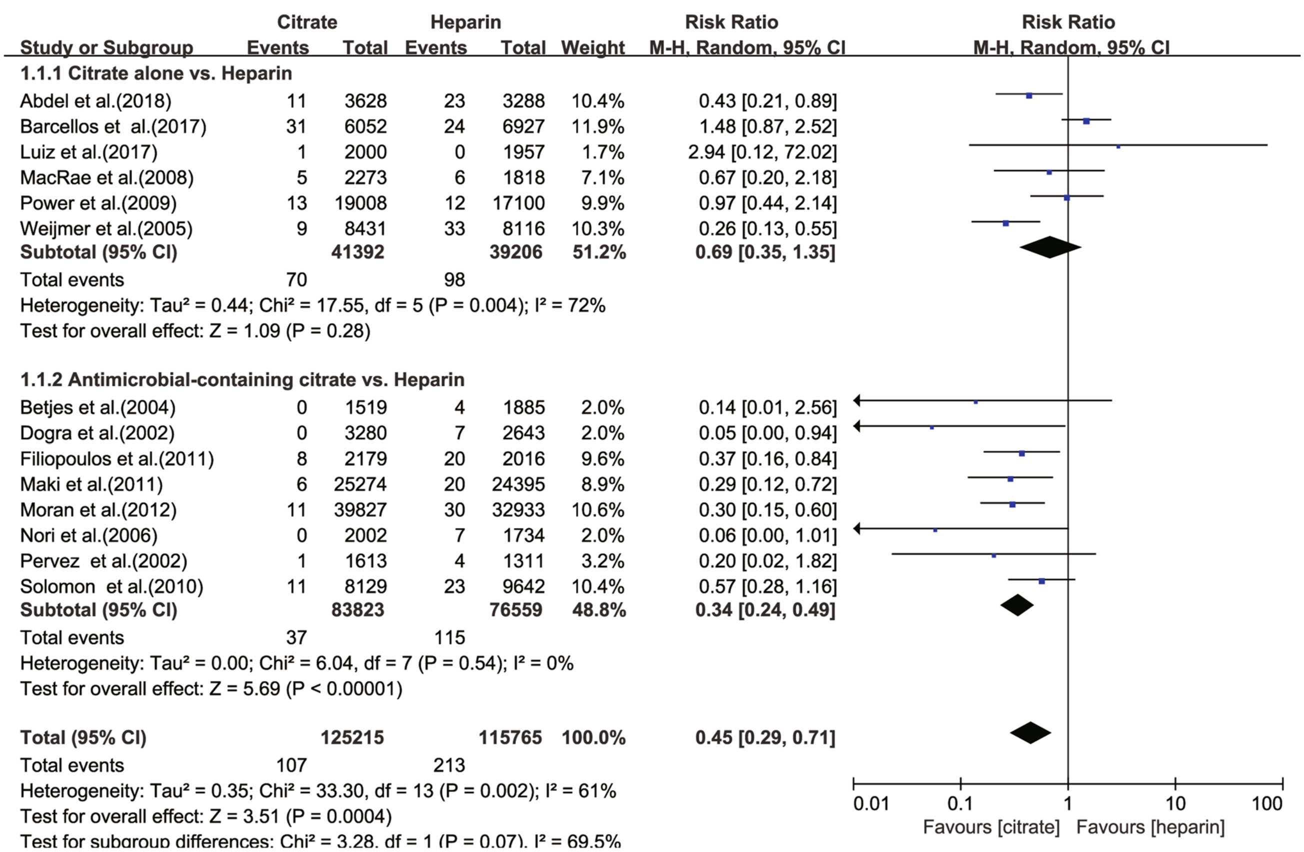

Fig. 2 Catheter-related bloodstream infection per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

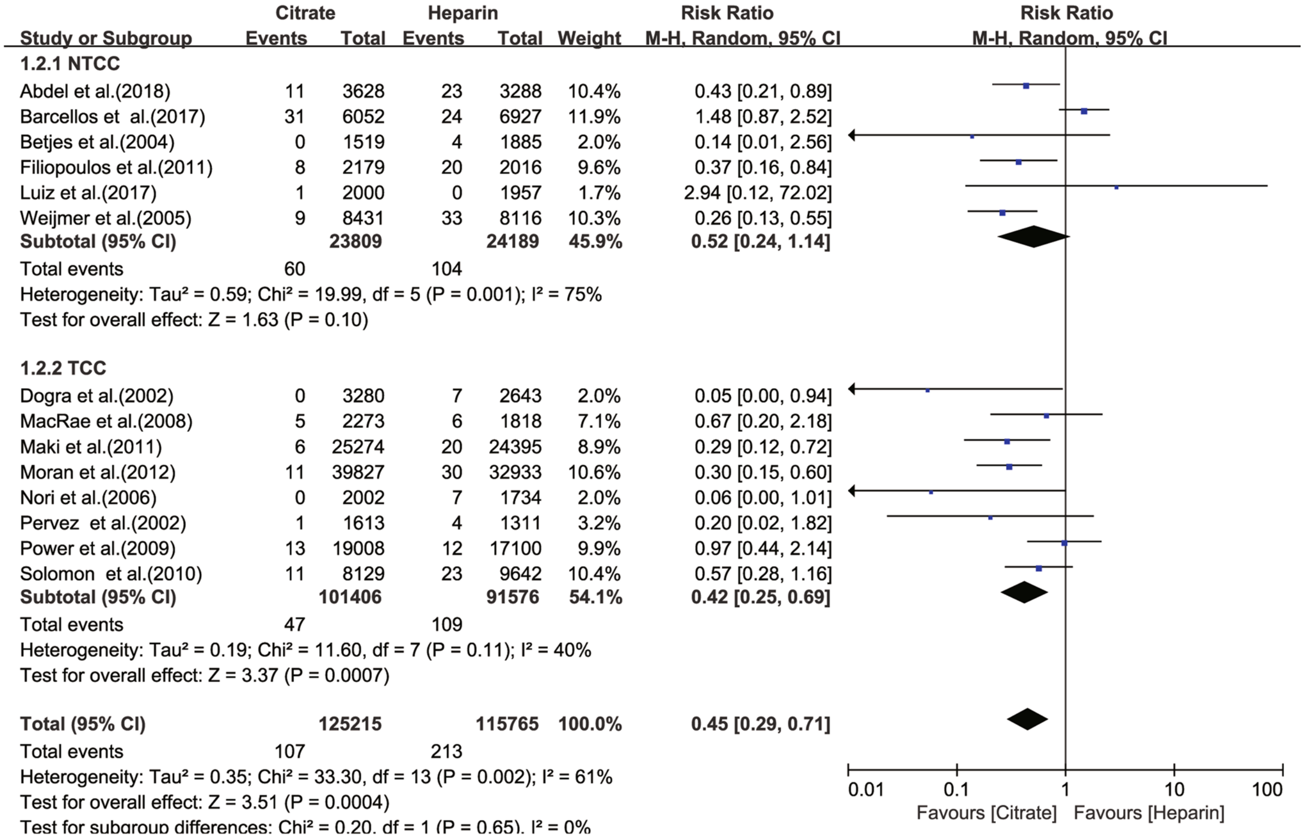

Fig. 3 Catheter-related bloodstream infection per catheter-day. The analysis was stratified by different catheter types. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel. NTCC, non-tunneled cuffed catheter; TCC, tunneled cuffed catheter

$P=0.66$) (Fig. 10). The overall RR of the random-effects model was 1.02 (95% CI, 0.76–1.36; $I^2=0\%$; $P=0.91$), with the incidence of catheter removal for poor flow being similar in hemodialysis patients receiving citrate versus heparin.

Thrombolytic treatment

There were nine studies (1670 patients, 210,794 catheter-days) that described thrombolytic treatment, with a subgroup analysis on different types of citrate lock showing no statistically significant difference in risk. The RR of the citrate containing antimicrobials was 1.07 compared with that of heparin, suggesting a similar incidence of thrombolytic treatment in hemodialysis patients (95% CI 0.54–2.10; $I^2=91\%$; $P=0.85$). Citrate lock failed to significantly decrease the risk of thrombolytic treatment in comparison with heparin alone (RR: 0.94, 95% CI 0.62–1.42; $I^2=88\%$; $P=0.76$) (Fig. 11). No difference was found between the two arms in subgroup analysis by different types of catheter ($P=1.00$ and $P=0.76$, respectively; Fig. 12).

Secondary outcomes

Tests for secondary outcomes, including thrombocytopenia (669 patients, 45,325 catheter-days), access-related admission (1037 patients, 120,095 catheter-days), and all-cause death (2101 patients, 223,779 catheter-days), were all not statistically significant by subgroup analysis in the random-effects model. Results from the pooled-analysis of each secondary outcome are shown in Table 4.

Publication bias

An Egger's test for CRBI was used to assess publication bias, showing that there was no publication bias in the meta-analysis ($t=-0.34$, $P=0.744$) (Fig. 13).

Sensitivity analysis

Sensitivity analysis results were obtained by analyzing the overall effect for each comparison after the exclusion of each individually, to assess the stability of the results of the present meta-analysis (Table 5). The analysis showed there was a significant decrease in I^2 (from 61 to 21%) after omitting

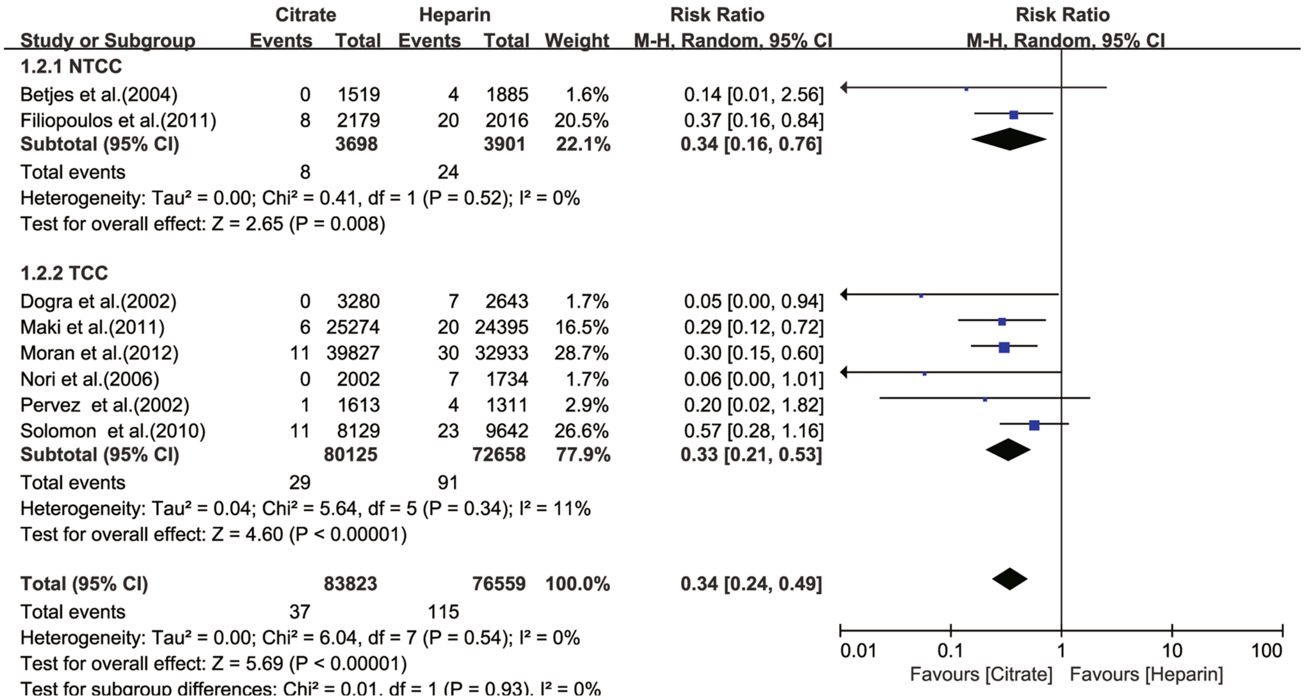

Fig. 4 Catheter-related bloodstream infection per catheter-day. The analysis was stratified by different catheter types without citrate alone groups. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel. NTCC, non-tunneled cuffed catheter; TCC, tunneled cuffed catheter

Table 3 The microbiology of CRB and CRB incidence

Study	Group	Gram positive		Gram negative	CRB incidence (episodes per 1000 catheter days)
		S. aureus	Other		
Moran et al. [14]	Citrate	2	6	1	0.28
	Heparin	6	10	10	0.91
Dogra et al. [10]	Citrate	0	0	0	0.00
	Heparin	0	7	6	2.65
Betjes et al. [8]	Citrate	0	0	0	0.00
	Heparin	3	1	0	2.12
Solomon et al. [18]	Citrate	5	4	2	1.35
	Heparin	6	6	11	2.39
Filiopoulos et al. [11]	Citrate	8	0	0	3.67
	Heparin	4	5	11	9.92
Maki et al. [13]	Citrate	5	0	1	0.24
	Heparin	9	4	7	0.82

the study by Barcellos et al. Considering the largest sample size, the study by Barcellos et al. may be the main source of heterogeneity at the level of individual study.

Discussion

Despite the priority of internal fistula placement, long-term indwelling catheters are still one of the main vascular pathways in patients with maintenance hemodialysis, especially for patients with poor vascular condition. Catheter lock during dialysis can effectively prevent thrombosis and maintain catheter patency. Heparin is currently a widely used lock solution; however, studies have shown that heparin is associated with increased risk of adverse reactions such as systemic anticoagulation, bleeding complications, heparin-induced thrombocytopenia, catheter-related infection, catheter thrombosis, and an increase in the number of thrombolytic treatments. In recent years, the antibacterial properties of the citrate lock have been

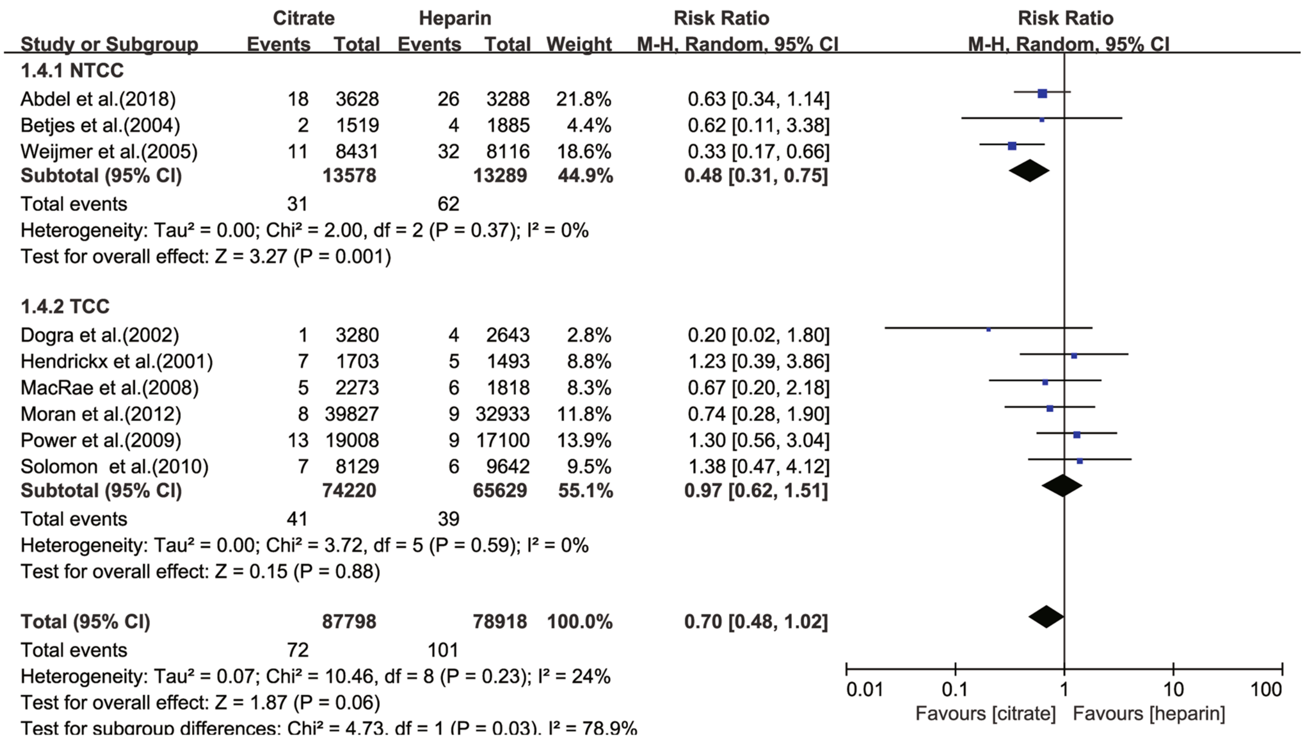

Fig. 5 Exit-site infection per catheter-day. The analysis was stratified by different catheter types. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

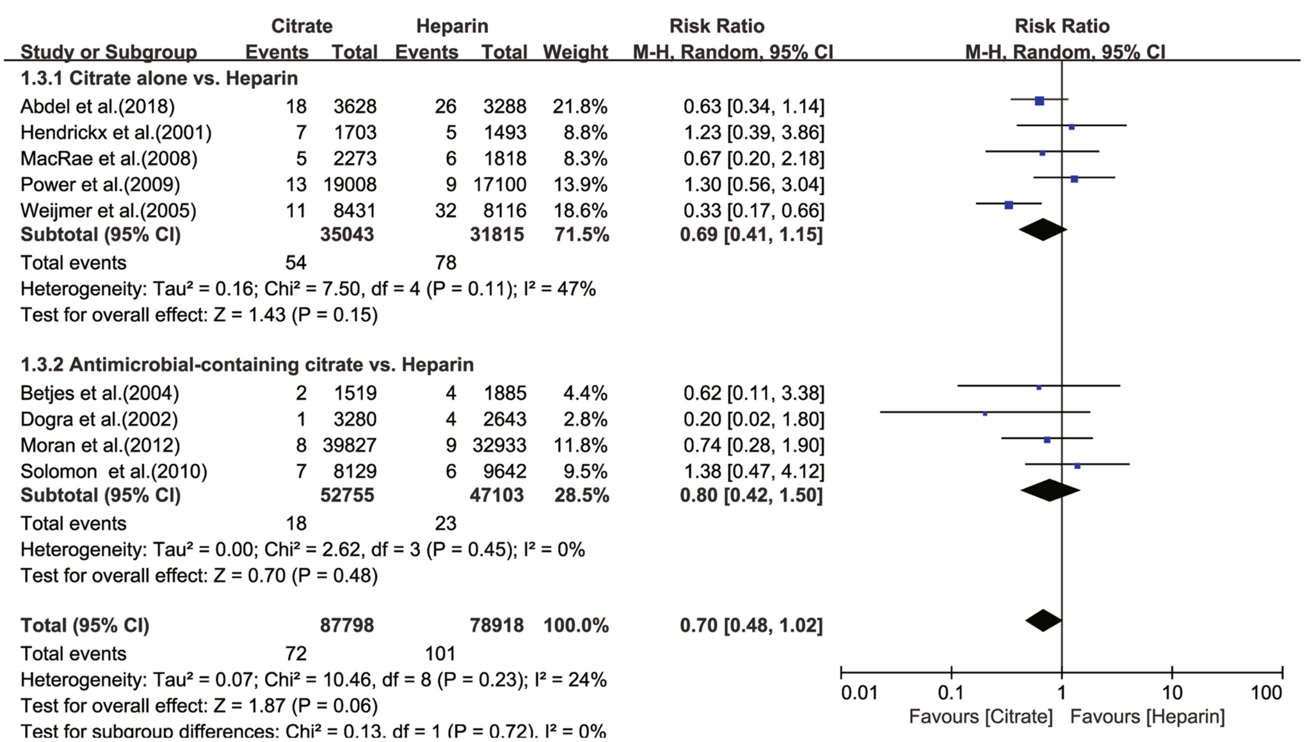

Fig. 6 Exit-site infection per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

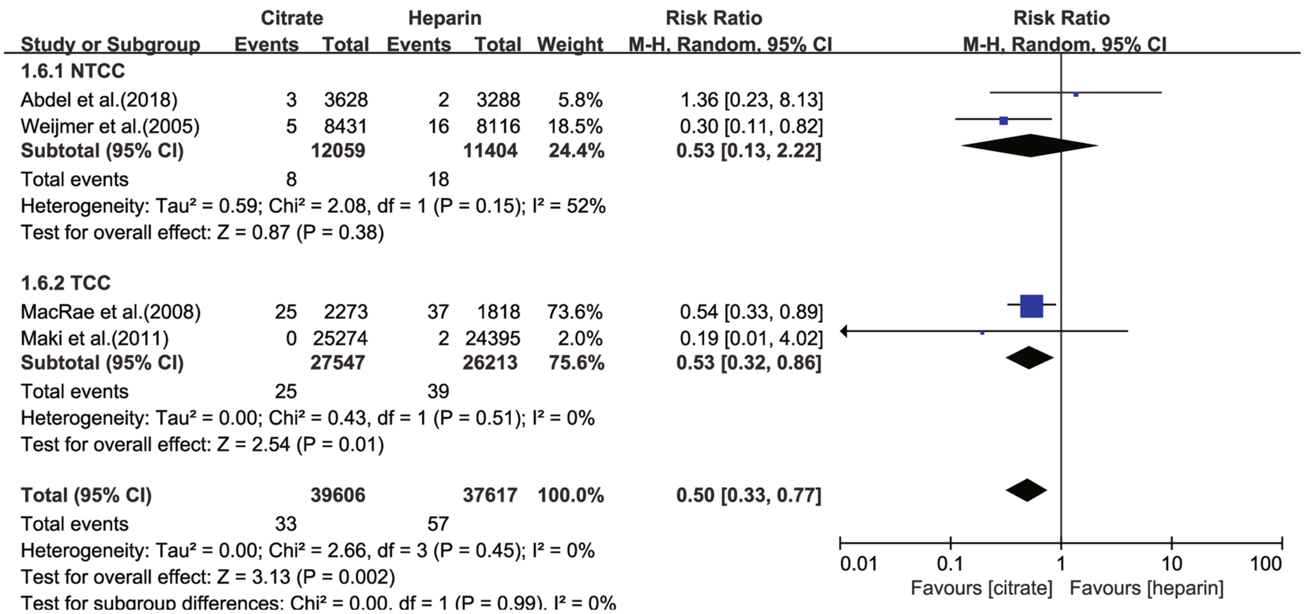

Fig. 7 Bleeding episodes per catheter-day. The analysis was stratified by different catheter types. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

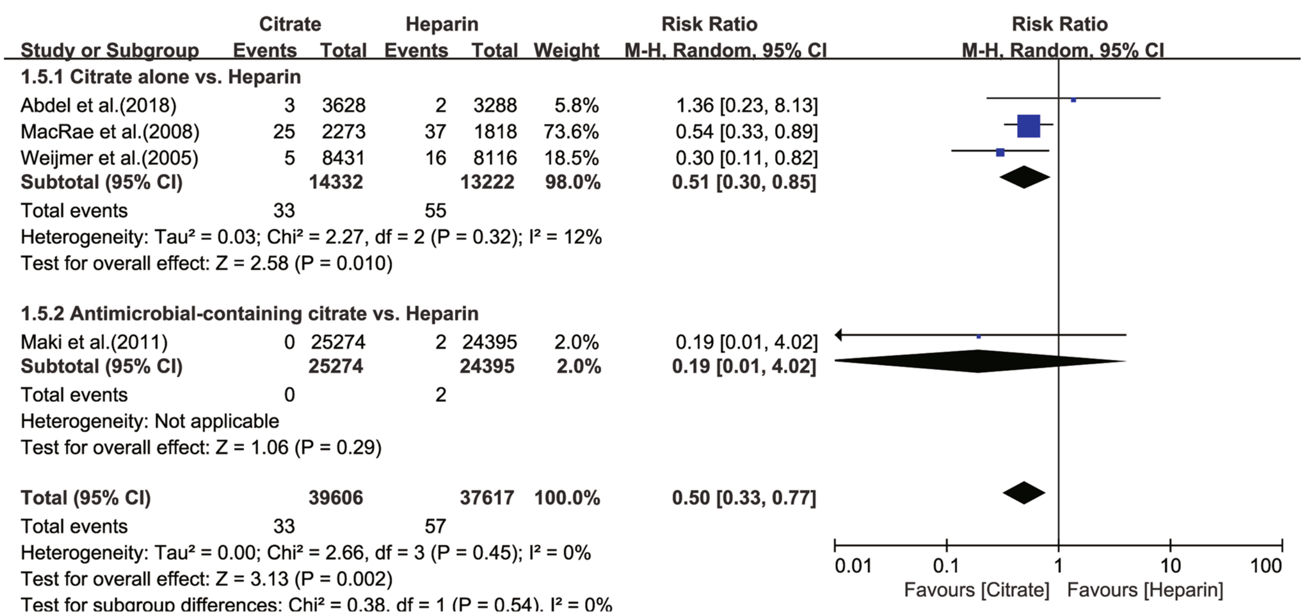

Fig. 8 Bleeding episodes per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

gradually recognized, but the effect of the citrate and heparin lock is still controversial.

This study is an update of our previous meta-analysis [1] to compare the efficacy of citrate and heparin lock in the prevention of catheter CRBI, bleeding events, and catheter dysfunction. The updated included not only more trials, but also subgroup analyses of different catheter types and a detailed analysis of bacterial infections for CRBI. The current analysis of the 16 included RCT articles [3–5, 8–20] found that, compared with the heparin lock, patients using the citrate lock had a reduced risk of CRBI and bleeding events, while the risk of catheter dysfunction was similar. For the first time, we found that locking tunneled catheter with citrate solution was more

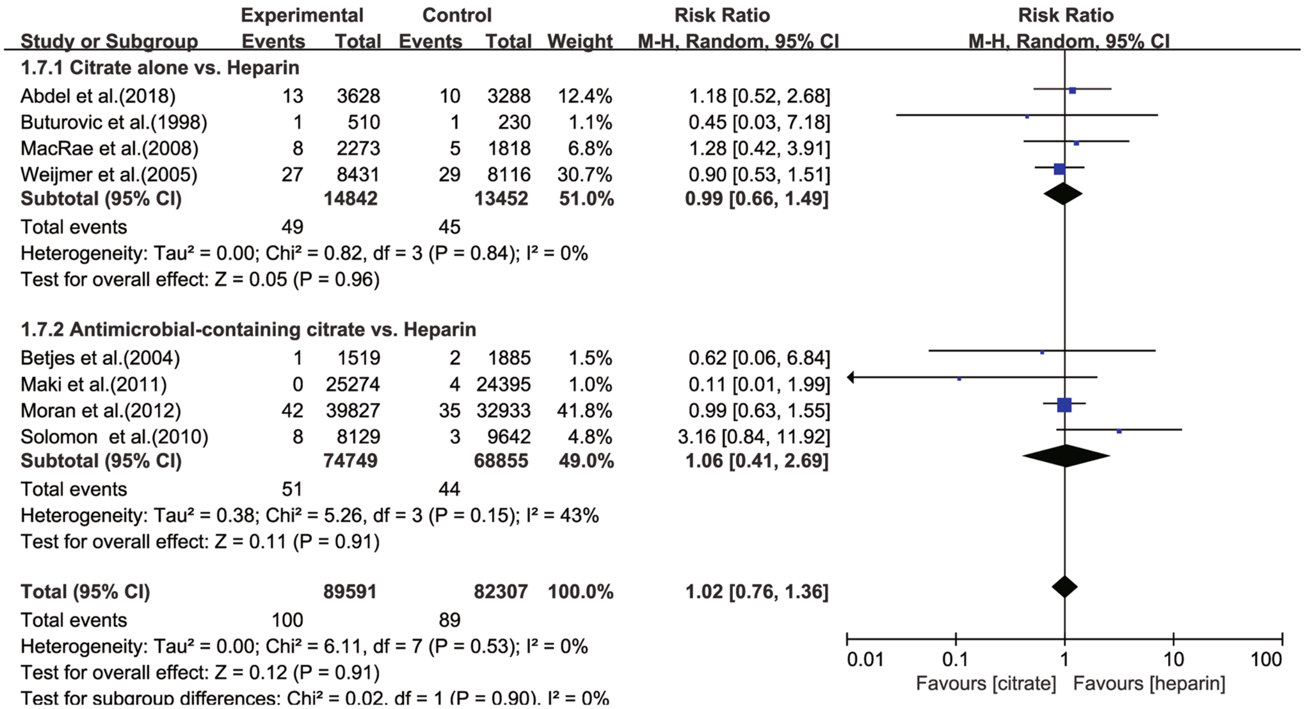

Fig. 9 Catheter removal for poor flow per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

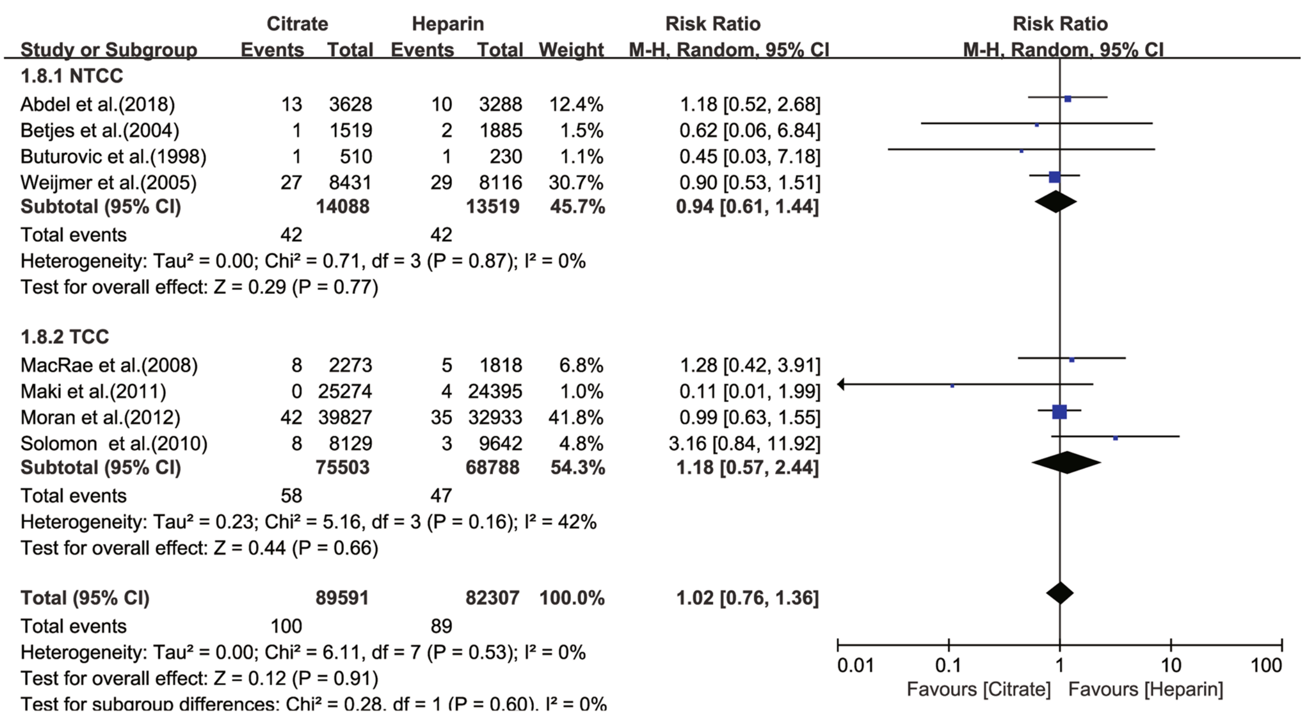

Fig. 10 Catheter removal for poor flow per catheter-day. The analysis was stratified by different catheter types. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

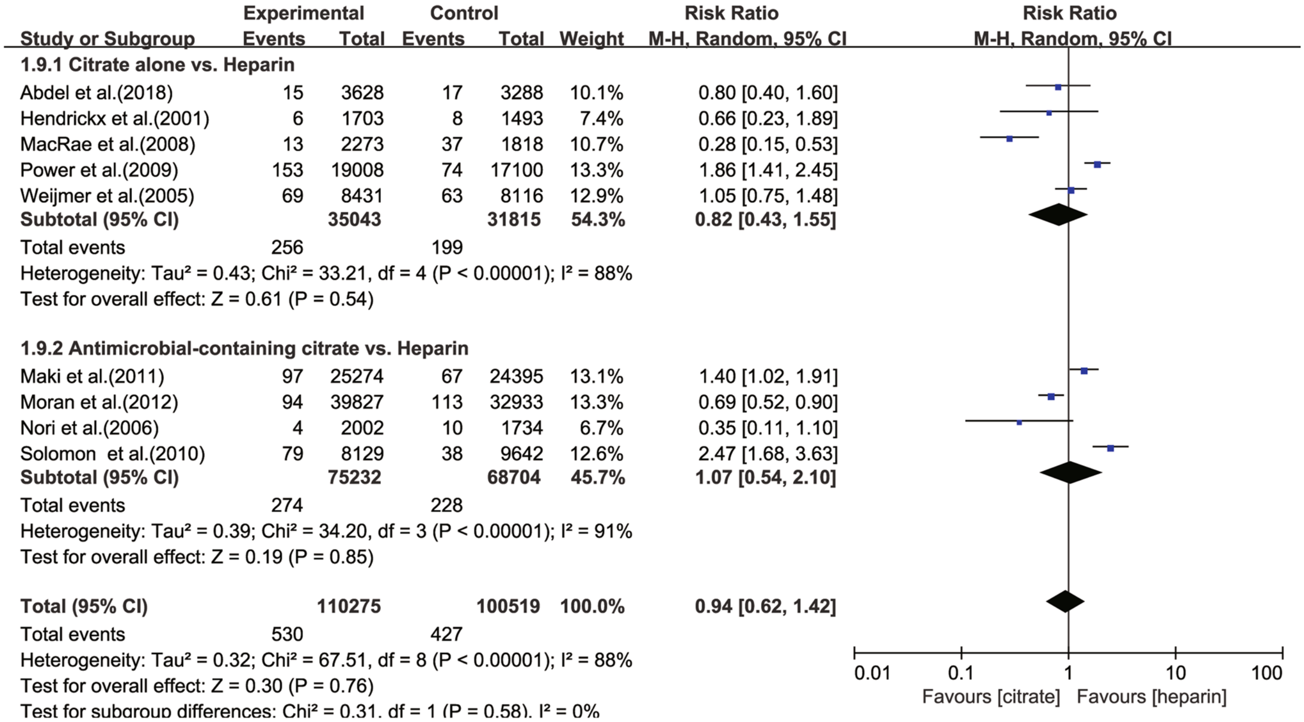

Fig. 11 Thrombolytic treatment per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

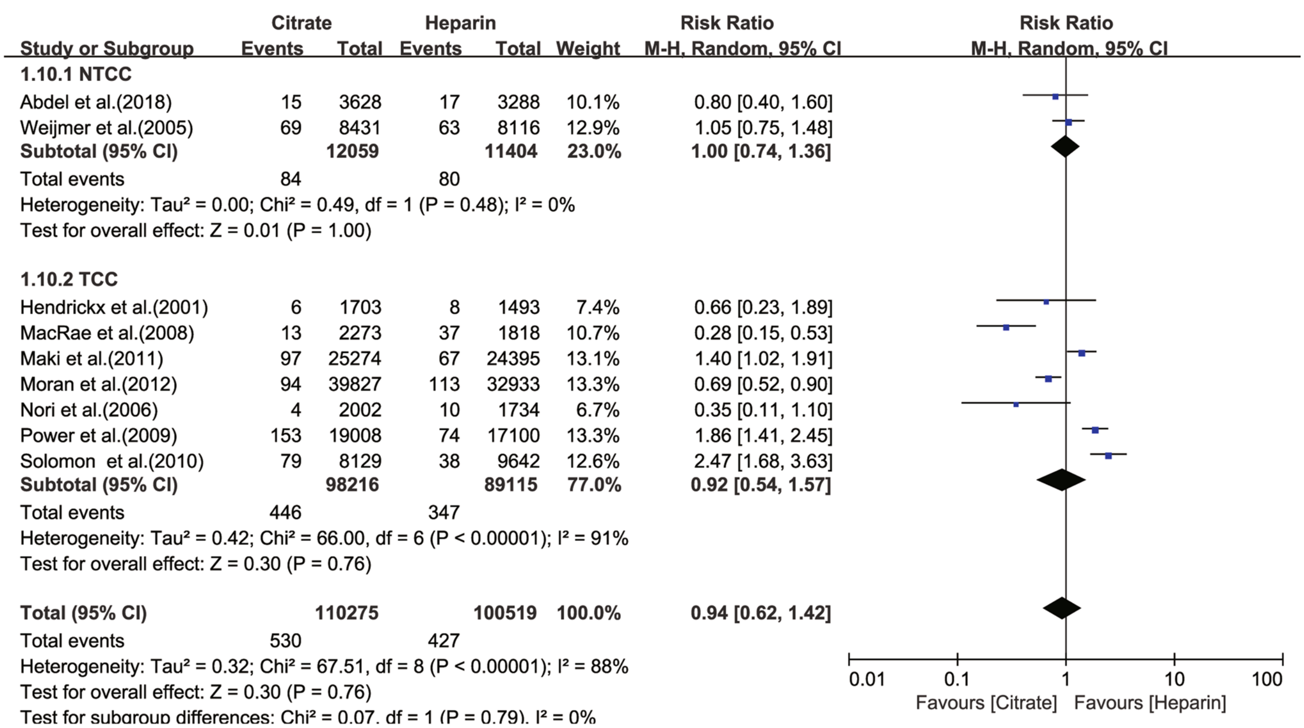

Fig. 12 Thrombolytic treatment per catheter-day. The analysis was stratified by different catheter types. Risk ratio (RR) < 1.0 favors the citrate lock. CI, confidence interval; M–H, Mantel–Haenszel

Table 4 Pooled analysis and heterogeneity analysis of secondary outcomes

Outcome	No. of studies	RR or 95% CI	Z score	P	I^2 (%)	Description
Thrombocytopenia	4	0.76 [0.41, 1.39]	0.90	0.37	0	RR < 1; favors citrate
Access-related admission	4	1.00 [0.44, 2.27]	0.01	1.00	87	RR = 1; favors neither
All-cause mortality	8	0.92 [0.68, 1.26]	0.50	0.62	2	RR < 1; favors citrate

RR, risk ratio; CI, confidence interval

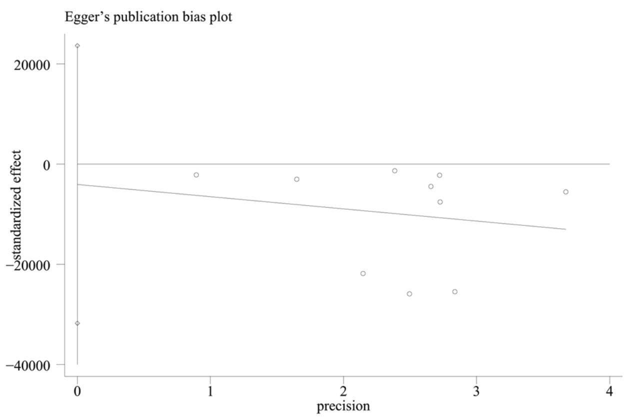

Fig. 13 Egger's test on the CRBI of different catheter locks per catheter-day in hemodialysis patient

Table 5 Sensitivity analysis by omitting each study in random-effects model on CRBI

Study omitted	RR	95% CI	P	I^2 (%)
Abdel et al. [5]	0.45	[0.27, 0.74]	0.001	64
Barcellos et al. [3]	0.40	[0.29, 0.56]	< 0.00001	21
Luiz et al. [4]	0.44	[0.28, 0.69]	0.0003	63
MacRae et al. [12]	0.44	[0.27, 0.70]	0.0006	64
Power et al. [17]	0.42	[0.26, 0.67]	0.0003	61
Weijmer et al. [19]	0.48	[0.31, 0.77]	0.002	59
Betjes et al. [8]	0.46	[0.30, 0.73]	0.0008	63
Dogra et al. [10]	0.48	[0.31, 0.74]	0.0008	61
Filiopoulos et al. [11]	0.46	[0.28, 0.74]	0.002	63
Maki et al. [13]	0.47	[0.30, 0.76]	0.002	62
Moran et al. [14]	0.47	[0.29, 0.76]	0.002	61
Nori et al. [15]	0.48	[0.31, 0.73]	0.0008	61
Pervez et al. [16]	0.47	[0.30, 0.73]	0.0009	63
Solomon et al. [18]	0.44	[0.27, 0.72]	0.0003	64

RR < 1 favors citrate

CI, confidence interval; RR, risk ratio; CRBSI, catheter-related bloodstream infection

effective in reducing bleeding events than a non-tunneled catheter. In addition, this study also showed that CRBI *S. aureus* was closely related with catheters using citrate lock rather than heparin lock.

Vercaigne et al. showed that compared with heparin, citrate lock solution is effective in preventing CRBI and prolonging catheter survival [21]. Other studies [1, 2, 22] have shown that a combination of citrate and antimicrobials (gentamicin, taurolidine, EDTA, etc.) can reduce the incidence of sepsis and the number of days of treatment. This meta-analysis also suggests that the use of citrate lock can better prevent CRBI. Subgroup analysis showed that a mixed lock of citrate and antibacterial drugs could effectively prevent CRBI, while citrate alone failed to have a statistically significant difference compared with heparin, which is consistent with our previous research. The study conducted by Timsit et al. suggested that the incidence of CRBI can be reduced using tunneled catheters [6]. To determine the correlation between CRBI and catheter type, we conducted a subgroup analysis on the different catheter types in this updated analysis. Subgroup analysis stratified by catheter type found that the citrate lock is better than heparin for the prevention of CRBI in TCC, while no difference was found between citrate and heparin in NTCC.

In the correlation analysis of CRBI microbiology, we found that the occurrence of CRBI in hemodialysis patients using citrate lock solution was associated with *S. aureus*. However, no similar association was found between CRBI and *S. aureus* for patients receiving maintenance hemodialysis with heparin lock. This finding is interesting when taking the antimicrobial spectrum of citrate into consideration, though a limited sample size for this comparison warrants caution when interpreting these results.

We then compared the risk of exit-site infection between citrate and heparin lock in hemodialysis patients. Subgroup analysis stratified by catheter type found that citrate with NTCC was effective in reducing exit-site infection, consistent with the findings of Liu et al. [2]. However, the risk of exit-site infection of citrate is similar to that of heparin lock when using TCC. Since the incidence of exit-site infection differs between NTCC and TCC, future studies are needed to shed light on whether infection incidence and other confounding factors contribute this difference and its mechanism for exit-site infection prevention by locking solutions [23].

Our previous study reported the incidence of bleeding episodes was significantly lower in patients receiving citrate locks [1]. Subgroup analysis in this current study further found that compared with heparin, citrate can reduce the incidence of bleeding events, especially when used for TCC. Since the incidence of bleeding episodes is relatively low, patients dialyzed through TCC are more likely to benefit from citrate lock in a longer period of time, compared with limited length of use for NTCC. It has been reported that a decrease in the heparin concentration is associated with a lower risk of bleeding [23]. It warrants further studies to investigate whether a citrate lock of lower concentration would be more beneficial than that of higher concentration in regard to bleeding episodes.

Other endpoint events, such as catheter removal for poor flow, thrombolytic treatment, thrombocytopenia, access-related admission, and all-cause mortality, were similar between the citrate and heparin lock groups, which is consistent with previous reports.

Although this study included more RCTs and patients, the following limitations should be noted. (1) Due to the limited number of studies, subgroup analyses were not conducted for catheter site, follow-up time, etc., which may cause bias. (2) Different follow-up time between the studies may lead to result heterogeneity. However, the follow-up time of the experimental group and the control group within a single study was consistent; therefore, the general results are unlikely to be biased. (3) Both tunneled and non-tunneled catheters can be used for a short time or a longer time. However, the original studies were not classified as permanent or contemporary catheters; therefore, we were unable to divide them in subgroups of either permanent or contemporary catheters. More researches with clear definition on type of catheters are needed. (4) We only included literature from major English databases, and the lack of literature reported in other languages and countries inevitably raised concerns about the conclusion's generalizability to other geographical regions. Nevertheless, in the process of literature screening, data extraction, and statistical analysis, we attempted to mitigate bias by conducting subgroup analyses, a sensitivity analysis, and a publication bias analysis to ensure the authenticity and reliability of the research results.

Conclusion

Our meta-analysis suggested that the citrate lock with other antimicrobials could reduce the risk of CRBI in hemodialysis patients, while citrate alone failed to show similar benefit. The citrate lock was effective in reducing exit-site infection with NTCC and bleeding events with TCC. However, no difference was found in hemodialysis patients using citrate lock or heparin lock in terms of catheter removal for poor flow, thrombolytic treatment, thrombocytopenia, access-related admission, or all-cause mortality. In addition, *S. aureus* was closely related with CRBI in catheters using citrate lock rather than heparin lock. More RCT studies are needed to evaluate the safety and effectiveness of the citrate lock compared to other lock solutions for different catheter types in the future.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

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