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Chlorhexidine solutions are more effective than povidone-iodine solutions as skin disinfectants for the prevention of intravascular catheter-related infections: A meta-analysis

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Catheter-related infections pose a significant risk to critically ill patients, making it crucial to select an appropriate sterilization solution. However, there is currently no consensus on the use of chlorhexidine-containing solutions or povidone-iodine (PVI) and the auxiliary ingredients in solutions. Meta-analysis. PubMed, EMBASE, OVID, Web of Science, and Cochrane Library databases. Two reviewers independently performed study screening and data extraction and used the Cochrane risk-of-bias tool 2.0 (RoB 2.0) for quality assessment. We included 10 fully published RCTs with 12 pairs of comparisons, which included a total of 9,689 catheters. The analysis revealed that chlorhexidine gluconate (CHG)-containing solutions were significantly more effective than PVI in preventing CRBSI (RR = 0.460, 95% CI 0.323–0.654, P < 0.001), catheter-related sepsis (RR = 0.419, 95% CI 0.206–0.853, P = 0.016), and catheter colonization (RR = 0.409, 95% CI 0.266–0.630, P < 0.001). Further subgroup analysis demonstrated that, regardless of the concentration of CHG (≤ 1% or > 1%), it was superior to PVI in preventing CRBSI and catheter colonization (RR = 0.271 ~ 0.585, 95% CI 0.110 ~ 0.400–0.590–0.926). CHG-alcohol is most effective at preventing catheter-related infections, especially those caused by 70% alcohol. Compared to PVI, CHG-70% alcohol is the most effective disinfectant for preventing catheter-related infections, as it combines the rapid disinfection and evaporation properties of alcohol with the prolonged antimicrobial effects of chlorhexidine.

***PROSPERO registration number*: CRD42024507163.**

Keywords Catheter-related bloodstream infections, Chlorhexidine, Povidone-iodine

Abbreviations

CHG	Chlorhexidine gluconate (CHG)
PVI	Povidone-iodine
CRBSI	Catheter-related bloodstream infection
PRISMA	Preferred reporting items for systematic reviews and meta analyses
RCT	Randomized controlled trial
CFUs	Colony-forming units

Venous and arterial catheters, often referred to as 'lifelines', are essential for delivering medicines, fluids, and nutrients, as well as monitoring patients. This is particularly crucial for patients residing in intensive care units

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or emergency departments. However, there is a risk of catheter-related infections during the time the catheter is in place. Catheter-related infection refers to an infection that occurs while the catheter is indwelling and within 48 h after its removal, and it is not associated with infections at other sites[1]. This includes catheter-related bloodstream infection (CRBSI), catheter-related sepsis or local infection, and catheter colonization. The incidence rates of CRBSIs range from 0.4–4.78 per 1000 catheter-days[2–4]. However, once catheter-related infection occurs, it may lead to interruption of treatment, increased treatment costs, prolonged hospital stays, and even death in severe cases[5,6].

Catheter-related infections can be prevented by selecting a robust and durable skin sterilization solution during catheter placement and maintenance. This measure is widely recognized as effective in reducing CRBSI[7]. However, the choice of disinfectant—chlorhexidine gluconate (CHG) or povidone iodine (PVI)—and its ability to prevent catheter-related infections are controversial[8,9]. Although the Centers for Disease Control and Prevention (CDC) guidelines of the United States of America recommend the use of agents with > 0.5% CHG-alcohol to prevent intravascular-catheter-related infections[10,11], CHG-containing solutions are not consistently used for skin disinfection to prevent catheter-related infections[12,13]. For evidence-based medical practice, obtaining sufficient samples for a single randomized controlled study is challenging due to the low incidence of CRBSIs and catheter-related local infections[14]. In previous meta-analyses on the effects of CHG-containing solutions and PVI as skin disinfectants in preventing catheter-related infections, several nonfull-text conference abstracts without trial details were included[15,16] or the total number of included full-text articles was relatively small (only 4 and 5 articles)[14,17]. Therefore, an updated comprehensive analysis of the literature that can synthesize the results of multiple similar studies is needed to solve this problem. Moreover, to the best of our knowledge, no studies have analyzed the different disinfection effects of different CHG auxiliary ingredients and alcohol concentrations. However, different auxiliary ingredients and alcohol concentrations have different characteristics, and combining with CHG may lead to great differences in disinfection effects. In the current meta-analysis, we included 10 full-text articles with 12 pairs of comparisons on the effects of CHG-containing solutions versus PVI as skin disinfectants for preventing catheter-related infections and analyzed the differences in the effects of different auxiliary ingredients and alcohol concentrations. The total number of catheters was 9,689, which is the largest among all related meta-analyses to date.

Methods

Literature search

We searched online for original articles published until July 20, 2023, in English databases, including PubMed, EMBASE, Web of Science, OVID, and the Cochrane Library, using combinations of the following theme words: chlorhexidine, infection or colonization or colonization, randomized or randomized or randomization or random or random or prospective or prospective, and catheter. We also searched for articles from other sources, including references in related published articles.

Inclusion and exclusion criteria

Patients: We included studies involving patients ≥ 16 years of age who received central venous, peripheral venous, hemodialysis, or arterial catheters in hospital settings. Studies involving neonates were excluded because the types of catheters used, insertion techniques, and possible complication factors are different from those of older or adult patients.

Intervention: A CHG-containing solution was used for skin disinfection around the catheter insertion site.

Comparison: A PVI-containing solution was used for skin disinfection around the catheter insertion site.

The outcome measures were as follows: (1) catheter-related bloodstream infection (CRBSI) or its synonym "catheter-related septicemia" or "catheter-associated bacteremia", which is defined as the isolation of the same microorganism from the cultured blood sample as from the colonized catheter and no other apparent infection source except the catheter; (2) catheter tip culture positive for a microorganism with fever of ≥ 38.5 °C and a reduction in body temperature for at least 1 °C within 48 h. after catheter removal without other apparent causes of fever[18,19]; (3) catheter colonization, which is defined as ≥ 15 colony-forming units (CFUs) in a semiquantitative catheter tip culture[20,21].

Type of studies: We included full-text articles on randomized controlled trials (RCTs) comparing CHG-containing solutions with PVI-containing solutions for skin disinfection around the catheter insertion site. Crossover studies were excluded because of the possible contamination of intervention effects. We also excluded conference abstracts that did not provide the details of the trial methods.

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[22] were followed. Two reviewers independently reviewed each of the included articles and extracted the following information: authors, year of publication, study design, participants, sample size, intervention, comparison, definition of outcome measures, setting, and outcomes. Two reviewers independently evaluated the quality of each included study by using the Cochrane risk-of-bias tool 2.0 (RoB 2.0) for randomized controlled trials[23]. If there was any disagreement on the extracted information in a study, it was resolved by discussion or re-evaluated by another reviewer until a consensus was reached. The protocol of this systematic review has been registered on the PROSPERO website (CRD42024507163), and more information can be found in Supplement 1.

Statistical analysis

The outcomes in the studies included in this meta-analysis were categorical data, which were synthesized as risk ratios (RRs) with 95% confidence intervals (CIs). The heterogeneity of the included studies was evaluated through X^2 and I^2 tests. If statistically high heterogeneity was identified ($I^2 \geq 50\%$; $P \leq 0.10$), we used a random effects model. In contrast, if low heterogeneity was identified ($I^2 < 50\%$ and $P > 0.10$), a fixed effects model was used. Owing to differences in the composition of disinfectants, we conducted subgroup analyses according to

different concentrations of CHG. We also perform sensitivity analysis to test the robustness of the findings. For risk ratios, $P < 0.05$ was regarded as statistically significant. R language software (R version 4.2.2, https://cran.r-project.org/) was used for data analysis.

Results

Study selection and characteristics

We first retrieved 715 articles from various databases and other sources. After excluding duplicate articles, this number was reduced to 327. After review according to the inclusion and exclusion criteria, we ultimately included 10 RCTs (Fig. 1). The characteristics of the included studies are shown in Table 1.

Assessment of risk of bias in the included studies

Overall, there was wide variation in the risk of bias for the included studies. One of these studies was assessed to have a high risk of bias[28]. Four studies were judged to have a lower risk of bias[9,26,30]. Seven studies were considered to have some concerns[8,24,25,27,29,31]. Atahan (2012)[28] was determined to have a high risk of bias because of the lack of clarity regarding the method of randomization. Four studies employed a blinded block randomization schedule[8,24,27], whereas two studies[29,31] used computer-generated random numbers for grouping. However, the process of randomization was not adequately described in these two studies, resulting in a low risk of bias. All studies had a low risk of bias in deviations from the intended interventions and measurement of the outcome. In the assessment of missing outcome data, 1 study was deemed to have a certain risk[25]. Two studies were considered to be at risk of selective reporting of results[24,27]. The risk of bias in the included studies is shown in Fig. 2.

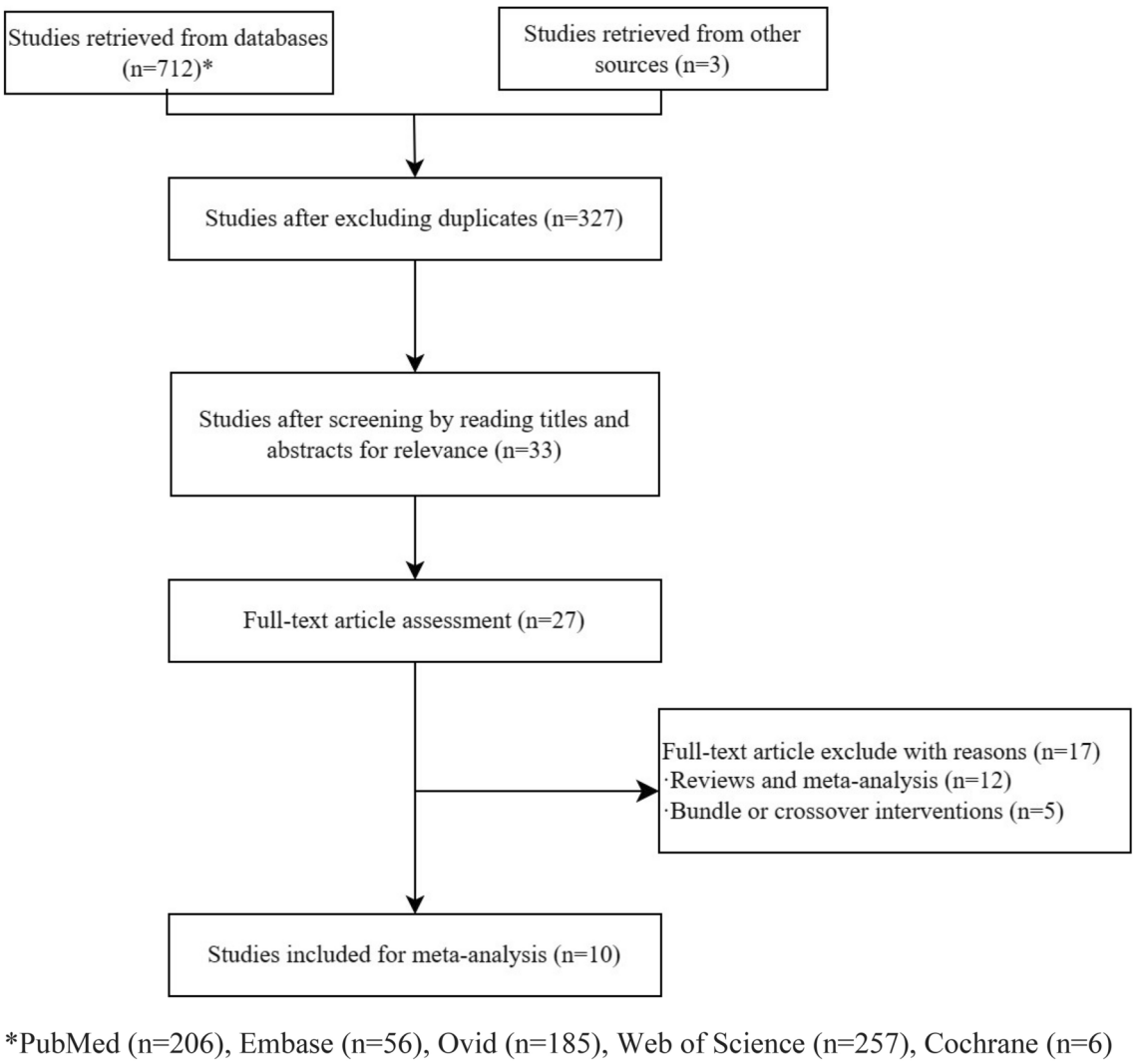

Fig. 1. Flow diagram of the literature search and study selection.

First author, year	Setting	Type of catheters	Intervention	Control	Mean or median catheter duration, d		CRBSI	Catheter-related sepsis	Catheter colonization	Skin reaction
					CHGgroup	PVIgroup				
Maki1991[24]	ICU	Central venous, arterial catheters	2% CHG- aqueous	10% PVI-aqueous	Mean:4.9	Mean:4.8	I: 1/214 C: 6/227	NA	I: 5/214 C: 21/227	NA
Mimoz1996[25]	ICU	Central venous, arterial catheters	0.25% CHG- benzyl alcohol	10% PVI-aqueous	Mean:5.7	Mean:5.3	I: 3/170 C: 3/145	I: 6/170 C: 12/145	I: 12/170 C: 24/145	I: 0/170 C: 0/145
Humar2000[8]	ICU	Central venous catheters	0.5% CHG- alcohol	10% PVI-aqueous	Mean:6.9	Mean:8.3	I: 4/125 C: 4/117	NA	I: 31/92 C: 24/88	NA
Mimoz2007[26]	ICU	Central venous catheters	0.25% CHG-benzylic alcohol	5% PVI-alcohol	Mean:12.0	Mean:12.1	I: 4/242 C: 10/239	NA	I: 28/242 C: 53/239	I: 0/242 C: 0/239
Vallés200827[27]	ICU	Central venous, arterial catheter	① 2% CHG- aqueous ② 0.5% CHG- alcohol	10% PVI-aqueous	Mean: ①7.5 ②7.1	Mean:7.7	I:①9/211 ②9/226 C: 9/194	I:①17/211 ②15/226 C: 19/194	I:① 34 /211 ② 32/226 C: 48/194	I: ①0/211 ②0/226 C: 0/194
Atahan2012[28]	Surgical clinic service	Central- venous catheters	1.5% CHG-alcohol	10% PVI-aqueous	NA	NA	I: 0/23 C: 4/27	NA	I: 6/23 C: 9/27	NA
Yamamoto2014[29]	Hematology departments	Central- venous catheters	1% CHG –79% alcohol	10% PVI-aqueous	Mean:45.2	Mean:40.3	I: 2/59 C: 7/48	NA	I: 7/59 C: 14/48	NA
Mimoz2015[30]	ICU	Central- venous, hemodialysis, arterial catheters	2% CHG– 70% alcohol	5%PVI-alcohol	Median:6.0	Median:6.0	I: 6/2574 C: 29/2612	I: 6/2547 C: 39/2612	I: 71/2547 C: 412/2612	I: 27/2574 C: 7/2612
Yasuda2017[9]	ICU	Central- venous, arterial catheters	①0.5% CHG- 79% alcohol ②1% CHG- 79% alcohol	10% PVI-aqueous	Median: ①3.8 ②4.0	Median: 3.7	I:①4/261 ②3/278 C: 6/257	NA	I:①5/262 ②6/278 C: 13/257	NA
Guenezan2021[31]	ED	Peripheral venous catheters	2% CHG- 70% alcohol	5% PVI-alcohol	Median:1.6	Median:1.7	I: 0/496 C: 0/493	I: 0/496 C: 6/493	I: 4/431 C: 70/415	I: 9/496 C: 7/493

Table 1. Characteristics and results of RCT comparing chlorhexidine-containing solutions with povidone-iodine solutions for skin disinfection to prevent vascular catheter colonization and infection. CRBSI: catheter-related bloodstream infection or bacteremia; ICU: intensive care unit; ED: emergency department; CHG: chlorhexidine gluconate; PVI: povidone-iodine; I: intervention; C: control; NA: not available.

Outcomes

In this meta-analysis, we first analyzed and compared the differences in the effects of CHG-containing solutions and PVI-containing solutions in preventing CRBSI, catheter-related sepsis, and catheter colonization. Considering the different skin irritation and disinfection effects of different concentrations of CHG, we then divided the analysis into two subgroups according to CHG concentration (CHG ≤ 1%, CHG > 1%), and compared the difference in effect with PVI again[32]. Finally, another subgroup analysis was conducted on the basis of the main excipients and alcohol concentration of the CHG disinfectant.

Catheter-related bloodstream infections

We conducted a comprehensive analysis of 12 pairs of comparisons from 10 RCTs, which included a total of 9,689 catheters. Among these, 4,879 catheters were in the intervention group, and 4,810 catheters were in the control group. After performing a heterogeneity test, we found that the studies had low heterogeneity ($I^2 = 11\%$), so we used the common effect model for analysis. The results of our analysis revealed that CHG-containing solutions were more effective than PVI-containing solutions in preventing CRBSI (RR = 0.460, 95% CI 0.323–0.654, $P < 0.001$). We also conducted a sensitivity analysis by eliminating each study one by one, and the results remained consistent. The publication bias test indicated that all the included studies had a low risk of bias (Begg's $P = 0.312$), confirming the stability and reliability of our meta-analysis results (Supplemental Fig. 1). The subgroup analysis also yielded consistent results. For CHG > 1%, the RR was 0.337, with a 95% CI of 0.193–0.590. For CHG ≤ 1%, the RR was 0.585, with a 95% CI of 0.369–0.926. No differences were observed in the subgroup analysis (test for subgroup differences: P = 0.136) (Figs. 3 and 4).

Catheter-related sepsis

Five studies, involving a total of 7288 catheters, examined the occurrence of catheter-related sepsis. The intervention group consisted of 3650 catheters, whereas the control group had 3638 catheters. A heterogeneity test revealed significant heterogeneity ($I^2 = 67\% > 50\%$), which led to the utilization of a random effects model. The findings indicated that CHG-containing solutions were more effective than PVI-containing solutions in preventing catheter-related sepsis or local infection (RR = 0.419, 95% CI 0.206–0.853, P = 0.016). However, sensitivity analysis revealed that the removal of the Mimoz[25] 1996 study altered the research outcomes (RR = 0.396, 95% CI 0.152–1.031; $P = 0.058$). In the subgroup analysis, regardless of the concentration of CHG, its effect was not statistically significant compared with that of PVI (CHG ≤ 1%: RR = 0.585, 95% CI 0.342–1.001; CHG > 1%: RR = 0.290, 95% CI 0.072–1.166), and no differences were observed in the subgroup analysis (test for subgroup differences: $P = 0.335$) (Fig. 4). The risk of publication bias analysis indicated a low risk of bias in the five included studies (Begg's $P = 0.142$) (Supplemental Fig. 1).

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
A1	Maki 1991	2% CHG	10% PVI	CRBSI	1	!	+	+	+	!	!
A2	Mimoz 1996	0.25% CHG	10% PVI	CRBSI	1	+	+	!	+	+	!
A3	Humar 2000	0.5% CHG	10% PVI	CRBSI	1	!	+	+	+	+	!
A4	Mimoz 2007	0.25% CHG	5% PVI	CRBSI	1	+	+	+	+	+	+
A5	Vallés 2008	2% CHG	10% PVI	CRBSI	1	!	+	+	+	+	!
A6	Vallés 2008 (2)	0.5% CHG	10% PVI	CRBSI	1	!	+	+	+	+	!
A7	Atahan 2012	1.5% CHG	10% PVI	CRBSI	1	-	+	+	+	!	-
A8	Yamamoto 2014	1% CHG	10% PVI	CRBSI	1	!	+	+	+	+	!
A9	Mimoz 2015	2% CHG	5% PVI	CRBSI	1	+	+	+	+	+	+
A10	Yasuda 2017	0.5% CHG	10% PVI	CRBSI	1	+	+	+	+	+	+
A11	Yasuda 2017 (2)	1% CHG	10% PVI	CRBSI	1	+	+	+	+	+	+
A12	Guenezan 2021	2% CHG	5% PVI	CRBSI	1	!	+	+	+	+	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

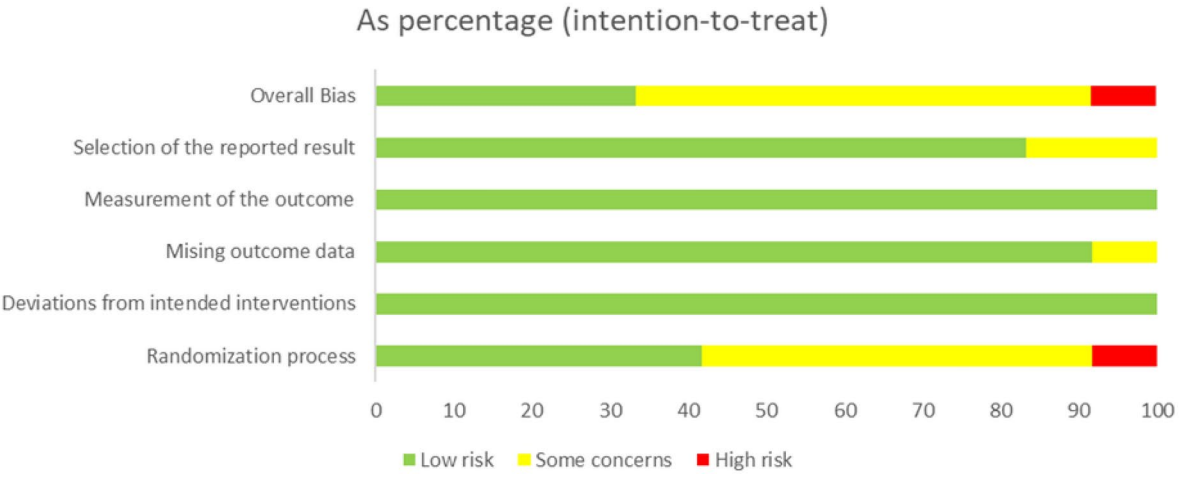

Fig. 2. Risk of bias of RCT comparing chlorhexidine-containing solutions with povidone-iodine solutions for skin disinfection to prevent vascular catheter colonization and infection.

Catheter colonization

Twelve pairs of comparisons were analyzed, involving a total of 9,458 catheters, with 4,755 in the intervention group and 4,703 in the control group. After a heterogeneity test was conducted, it was determined that the included articles exhibited significant heterogeneity (I2 = 88% > 50%). Therefore, a random effects model was selected for analysis. The comprehensive analysis results indicated that CHG-containing solutions were more effective at preventing catheter colonization than were PVI-containing solutions (RR = 0.409, 95% CI 0.266–0.630, P < 0.001) (Fig. 3). Subgroup analysis also yielded consistent results (CHG ≥ 1%: RR = 0.271, 95% CI 0.110–0.668; CHG ≤ 1%: RR = 0.566, 95% CI 0.400–0.801) (Fig. 3). The analysis of publication bias revealed a low risk among the included studies (Begg's $P = 0.075$) (Supplemental Fig. 1). Furthermore, when the influence of each individual study was systematically excluded, the results of this study remained stable and consistent without apparent fluctuations (Fig. 3).

Subgroup analysis based on different excipients and alcohol concentrations of CHG

The main ingredients of CHG-containing solutions are alcohol, benzyl alcohol, and water. Subgroup analysis was performed according to different excipients. The results showed that the antibacterial effect of CHG-alcohol was better than that of CHG-benzyl alcohol and CHG-water, but it was statistically significant only in preventing catheter-related sepsis ($P = 0.000$).

The excipient of the CHG-containing solutions used in 7 studies was alcohol, and 5 studies reported the alcohol concentration. The alcohol concentration was 79% in 3 studies and 70% in two studies. Subgroup analysis was performed on the basis of alcohol concentration to compare its effect with that of PVI-containing solutions in preventing CRBSI and catheter colonization (other outcome indicators are unavailable). The results shown the rates of CRBSI and catheter colonization were lower in the CHG-70% alcohol group than in the CHG-79% alcohol group, but a significant difference was shown only in preventing catheter colonization ($P = 0.040$) (Supplemental Fig. 2).

Discussion

This article offers a comprehensive analysis of the role of CHG-containing solutions and PVI-containing solutions as skin disinfectants in the prevention of intravascular catheter-related infections. The total number

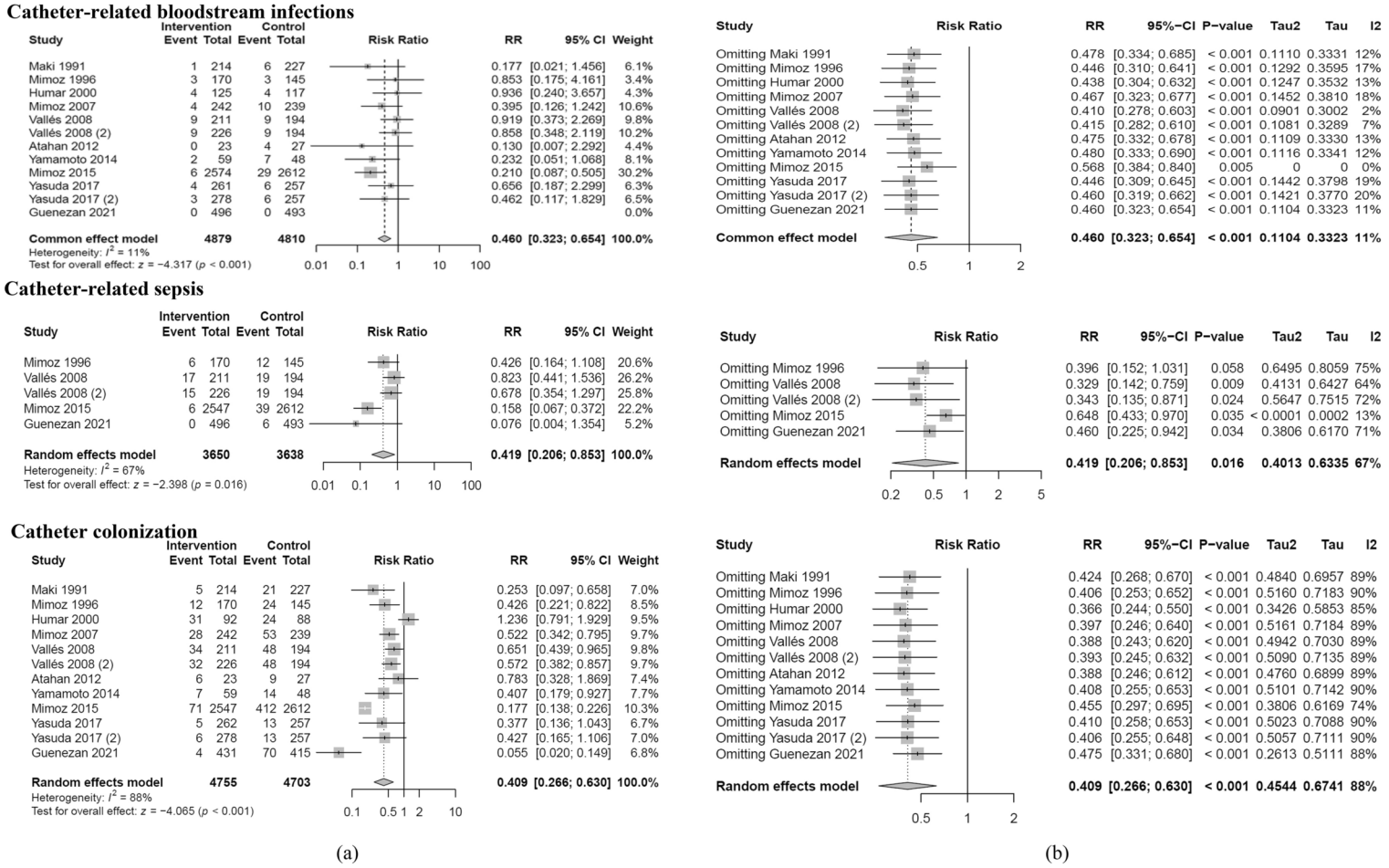

Fig. 3. (**a**) Forest map of RCT comparing chlorhexidine-containing solutions with povidone-iodine solutions for catheter-related bloodstream infections, catheter-related sepsis and catheter colonization. (**b**) Sensitive analysis of RCT comparing chlorhexidine-containing solutions with povidone-iodine solutions for catheter-related bloodstream infections, catheter-related sepsis and catheter colonization.

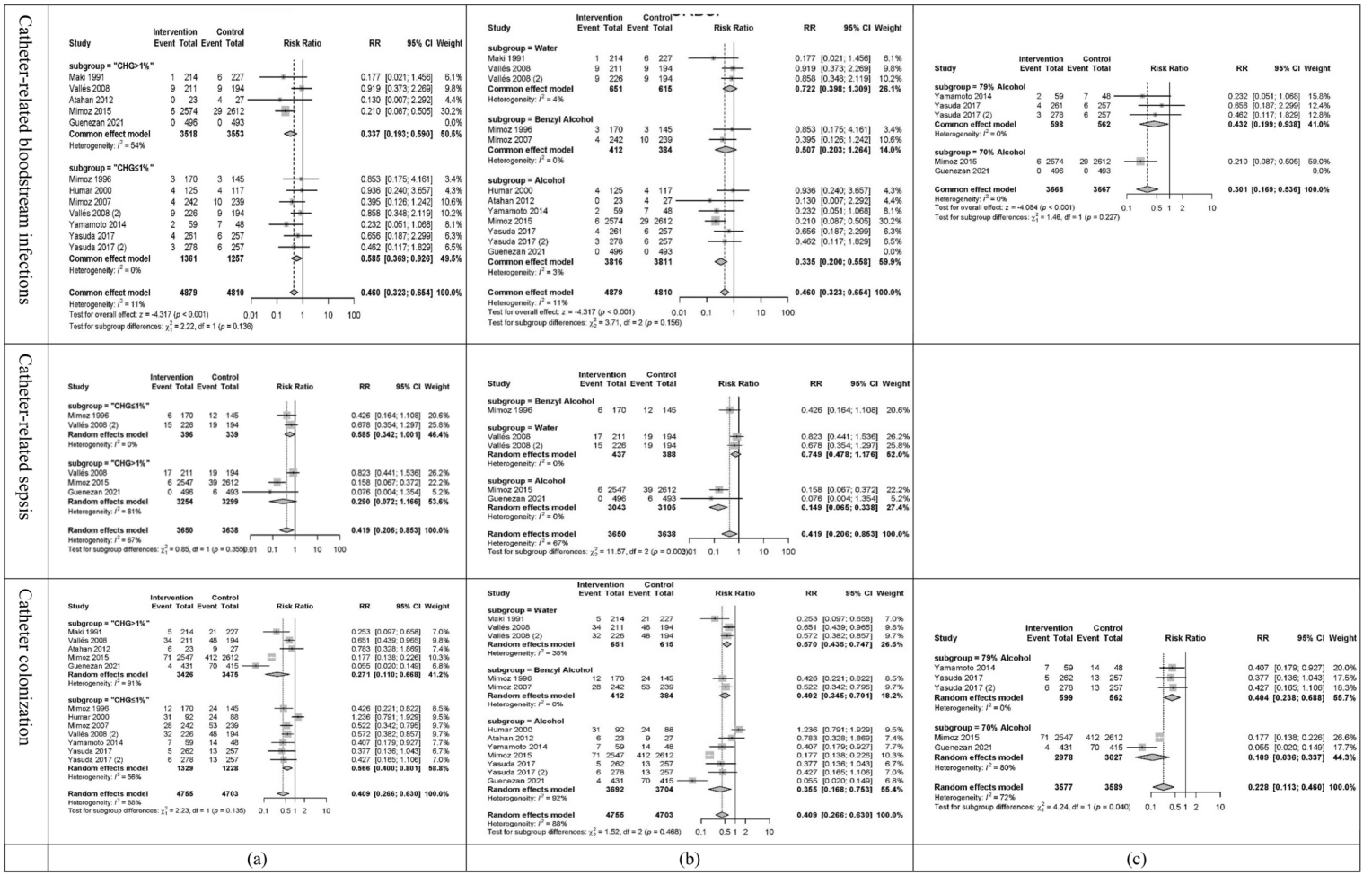

Fig. 4. Subgroup besed on different (**a**) concentrations, (**b**) excipients or (**c**) alcohol concentrations of CHG.

of included full-text RCT articles and catheters is the largest among the related meta-analyses thus far. The results of our meta-analysis indicate that CHG-containing solutions are more effective than PVI-containing solutions in preventing catheter-related bloodstream infections (CRBSIs), catheter-related sepsis, and catheter colonization. For preventing catheter-related sepsis, only 5 RCTs were available for this meta-analysis[17]; when CHG concentrations were divided into two subgroups (≤ 1% CHG or > 1% CHG), no significant effect of CHG-containing solutions was found for either subgroup compared with PVI-containing solutions. Notably, the sensitivity analysis heavily relied on the Mimoz[25] 1996 study, which utilized a CHG antiseptic solution containing benzalkonium chloride, an ingredient not present in other studies. This additional component is known to synergistically enhance the sterilizing effect of CHG[33]. Consequently, both the results of that study (RR = 0.3, 95% CI 0.1–1, P = 0.02) and the meta-analysis of 5 RCTs support the notion that CHG-containing solutions are more effective than PVI-containing solutions in preventing catheter-related sepsis or local infection. In addition, prolonged indwelling time of the catheter increases the risk of catheter-related sepsis, emphasizing the importance of the sterilization solution[34]. In addition, the incidence of catheter-related sepsis is very low. Therefore, many catheters need to be included to achieve an effective sample size[10,37]. This may be an important reason for the inconsistency between the meta-analysis results of the 5 RCTs and the subgroup analysis results.

In the prevention of catheter-related infections, CHG is generally considered superior to PVI, as indicated by various meta-analyses[16,17]. CHG is a potent and effective antibacterial disinfectant for the skin. Compared with povidone, it has a longer duration of antibacterial activity and has a stronger sterilizing effect on gram-positive bacteria than gram-negative bacteria[22]. Since gram-positive bacteria are the main cause of central catheter bloodstream infection and associated mortality[35], CHG can be recommended as the preferred disinfectant for catheter placement and maintenance care. With respect to the concentration of CHG, this study did not find that a concentration greater than 1% is more effective in reducing the risk of CRBSI than a concentration of 1% or less. However, according to a network meta-analysis conducted by Masuyama17, 1% CHG-alcohol has been shown to be more effective than 0.5% CHG-alcohol and 2% CHG-aqueous in reducing the risk of CRBSI (RR = 0.48, 95% CI 0.32–0.71; RR = 0.49, 95% CI 0.31–0.78). This difference in findings may be attributed to the subgroup analysis in this study, which had limited categorization, and the absence of a direct comparison of the effects of different CHG concentrations on reducing catheter-related infections.

There are variations in the sterilization efficacy of CHG when it is combined with different auxiliary ingredients. The performance of CHG-alcohol is superior to that of CHG-benzyl alcohol, followed by CHG-water. When the alcohol concentration is 70%, it is most effective in preventing catheter-related infections. When combined with other biocidal agents, the combination of alcohol and chlorhexidine is beneficial to health, can effectively prevent catheter-related bloodstream infections[15,36], and has less antibiotic resistance[37]. The 70% alcohol concentration can efficiently penetrate bacterial cell walls and deactivate bacteria. Conversely, 79% alcohol may evaporate too quickly due to its high concentration, resulting in less effective disinfection[38,39]. Benzyl alcohol is capable of killing bacteria, but it notably irritates the skin, particularly in adults, and may increase the likelihood of skin allergies compared with other disinfectants[40]. And Menyhay et al. compared the disinfection effects of 70% alcohol and CHG-70% alcohol disinfectants for needleless catheter connectors. They found that 15 connectors that were not disinfected were all infected, and 67% of the connectors that were disinfected with alcohol alone were contaminated with bacteria. However, only 1 (1.6%) of the s joints using CHG-70% alcohol was infected[41]. Current research supports that CHG-70% alcohol disinfectant has a prominent role in preventing catheter-related infections. This is because this component can not only utilize the rapid and bactericidal properties of alcohol, but also utilize the long-lasting antibacterial effect of chlorhexidine.

Catheter-related infections not only increase patient discomfort and adversely affect prognosis, they also prolong hospital stays and increase medical costs and workload for healthcare professionals. The use of disinfectants with potent antiseptic properties during catheter placement and maintenance can significantly reduce the incidence of these infections. The results of this study can help clinicians select effective and less irritating antiseptics.

Limitations

Notably, only English-language articles were included in this meta-analysis, which could introduce bias. However, according to relevant research, including only English literature will not affect the conclusion[42]. Additionally, in our subgroup analysis, we categorized CHG into only two subgroups on the basis of a 1% concentration threshold. Our analysis did not reveal a correlation between higher CHG concentrations and increased effectiveness. Nevertheless, this should not discourage further investigation into comparisons of the effects of various concentrations of CHG and PVI. Future research could delve deeper into this aspect. Finally, when subgroup analysis of different CHG excipients and alcohol concentrations was conducted, relatively few studies could be included, so the results require further exploration.

Conclusion

This meta-analysis included a total of 9,689 catheters (the largest number of catheters among the related meta-analyses thus far) and revealed that skin antiseptic solutions containing chlorhexidine gluconate were more effective than povidone-iodine in reducing the risk of catheter-related infections, especially CHG-70% alcohol. Therefore, CHG-70% alcohol solutions are recommended for catheter placement and maintenance.

Data availability

The data and materials used or produced throughout this study have been included in this manuscript.

Received: 7 August 2024; Accepted: 27 February 2025
Published online: 27 March 2025

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Author contributions

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Funding

This research was supported by the National Natural Science Foundation of China (Nos. 82002967 and 82372660), which promotes cutting-edge scientific endeavors of national significance.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-92476-w.

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