The efficacy and safety of prophylactic antibiotics for post-acute stroke infection: a systematic review and meta-analysis

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Abstract

Background: Infections are common complications after stroke and associated with unfavorable outcomes. We evaluated the efficacy and safety of prophylactic antibiotics for post-acute stroke infection. Methods: We searched PubMed, Embase, the Cochrane Library, SinoMed, China National Knowledge Infrastructure, and WanFangData from inception to February 15th, 2022. We calculated the pooled risk ratio (RR) and mean differences (MDs) with 95% confidence interval (CI), evaluated the risk of bias and conducted sensitivity analysis with RevMan version 5.4.1 and Stata version 14.0 software. The overall quality of evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Results: Twelve studies (4809 participants) were included in this meta-analysis. There was no significant difference in the mortality rate [RR 1.03 (95% Cl: 0.91-1.16)], pneumonia [RR 0.94 (95% CI: 0.79-1.11)], and the incidence of adverse events between the prophylactic antibiotics and control groups. Prophylactic antibiotics significantly reduced the incidence of infections [RR 0.72 (95% Cl: 0.58-0.89)], and urinary tract infections [RR 0.39 (95% Cl: 0.3-0.49)] in patients with acute stroke. We performed a subgroup analysis and found a decreasing trend in pneumonia in patients with early prophylactic use of antibiotics within 24 hours after admission [RR 0.81 (95%CI: 0.62-1.07)] as compared with those using prophylactic use of antibiotics within 48 hours after admission [RR 0.94 (95%CI: 0.79-1.11)]. Conclusions: Prophylactic antibiotics did not significantly reduce the mortality rate and pneumonia in patients with acute stroke but reduced the incidence of infections and urinary tract infections.

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Results: Twelve studies (4809 participants) were included in this meta-analysis. There was no significant difference in the mortality rate [RR 1.03 (95% Cl: 0.91-1.16)], pneumonia [RR 0.94 (95% CI: 0.79-1.11)], and the incidence of adverse events between the prophylactic antibiotics and control groups. Prophylactic antibiotics significantly reduced the incidence of infections [RR 0.72 (95% Cl: 0.58-0.89)], and urinary tract infections [RR 0.39 (95% Cl: 0.3-0.49)] in patients with acute stroke. We performed a subgroup analysis and found a decreasing trend in pneumonia in patients with early prophylactic use of antibiotics within 24 hours after admission [RR 0.81 (95%CI: 0.62-1.07)] as compared with those using prophylactic use of antibiotics within 48 hours after admission [RR 0.94 (95%CI: 0.79-1.11)].

Conclusions: Prophylactic antibiotics did not significantly reduce the mortality rate and pneumonia in patients with acute stroke but reduced the incidence of infections and urinary tract infections.

Keywords: acute stroke, prophylactic antibiotics, infection, efficacy, safety

Introduction

Acute stroke is a cerebrovascular disease. Infections are common severe complications after stroke , and the incidence of post-stroke infection is approximately 30% among patients with acute stroke. [1] Pneumonia and urinary tract infections are the most common stroke-related infections,[2] and these infections are associated with higher morbidity and mortality. [3]There are multiple risk factors for post-stroke infections, including elder, dysphagia, stroke severity, dependency, congestive cardiac failure, increased postvoid residual (PVR) volume, higher modified Rankin scale (mRS) score, and postischemic immune activation. [2,4,5] A meta-analysis showed that post-stroke infections accounted for over 48% of mortality among the patients with stroke, while the mortality rate was 18% among those without post-stroke infection. [1] And it was reported that the mRS score and disability rate were significantly increased in patients with stroke-related infections. [5,6]

The previous Cochrane review and meta-analysis revealed that prophylactic antibiotics reduced the incidence of infections and urinary tract infections in post-stroke patients, but couldn't reduce the mortality rate and incidence of pneumonia.[7,8] However, a randomized controlled trial (RCT) recently published afterwards showed that prophylactic antibiotics decreased the mortality rate and the incidence of early-onset ventilator-associated pneumonia in patients with acute stroke,[9] which were inconsistent with previous RCTs.[10-12] Therefore, prophylactic antibiotics in stroke patients remains a controversial issue.

Thus, we performed this meta-analysis of all RCTs to determine the efficacy and safety of prophylactic antibiotics in stroke patients, and provide recommendations for clinical practice as well as the development of relevant guidelines.

Methods

This systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [13] and has been registered in PROSPERO (registration no. CRD42022310121). The PRISMA checklists were available in Supplementary Materials Table S1.

We conducted a systematic search of PubMed, Embase, the Cochrane Library, Sinomed, China National Knowledge Infrastructure, and Wanfang Data from inception through February 15th, 2022, using a combination of MeSH terms, Emtree headings, and keywords: stroke, Anti-Bacterial Agents, antibiotic prophylaxis, and infections. In addition, a hand search of the reference lists of relevant reviews was performed to iden-

tify potential studies. We obtained data from the author or published meta-analysis for any missing or unpublished data. The full search strategy was presented in Supplementary Materials Table S2.

Inclusion Criteria and Study Selection

Two investigators (W.Q. and W.Z.Y.) selected the studies based on the following inclusion criteria: (1) participants: adults with acute stroke diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) and without infection; (2) interventions: prophylactic antibiotics in addition to conventional treatment within seven days of the onset of acute stroke, irrespective of the type, dosage, and route of administration; (3) comparisons: placebo or no treatment in addition to conventional treatments; (4) outcomes: the primary outcomes were mortality rate, pneumonia and the secondary outcomes included incidence of infections (including pneumonia, urinary tract infections, catheter-related phlebitis, other or unclear origin infections), urinary tract infections, length of hospital stay, National Institute of Health stroke scale (NIHSS) score, Functional Independence (FI, defined as the proportion of patients with a mRS score of [?] 2), and adverse events; (5) studies: RCTs. The studies were excluded if they were conference abstracts or duplicate publications, and publications in a language other than English and Chinese. We performed a preliminary screening by screening the title and abstract and a second screening by retrieving the full text for further evaluation to determine whether it was finally included.

Data Extraction

Two investigators extracted the following information: basic information of included studies, baseline characteristics of study subjects, details of the intervention, length of follow-up, key elements of risk of bias assessment, and outcomes of interest. Disagreements were resolved through consensus and, if necessary, consultation with a third investigator (Y.Z.M.).

Quality Assessment

Two investigators independently assessed the risk of bias according to the Cochrane Collaboration risk of bias tool, including the following domains: sequence generation, allocation concealment, blinding of participants or personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. [14] We rated each criterion as 'low' risk of bias, 'high' risk of bias, or 'unclear' risk of bias.

Statistical Analysis

Data analysis was conducted with RevMan version 5.4.1 and Stata version 14.0 software. Dichotomous outcomes were reported as risk ratios (RRs) with 95% confidence intervals (95% CIs). For continuous variables, data were presented as mean differences (MDs) with 95% CIs. Heterogeneity was investigated by the χ^2 test andI^2 statistics; if there was no significant heterogeneity (P[?]0.10, I^2 [?]50%), a fixed-effects model was used; if not, a random-effects model was used. Sensitivity analyses were performed for outcomes with significant heterogeneity by excluding one study at one time. Publication bias and sensitivity analysis were evaluated via Stata version 14.0 software. We performed a subgroup analysis based on the time of the first dose of antibiotic drugs.

GRADE evaluation

The quality of evidence was evaluated by two investigators according to the Grading of Recommendations, Assessment, Development and Evaluations(GRADE) approach, [15] whereas reasons for reducing confidence were based on risk of bias, imprecision, consistency of effect, indirectness and publication bias. The evaluation results were divided into four levels: high, moderate, low and very low.

Results

Literature Selection Process and Result

We retrieved a total of 5284 records from electronic databases. According to the inclusion and exclusion criteria, twelve RCTs were finally included, [9-12,16-23] involving 4809 patients, with 2403 patients in the prophylactic antibiotics group and 2406 patients in the control group (Figure 1).

Characteristics of the Included Studies

Among the twelve included RCTs, eleven were published in English[9-12,16,18-23] and one in Chinese. [17]The mean ages of patients were similar in both groups (69.5 years vs. 69.6 years). The follow-up periods ranged from 90 to 180 days. Eight RCTs [10-12,16,18-20,22]reported the NIHSS scores, ranging from five to 17. Since the data could not be obtained from the full text of three studies, we obtained these data from the published meta-analysis[24] for mortality rate, the proportion of patients with mRS [?] 2, and NIHSS score. Characteristics of the included studies were shown in Table 1.

Three studies were rated as low risk of bias, [10,11,22] two studies were at high risk of bias, [19,23] and the others were at unclear risk of bias. [9,12,16-18,20,21]The randomization method of one study was unclear; [21]randomization and allocation concealment were not performed for one study, [19] and the allocation concealment method was unclear for three studies; [9,20,21] participant blinding was unclear in one study; [17] outcome assessment was not blinded in three studies for partial outcomes;[16,17,21] three studies did not mention the reasons for the loss to follow-up; [9,12,23] three studies had selective reporting. [18,21,23] The risk of bias assessments of the included studies were shown in Figure 2.

Meta-Analysis

Mortality rate

Twelve studies reported the mortality rate among 4740 patients.[9-12,16-23] Meta-analysis showed that there was no significant difference in mortality rate between the prophylactic antibiotics group and the control group [RR 1.03 (95% CI: 0.91-1.16,I^2 =1%; Figure 3)]. Consistent results were observed between the subgroups of different administration times.

Pneumonia

Pneumonia was reported in seven studies including 4352 patients.[10-12,16,18,20,22] Pneumonia was not significantly reduced with prophylactic antibiotics treatment [RR 0.94 (95%CI: 0.79-1.11, I^2 =0%; Figure 4)]. Results of subgroups analysis were similar.

Incidence of infections

Infection was reported in eight studies including 4517 patients.[10-12,16-18,20,22] Incidence of infections was significantly lower in the prophylactic antibiotics group than that in the control group [RR 0.72 (95% CI: 0.58-0.89,I^2 = 58%; Figure 5)]. The results of the subgroups were similar to the main analysis.

Urinary tract infections

Seven studies, [10-12,16,18,20,22] including 4352 patients, reported data on urinary tract infections. Pooled results showed that the urinary tract infections in the prophylactic antibiotics group was significantly lower than that in the control group [RR 0.39 (95%CI 0.3-0.49, I^2 = 0%; Figure 6)]. Results of subgroups analysis were similar.

The proportion of patients with mRS [?] 2

A total of nine studies (4385 patients) reported[10-12,16,18-21,23] the proportion of patients with mRS [?] 2. Pooled results showed that there was no significant difference in the proportion of patients with mRS [?] 2 between the prophylactic antibiotics group and the control group [RR 1.19 (95%CI: 0.97-1.45,I^2 = 75%; Supplementary Materials Figure S1)].

NIHSS score

Meta-analysis of two studies [19,21] showed that there was no significant difference in NIHSS score between the prophylactic antibiotics group and the control group [MD -4.89 (95%CI: -5.84,-3.94, I^2 = 0%; Supplementary Materials Figure S2)].

Length of hospital stay

Three studies reported the length of hospital stay in 3839 patients.[9-11] Meta-analysis showed that there was no significant difference in the length of hospital stay between the prophylactic antibiotics group and the control group [MD -0.07 (95%CI: -7.12-6.98, I^2 = 93%; Figure 7)].

Adverse events

Only three studies reported adverse events, [10,11,16]one reported serious adverse event, and two reported total serious adverse events. Due to different types of outcomes, we did not synthesize data for adverse events. The incidence of serious adverse events was similar between the two groups in one study.[11] The other two studies found no statistically significant differences in the incidence of adverse events.[10,16]

GRADE Evidence Quality Assessment

Based on the GRADE approach, [15] mortality rate, pneumonia, and urinary tract infections were rated as high-quality evidence; the incidence of infections, proportion of patients with mRS [?] 2, and length of hospital stay were as moderate-quality evidence; NIHSS score was rated as low-quality evidence.(Table 2).

Publication bias

Egger's test showed that there was no publication bias (P=0.714) for the outcome of mortality. The publication bias assessment was unavailable for other outcomes due to fewer than ten studies included.

Sensitivity analyses

To perform sensitivity analysis for the outcome of mortality rate, we excluded the study by Fouda et al. as this RCT was not explicitly indicating the infection status of patients in the exclusion criterion. This analysis did not change the results significantly, suggesting they were relatively stable. (Supplementary Materials Figure S3).

For the proportion of patients with mRS [?] 2 points, the heterogeneity was decreased (P = 0.31, I^2 = 15%) and the results were not changed by excluding the Lampl et al. study. (Supplementary Materials Figure S4).

Discussion

This systematic review and meta-analysis revealed that prophylactic antibiotics could not reduce the mortality rate and pneumonia of stroke patients, nor could they improve functional outcomes, and length of hospital stay. However, we find a significant reduction in infection and urinary tract infection after stroke without increasing the incidence of adverse events.

Several factors might influence the result. First of all, the duration of prophylactic antibiotics was insufficient. Finlayson et al. found pneumonia was associated with longer hospitalization.[25] And a retrospective study revealed that the length of hospitalization was a strong predictor for post-stroke pneumonia, the incidence of pneumonia for patients with hospitalization for more than two weeks was 3.9 times more than that for patients hospitalized for four days to one week [OR 3.90 (95%CI: 3.73-4.08, P $<$ 0.0001)]. [26] Among the RCTs included in this meta-analysis, [9-11] the mean length of hospital stay in the prophylactic antibiotics group was 23.5 days, but the use of prophylactic antibiotics was only two to seven days. Therefore, it was difficult to avoid the occurrence of pneumonia in stroke patients throughout the treatment. In particular, the length of the hospital stay was too long. Second, in most studies, the time window before the start of prophylactic antibiotic therapy was quite long-up to 24h after stroke. To evaluate the effects of different administration times, we performed a subgroup analysis and found a decreasing trend in pneumonia in patients with early prophylactic use of antibiotics within 24 hours after admission [RR 0.81 (95%CI: 0.62-1.07,I^2 = 0%)] as compared with those using prophylactic use of antibiotics within 48 hours after admission [RR 0.94 (95%CI: 0.79-1.11, I^2 = 0%)]. Third, the severity of stroke is a risk factor for infection after stroke.[27] Thus, patients with severe stroke who are at high risk for infection should be considered for prophylactic antibiotics. However, an RCT with a large sample size included in our meta-analysis involved patients with mild stroke, and the average hospital stay of patients was only 6.35 days. [10] Considering the low incidence

of nosocomial infection, [26] the role of prophylactic antibiotics in reducing post-stroke infection was not fully reflected.

Stroke-related infections, particularly pneumonia, are regarded as an independent risk factor associated with mortality after stroke.[1] The results of this study did not find a reduction in pneumonia, so the mortality rate was not significantly reduced.

In two studies, [12,22] fluoroquinolones were used as prophylactic antibiotics for post-stroke infection. There concerns about the adverse events of fluoroquinolones on the nervous system. However, no serious adverse events were reported in these two studies. And several preclinical studies had described the neuroprotective effects of moxifloxacin after transient focal brain ischemia. [28]Nevertheless, attention still should be paid to the adverse events in the clinical application of fluoroquinolones.

There are several strengths in this meta-analysis. First, compared with previous studies, [7,8,29] this meta-analysis included more RCTs and sample size; thus, the confidence interval of the study and the heterogeneity between studies for each outcome were reduced. Second, we performed a subgroup analysis by time to the first dose of antibiotic drugs. We found that patients with early prophylactic use of antibiotics within 24 hours after admission had a decreasing trend in mortality and pneumonia compared with those with prophylactic use of antibiotics within 48 hours. Third, we assessed the overall evidence according to the GRADE quality of evidence approach.

However, this study still has some limitations. First, the outcomes of patients with post-acute stroke infection might be impacted by stroke severity, chronic conditions, dysphagia, age, invasive procedure, different timings, types, and duration of antimicrobial use.[30,31] The invasion procedures, such as urinary catheterization or mechanical ventilation, could increase the risk of infection by facilitating the entry of a pathogen; However, we could not perform these subgroup analyses due to unavailable data. For example, only one RCT in our meta-analysis described the use of urinary catheterization, [12] so we could not evaluate the effect of urinary catheterization on prophylactic antibiotics. Secondly, clinical heterogeneity is inevitable due to different criteria used for infection in RCTs; therefore, the results of this meta-analysis should be interpreted with caution. Thirdly, most of the RCTs included in this study were performed in developed countries with standard stroke units. Due to the differences in medical resources and nursing levels between developing and developed countries, standard stroke unit management is unconditionally carried out in some places, and the medical environment is poor, [32,33] which increases the incidence of infection in patients. Evidence for prophylactic antibiotics in stroke patients is lacking in developing countries or remote areas. Therefore, whether to recommend prophylactic antibiotics in patients with post-acute stroke infection needs to be further confirmed by large-scale RCTs.

Conclusions

Prophylactic antibiotics in patients with acute stroke did not reduce the mortality rate and pneumonia but could reduce the incidence of infections and urinary tract infections. No increase in the risk of adverse events was observed. Whether to use antibiotics prophylactically in patients with acute stroke should be balanced their benefits and risks. Further studies should consider the effect of timing and duration of prophylactic antibiotics on clinical outcomes to identify patients who get benefits from prophylactic antibiotics therapy after stroke.

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Supplementary Data: Table S1: PRISMA checklist, Table S2: Search strategies through electronic databases, Figure S1: Forest plot for the proportion of patients with mRS [?] 2, Figure S2: Forest plot for NIHSS score, Figure S3: Sensitivity analyses of mortality rate at different administration time, Figure

S4: Sensitivity analyses of the proportion of patients with mRS [?] 2.

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Table 1. Characteristics of the included studies.

Author	Total Patient (n)	Patient (n) PA/ Controls	Baseline of NIHSS or GCS PA/Controls	Intervention Measures PA	Intervention Measures Controls	Duration	Duration	Outcomes	Length of follow-up (days)
Chamorro et al. 2005 [22]	136	67/69	NIHSS: 14 (7-19)/11 (7-18)	Levofloxacin 500 mg IV daily	Placebo	3 days	3 days	a, b, c, d	a, b, c, d
Lampl et al. 2007 [19]	151	74/77	NIHSS: 7.5 ± 3.2/7.6 ± 3.8	Minocycline 200mg orally daily	NPA	NPA	5 days	a, e, f	9
Harms et al. 2008 [12]	79	39/40	NIHSS: 17 (12-21)/ 15 (12-15)	Moxifloxacin 400 mg IV daily	Placebo	5 days	5 days	a, b, c, d, e	180
Schwarz et al. 2008 [16]	60	30/30	NIHSS: 16.5 (8-28)/ 15 (5-27)	Mezlocillin 2 g plus sulbactam 1 g IV every 8 hours	NPA	4 days	4 days	a, b, c, d, e, h	90
Wang et al. 2012 [17]	165	83/82	GCS: 8.99 ± 3.92/ 8.91 ± 4.16	Cefuroxime 3 g IV every 12 hours plus metronidazole 0.5 g IV every 12 hours, moxifloxacin 0.4 g IV daily for allergy to cephalosporins	NPA	NR	NR	a, c	NR
Kohler et al. 2013 [20]	92	44/48	NIHSS: 9.1 ± 7.2/8.7±6.5	Minocycline 100 mg IV every 12 hours	NPA	5 doses	5 doses	a, b, c, d, e	90

Author	Total Patient (n)	Patient (n) PA/ Controls	Baseline of NIHSS or GCS PA/Controls	Intervention Measures	Intervention Measures	Duration	Duration	Outcomes	Length of follow-up (days)
Blacker et al. 2013 [23]	44	21/23	NR	Minocycline 200 mg IV every 12 hours	NPA	5 doses	5 doses	a, e	90
Kalra et al. 2015 [11]	1217	615/602	NIHSS: 15 (9–20)/ 14 (9–20)	Local protocol	NPA	7 days	7 days	a, b, c, d, e, g, h	90
Ulm et al. 2016 [18]	227	112/115	NIHSS: 14 (12-18)/ 15 (12-19)	The type and duration of antibiotic treatment were left to the discretion of the treating physician	NPA	Local policy	Local policy	a, b, c, d, e	90
Westendorp et al. 2015 [10]	2538	1268/ 1270	NIHSS: 5 (3-9)/5 (3-9)	Ceftriaxone 2 g IV daily	NPA	4 days	4 days	a, b, c, d, e, g, h	90
Fouda et al. 2017 [21]	16	8/8	NR	Minocycline 400 mg IV once followed by 400 mg oral	Placebo	5 days	5 days	a, e, f	90
Mirtalaei et al. 2019 [9]	84	42/42	GCS: 6 ± 1.3/6.2 ± 1.5	Piperacillin-tazobactam 4 g/0.5 g IV	NPA	NR	NR	a, g	NR

GCS: Glasgow Coma Scale, NR: not reported, NPA: no prophylactic antibiotics, NIHSS: National Institute of Health stroke scale, PA: prophylactic antibiotics, IV: intravenous.

a: mortality rate, b: pneumonia, c: incidence of infections, d: urinary tract infections, e: the proportion of patients with a mRS [?] 2, f: NIHSS score, g: length of hospital stay, h: adverse events, Data are mean, standard deviation (SD), or median, interquartile (IQR).

Table 2. Rating the certainty of evidence by GRADE criteria.

Patient or population: adults with acute stroke **Intervention:** antibiotics

Comparison: conventional treatment/placebo **Outcomes**	**Comparison:** conventional treatment/placebo **Outcomes** **Risk with conventional treatment/placebo**	**Comparison:** conventional treatment/placebo **Anticipated absolute effects [a] (95% CI)** **Risk with conventional treatment/placebo**	**Comparison:** conventional treatment/placebo **Anticipated absolute effects [a] (95% CI)** **Risk with prophylactic antibiotic treatment**	**Comparison:** conventional treatment/placebo **Relative effect (95% CI)**	**Comparison:** conventional treatment/placebo **NO. of participants (studies)**	**Comparison:** conventional treatment/placeb **Quality of the evidence (GRADE)**
Mortality rate	153 per 1000	153 per 1000	157 per 1000 (139 to 177)	RR 1.03 (0.91, 1.16)	4740 (12 RCTs)	[?][?][?][?] High [b, c]
Pneumonia	151 per 1000	151 per 1000	142 per 1000 (119 to 168)	RR 0.94 (0.79, 1.11)	4352 (7 RCTs)	[?][?][?][?] High [b]
Incidence of infections	297 per 1000	297 per 1000	214 per 1000 (172 to 21264)	RR 0.72 (0.58, 0.89)	4517 (8 RCTs)	[?][?][?] Moderate [b, d]
Urinary tract infections	100 per 1000	100 per 1000	39 per 1000 (30 to 49)	RR 0.39 (0.3, 0.49)	4352 (7 RCTs)	[?][?][?][?] High [b]
The proportion of patients with mRS [?] 2	275 per 1000	275 per 1000	327 per 1000 (267 to 399)	RR 1.19 (0.97, 1.45)	4385 (9 RCTs)	[?][?][?] Moderate [b, e]
NIHSS score	The mean NIHSS was 0	The mean NIHSS was 0	MD 4.89 lower (5.84 lower to 3.94 lower)	-	160 (2 RCTs)	[?][?] Low [f]
Length of hospital stay	The mean length of hospital stay was 0	The mean length of hospital stay was 0	MD 0.23 lower (0.66 lower to 0.2 higher)	-	3839 (3 RCTs)	[?][?][?] Moderate [b, g]

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RCTs: randomized controlled trials; RR: risk ratio; MD: mean difference; NIHSS = National Institute of Health stroke scale.

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[b] A large number of studies were included, a large number of participants participate, and a large confidence interval was calculated (low bias risk).

[c] Mortality was 'low' risk of bias.

[d] We rated down one level: for inconsistency of effect (Heterogeneity was moderate, $I^2 = 58\%$).

[e] We rated down one level: for inconsistency of effect (Heterogeneity was high, $I^2 = 75\%$).

[f] We rated down two levels: one for risk of bias (No random and no allocation concealment), one for imprecision.

[g] We rated down one levels: for inconsistency of effect (Heterogeneity was high, $I^2 = 93\%$).