

Effectiveness of combination therapy for treating methicillin-susceptible *Staphylococcus aureus* bacteraemia: a systematic literature review and meta-analysis

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Search strategies

Ovid MEDLINE

1. Staphylococcus aureus/
2. exp Methicillin-Resistant Staphylococcus aureus/
3. staphylococcus aureus.tw,kw.
4. s aureus.tw,kw.
5. mrsa.tw,kw.
6. mssa.tw,kw.
7. mrsab.tw,kw.
8. mssab.tw,kw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Bacteraemia/
11. exp Endocarditis, Bacterial/
12. bacter?emia*.tw,kw.
13. bloodstream infection*.tw,kw.
14. blood stream infection*.tw,kw.
15. bsi.tw,kw.
16. bsis.tw,kw.
17. endocarditis.tw,kw.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. Drug Therapy, Combination/
20. ((combination* or combine* or combining or combo\$1 or second line) adj2 (therapy or therapies or therapeutic* or treatment* or regimen* or antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or group* or arm\$1)).tw,kw.
21. ((synergist* or synergy) adj3 (therapy or therapies or therapeutic* or treatment* or regimen* or antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or combination* or combo\$1 or activity)).tw,kw.
22. (standard* of care adj3 (combination* or combine* or combining or combo\$1 or second line)).tw,kw.
23. (adjunctive or concomitant or escalated therap*).tw,kw.
24. 19 or 20 or 21 or 22 or 23
25. 9 and 18 and 24

EMBASE

- #27. #10 AND #20 AND #26
- #26. #21 OR #22 OR #23 OR #24 OR #25
- #25. adjunctive:ti,ab,kw OR concomitant:ti,ab,kw OR 'escalated therap*':ti,ab,kw
- #24. ((synergist* OR synergy) NEAR/3 (therapy OR therapies OR therapeutic* OR treatment* OR regimen* OR antibiotic* OR 'anti biotic*' OR antimicrobial* OR 'anti microbial*' OR combination* OR combo\$ OR activity)):ti,ab,kw
- #23. ((synergist* OR synergy) NEAR/3 (therapy OR therapies OR therapeutic* OR treatment* OR regimen* OR antibiotic* OR 'anti biotic*' OR antimicrobial* OR 'anti microbial*' OR combination* OR combo\$ OR activity)):ti,ab,kw
- #22. ((combination* OR combine* OR combining OR combo\$ OR 'second line') NEAR/2 (therapy OR therapies OR therapeutic* OR treatment* OR regimen* OR antibiotic* OR 'anti biotic*' OR antimicrobial* OR 'anti microbial*' OR group* OR arm\$)):ti,ab,kw

#21. 'combination drug therapy'/de
 #20. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
 #19. endocarditis:ti,ab,kw
 #18. bsis:ti,ab,kw
 #17. bsi:ti,ab,kw
 #16. 'blood stream infection*':ti,ab,kw
 #15. 'bloodstream infection*':ti,ab,kw
 #14. bacter\$emia*:ti,ab,kw
 #13. 'bacterial endocarditis'/exp
 #12. 'bloodstream infection'/exp
 #11. 'bacteraemia'/exp
 #10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
 #9.mssab:ti,ab,kw
 #8.mrsab:ti,ab,kw
 #7.mssa:ti,ab,kw
 #6.mrsa:ti,ab,kw
 #5.'s aureus':ti,ab,kw
 #4.'staphylococcus aureus':ti,ab,kw
 #3.'methicillin susceptible staphylococcus aureus'/exp
 #2.'methicillin resistant staphylococcus aureus'/exp
 #1.'staphylococcus aureus'/de

Cochrane CENTRAL (Wiley)

#1 MeSH descriptor: [Staphylococcus aureus] explode all trees
 #2 ("staphylococcus aureus"):ti,ab,kw
 #3 ("s aureus"):ti,ab,kw
 #4 (mrsa):ti,ab,kw
 #5 (mssa):ti,ab,kw
 #6 (mrsab):ti,ab,kw
 #7 (mssab):ti,ab,kw
 #8 {OR #1-#7}
 #9 MeSH descriptor: [Bacteraemia] explode all trees
 #10 MeSH descriptor: [Endocarditis, Bacterial] explode all trees
 #11 (bacter*mia):ti,ab,kw
 #12 ("bloodstream infection"):ti,ab,kw
 #13 ("bloodstream infections"):ti,ab,kw
 #14 ("blood stream infection"):ti,ab,kw
 #15 ("blood stream infections"):ti,ab,kw
 #16 (bsi):ti,ab,kw
 #17 (bsis):ti,ab,kw
 #18 (endocarditis):ti,ab,kw
 #19 {OR #9-#18}
 #20 MeSH descriptor: [Drug Therapy, Combination] this term only
 #21 (((combination* or combine* or combining or combo or combos or "second line") NEAR/2 (therapy or therapies or therapeutic* or treatment* or regimen* or antibiotic* or "anti biotic" or "anti biotics" or antimicrobial* or "anti microbial" or "anti microbials" or group* or arm OR arms))):ti,ab,kw
 #22 ((synergist* or synergy) NEAR/3 (therapy or therapies or therapeutic* or treatment* or regimen* or antibiotic* or "anti biotic" or "anti biotics" or antimicrobial* or "anti microbial" or "anti microbials" or combination* or combo or combos or activity)):ti,ab,kw

#23 (("standard of care" or "standards of care") NEAR/3 (combination* or combine* or combining or combo or combos or "second line")):ti,ab,kw

#24 (adjunctive or concomitant or "escalated therapy" or "escalated therapies" or "escalated therapeutic" or "escalated therapeutics"):ti,ab,kw

#25 {OR #20-#24}

#26 #8 AND #19 AND #25

All database results were exported to EndNote and duplicates were removed using a multi-step process.

Results

Detailed descriptions of studies and pooled analyses per type of antibiotic

Combination with aminoglycosides

Study characteristics

Five studies (3 RCTS and 2 cohort studies) [1][2][3][4][5] comprising a total of 210 patients (128 combination group; 122 monotherapy) compared the use of beta-lactams monotherapy with beta-lactams plus aminoglycosides. These studies had small sample sizes and were published more than 2 decades ago, most of them before 1985 [1][2][3][4].

All but except one study [1] focused on patients with native valve endocarditis, in particular right-sided endocarditis in drug users. They evaluated the combination with gentamycin. However, the dose and the duration of gentamycin therapy varied across studies, usually ranging from 1 to 3 mg/kg of body weight every 8 hours for a total duration of 7 up to 14 days.

Mortality

None of these studies showed a reduction in mortality with combination therapy. However, mortality rates were evaluated at different time points: Two studies did not define the time point of assessment [2][3], two reported mortality during antibiotic treatment [1][5], and one reported 30-day mortality (among others) [4]. Death at any time point occurred in 14.1% (18 of 128) in the combination group and 12.3% (15 of 122) in the monotherapy group. One study had zero deaths in both arms [2]. When the remaining 4 studies were pooled together, combined therapy with aminoglycosides was not associated with a significant reduction of mortality (pooled RR 1.17, 95% CI 0.64–2.16; Table 2 within the manuscript). There was no significant heterogeneity between included studies ($I^2=0\%$, $p=0.60$).

Duration or persistent bacteraemia

One RCT of 78 patients with native valve endocarditis (68.8% right-sided) showed that patients who received additional gentamycin during the first 2 weeks of therapy had faster eradication of *S.aureus* bacteraemia [4]. Another RCT of 90 patients with MSSA right-sided native valve endocarditis [5] did not find that combination therapy with for the first 7 days of therapy was associated with any significant benefit in terms of persistent bacteraemia and relapse [5]. However, it should be noted that this later study had limited statistical power for these outcomes.

Adverse events

Only two studies reported detailed information about nephrotoxicity, and thus, we could not meta-analyze these data [4][5]. However, nephrotoxicity was probably more likely to occur in patients receiving adjunctive therapy with aminoglycosides (17.1% monotherapy group vs 37.2% combination group and 7.9% vs 13.9%, respectively) [4][5].

Combination with rifampicin

Study characteristics

Four studies comprising 2,011 patients (1,203 combination group; 808 monotherapy) compared the use of beta-lactams with the combination therapy with rifampicin [6][7][8][9]. Two non-randomised studies and one post-hoc analysis of a RCT focused on patients with deep-seated infections [6][8][9] whereas the single RCT involved all focuses of *S. aureus* bacteraemia [7], and only 40% of study participants had a deep-seated focus and <8% of prosthetic devices or hardware.

The dose and duration of the combined treatment with rifampicin was varied, usually ranging from 600 to 900 mg/day and administered for more than 12 days. However, one study accepted a lower dose of rifampicin (450 mg once daily for patients under 50 kg) and included a small proportion of patients who received a short-course of rifampicin (between 1 and 13 days) [6].

Mortality

Only 2 studies described 30-day mortality and could not be meta-analyzed [6][8]. We next examined 90-day mortality, which might provide a less accurate estimate of the true effectiveness of combination therapy. The pooled analysis of 4 studies [6][8][9][10] showed that the combination therapy did not reduce 90-day mortality (pRR 0.74, 95% CI 0.48–1.13). The test for heterogeneity was statistically significant ($p=0.003$, $I^2=78\%$). When the single study that did not focus on deep-seated infections [7] was excluded from the analysis, the combination therapy was associated with a reduced risk of 90-day mortality (pRR 0.62, 95% CI 0.42–0.92), but the heterogeneity was still high ($p=0.03$, $I^2=78\%$); Table 2 within the manuscript.

Duration bacteraemia

The RCT from Thwaites et al (ARREST) did not find that rifampicin shortened the duration of bacteraemia within the first 7 days of follow-up [7].

Relapse/recurrence

Three studies evaluated this outcome. Relapse was evaluated within 90 days of follow-up in one study [6] and within 180 days in the other [8]. The third one evaluated recurrence of microbiologically proven *S. aureus* infection after 7 days of clinical improvement [7]. The incidence of overall relapse/recurrence rate was 1.8% (12 of 660) in the combination group and 6.7% (34 of 509) in the monotherapy group. When these 3 studies were pooled together, combination therapy was significantly associated with a decreased risk of relapse (pRR 0.32, 95%CI CI, 0.18–0.58; $I^2=0\%$). Of note, however, 2 studies had moderate-high risk of bias.

Adverse events

According to Thwaites et al, patients in the rifampicin group had more frequently antibiotic or drug-modifying adverse events by week 12 (17% vs 10%; $p=0.004$), predominantly gastrointestinal disorders (2.7% vs 1.8%) and drug interactions (6% vs 2%). Two rifampicin patients (0.5%) experienced hepatic adverse events, both with prior liver disease. Additionally, 2 out of 270 patients (0.7%) who received rifampicin, developed resistance to this drug during the follow-up.

Combination with daptomycin

Study characteristics

Two studies (1 RCT and 1 cohort study) comprising 454 patients (189 combination group; 265 monotherapy) compared the use of beta-lactams with the combination therapy with

daptomycin[11][12]. These studies addressed patients with SAB and < 15% of patients with endocarditis, osteoarticular infections, and implanted foreign materials.

The standard therapy was either cloxacillin or cephalosporins. In the cohort study, however, other beta-lactams active against MSSA (i.e., meropenem or piperacillin-tazobactam) were also considered appropriate. The dose of daptomycin was lower in the RCT than in the cohort study (6 mg/kg/day versus 10 mg/kg/day, respectively). Daptomycin was given for a total of 5 days (RCT) to a median of 9 days (cohort study).

Mortality

The overall 30-day rate among the two studies was 18.0% (34/189) in the combination group and 15.1% (40/265) in the monotherapy group.

Duration bacteraemia

The RCT did not find any significant reduction in the median duration of bacteraemia with the use of the combination therapy compared to the monotherapy (3.06 days vs 3.0 days; $p=0.77$)[11]. In contrast, the observational study concluded that persistent bacteraemia was more frequent in the combination group compared to the monotherapy group (26.7% [35/131] vs 9.1% [18/197], respectively; $p<0.001$)[12]. However, this result might reflect unadjusted imbalances between study groups, with more severely ill patients receiving the combination with daptomycin.

Relapse

The RCT did not find that receiving combination therapy was associated with lower likelihood of relapsed bacteraemia within 30 or 90 days (1.9% vs 0%; 3.8% vs 3.9%, respectively).

Adverse events

According to the RCT, there were no significant differences in the proportion of patients who developed renal failure (47.7% vs 28.9%), hepatotoxicity (3.8% vs 5.9%) or rhabdomyolysis (0% vs 5.9%) within 5 days of enrollment between the combination and the monotherapy groups.

Combination with Levofloxacin

One single multicentric RCT assessed the combination therapy with levofloxacin (191 patients combination group; 190 monotherapy)[9]. Although this study included adult patients with SAB within 7 days of sampling, > 80% of patients had deep infections (e.g., infected prosthetic material, endocarditis, osteomyelitis).

Levofloxacin was dosed at 500 mg/day and was given for a long period of time (median of 42 days). Deep-seated infections and endocarditis could be treated with an additional therapy with an aminoglycosides or rifampicin apart from the study drug; this was more frequent in the monotherapy group.

Mortality

Combination therapy with levofloxacin did not decrease 28-day (14% combination vs 14% monotherapy) or 90-day mortality (18% combination vs 21% monotherapy).

Adverse events

Although data was not shown, authors reported no significant differences regarding the number of patients with liver enzyme elevations, *Clostridioides difficile* diarrhea or allergic reactions between the study groups.

Combination with vancomycin

One retrospective study including 46 patients in each study arm evaluated the role of combination therapy with vancomycin as empirical treatment; before knowing the antibiotic susceptibility of *S. aureus* [13]. Not surprisingly, the median duration of the combination therapy was as short as 2.8 days. Of note, the dose of vancomycin and the number of patients with endocarditis, osteoarticular infections, and implanted foreign materials were not reported.

Outcomes

The empirical use of vancomycin in combination with a beta-lactam was not associated with decreased 30-day mortality (adjusted HR 1.54, 95% CI 0.25–9.53) or duration of bacteraemia (2.8 days vs 2.2 days). More patients in the combination group developed acute renal failure (10.8% vs 2.4%). However, all these results should be interpreted with caution given the limited statistical power of the analyses.

Supplementary Table S1. Detailed description of study population

| Author, year country ^a | IV drug users, No (%) | Endocarditis, No (%) [% only right-sided] | Patients with prosthetic material ^b , n (%) | Renal impairment, No (%) [% dialysis] | ID consult | Polimicrobial bacteraemia | Quality-of-care indicators ^c |
|---|---|---|--|--|-------------------------|---------------------------|---|
| Watanakunakorn, 1977, United States | Yes, 7 (17.5%) | Yes, all study population [30.0%] | NR, but 2 patients with prosthetic valve (5%) | Probably included, but NR | Yes, per study protocol | No | A, C |
| Abrams, 1979, United States | Yes, all study population | Yes, all study population [76.9%] | NR | NR | Yes, per study protocol | Unknown | C |
| Rajashekaraiah, 1980, United States | Yes; 14 (42.4%, all patients with right endocarditis) | Yes, all study population [42.4%] | NR | Yes, 1 patient | Yes, per study protocol | No | C |
| Korzeniowski, 1982, United States | Yes; 48 (61.5%) | Yes, all study population [68.8%] | No | NR | Unknown | No | A |
| Ribera, 1996, Spain | Yes, all study population | Yes, all study population [100%] | NR | Yes, NR | Unknown | No | A, D |
| Ruotsalainen, 2006, Finland | NR | Yes, 70 (18%) [NR] | 129 (34%) | 59 (16%) | Yes, per study protocol | No | A, B, C |
| Ruotsalainen, 2006, Finland (post-hoc analysis) | NR | Yes, 70 (21%) [NR] | NR | 45 (14%) | Yes, per study protocol | No | A, B, C |
| Forsblom, 2015, Finland | NR | Yes, 62 (17.3%) | Yes (NR) | Yes (NR) | Yes, 91% | Unknown | C |
| Park, 2017, Korea | NR | NR | NR | 21 (23%) | Unknown | No | No |
| Thwaites, 2018, United Kingdom | NR | Yes, 33 (4%). Prosthetic valve endocarditis 7 (1%). | Infected implanted vascular device 36 (5%). Prosthetic valve and joint 14 (2%) | 198 (18%) | Yes, per study protocol | No | A, B, C |

| | | | | | | | |
|------------------------|----|-------------------------|---|------------|----------------------------|---------|-----------|
| Grillo, 2019, Spain | NR | Yes, 31 (8.9%) [NR] | Cardiac devices 16 (5.8%); osteoarticular prosthesis 25 (9%) | 98 (28.2%) | Yes, per study protocol | Unknown | B, C, D |
| Rieg, 2020, Germany | NR | Yes, 133 (23%) [NR] | 378 (65.4%) (orthopedic, vascular graft, pacemaker and cardiac prosthetic valve) | NR | Yes, 79% | Unknown | B, C |
| Cheng, 2020, Canada | NR | Yes, 12 (11.5%) [NR] | Intravascular 14, (13.5%); extravascular foreign body 9 (8.7%); prosthetic cardiac valve 9 (8.7%) | NR | Yes | No | A, B, C,D |

^aAbbreviations: ID, infectious diseases; IV, intravenous; SAB, *Staphylococcus aureus* bacteraemia; MSSA, methicillin-susceptible *S. aureus*; NR, not reported.

^bProsthetic material: cardiac devices (including pacemaker and cardiac prosthetic valve), orthopedic devices and vascular graft.

^cQuality-of-care indicators; A: follow-up blood culture obtained at a scheduled time; B: source control; C: infectious diseases consult; D: indications for the performance of an echocardiography reported.

Supplementary Table S2. Outcomes

| Monotherapy vs combination therapy | | | | | | | | | | | | | | | |
|--|------------------------------|---------------|------------------------------------|---------------|--------------------------------------|-------------|---|----------|---|--------------------------|------------------------------|-------------------------------------|---------------------|--------------|--|
| Author, year | 30-day mortality, n (%) | | 90-day mortality, n (%) | | Other mortality ^a , n (%) | | Persistent bacteraemia ^b , n (%) | | Duration of bacteraemia, mean days (SD) | | Relapse ^c , n (%) | Adverse events ^d , n (%) | | Conclusions | |
| Adjunctive Aminoglycoside | | | | | | | | | | | | | | | |
| Watanakunakorn, 1977 | NR | | NR | | 10/25 (40) | 6/15 (40) | NR | | NR | | NR | | No differences (NR) | | No significant differences |
| Abrams, 1979 | NR | | NR | | 0/12 (0) | 0/13 (0) | NR | | NR | | NR | | 0/12 (0) | 0/13 (0) | No significant differences |
| Korzeniowski, 1982 | 1/35 (2.9) | 5/43 (11.6) | NR | | NR | | NR | | 3.75 (1.3) | 2.85 ^e (1.25) | NR | | 6/35 (17.1) | 16/43 (37.2) | Combination reduced the bacteraemia duration. No significant differences in mortality. More nephrotoxicity with combination therapy. |
| Rajashekaraiah, 1980 | NR | | NR | | 3/12 (25.0) | 5/21 (23.8) | NR | | NR | | NR | | NR | | No significant differences |
| Ribera, 1996 | NR | | NR | | 1/38 (2.6) | 2/36 (5.6) | 1/38 (2.6) | 0/36 (0) | NR | | 0/38 (0) | 1/36 (2.7) | 3/38 (7.9) | 5/36 (13.9) | No significant differences |
| Adjunctive Rifampicin | | | | | | | | | | | | | | | |
| Ruotsalainen, 2006 (post-hoc analysis) | NR | | 25/66 (37.9) | 44/265 (16.6) | NR | | NR | | NR | | NR | | NR | | Combination decreased 90-day mortality |
| | | | 3.06; 95%CI (1.69–5.54), p < 0.001 | | | | | | | | | | | | |
| Forsblom, 2015 | 16/96 (16.7) | 28/261 (10.7) | 25/96 (26.0) | 41/261 (15.7) | NR | | NR | | NR | | 2/96 (2.0) | 2/261 (0.7) | NR | | Combination decreased 90-day mortality |
| | OR 0.60 (0.31–1.17), p=0.130 | | OR 0.53 (0.30–0.93), p = .026 | | | | | | | | OR 0.40 (0.06–2.89), p=0.349 | | | | |

| | | | | | | | | | | | | | |
|--------------------------------|---------------------------------|-----------------------------|---|------------------------------|-----------------|-----------------|-----------------------------|---|------------------------------|---------------------|---|----------------------------|----------------------------|
| Rieg, 2020 | 59/262 (22.5) | 50/313 (16.0) | 96/258 (37.2) | 94/307 (30.6) | NR | NR | NR | 16/255 (6.3) | 7/297 (2.4) | NR | Combination decreased 90-day mortality in patients with implanted foreign devices | | |
| | P=0.054 | | Adjusted HR 0.69 (0.47-1.02) p = 0.061 | | | | | P=0.031 | | | | | |
| Thwaites, 2018 | NR | 56/388 (14.4) | 56/370 (15.1) | 17/388 (4.3) | 25/370 (6.7) | NR | No differences (NR) | NR | 39/388 (24.2) | 63/370 (27.2) | No significant differences | | |
| | | HR 1.10 (0.76-1.60), p=0.60 | | HR 1.60 (0.86-2.95), p = .13 | | | | | HR 1.78 (1.20-2.65), p=0.004 | | | | |
| Adjunctive Levofloxacin | | | | | | | | | | | | | |
| Ruotsalainen, 2006 | 27/190 (14.2) | 26/191 (13.6) | 39/190 (20.5) | 34/191 (17.8) | NR | NR | NR | 3 patients in total (differences between groups NR) | | No differences (NR) | No significant differences | | |
| | OR 1.05 (0.59-1.88), p=0.87 | | OR 1.19 (0.72-1.99), p=0.50 | | | | | | | | | | |
| Adjunctive Vancomycin | | | | | | | | | | | | | |
| Park, 2017 | 2/46 (4.3) | 4/46 (8.7) | NR | NR | NR | 2.58 (0.82) | 3.03 ^e (0.97) | NR | 1/42 (2.4) | 4/37 (10.8) | No significant differences | | |
| | HR 1.54 (0.249-9.532), p= 0.642 | | | | | | | | | | | | |
| Adjunctive Daptomycin | | | | | | | | | | | | | |
| Grillo, 2019 | 34/214 (15.9) | 26/136 (19.1) | 47/214 (22.0) | 37/136 (27.2) | 15/214 (7.0) | 12/136 (8.8) | 18/197 (9.1) | 35/131 (26.7) | NR | NR | NR | No significant differences | |
| | | | Adjusted HR 0.9 (0.57-1.43), p=0.67 | | | | P < .001 | | | | | | |
| Cheng, 2020 | 6/51 (11.8) | 8/53 (15.1) | 9/51 (17.6) | 10/53 (18.9) | NR | NR | 1.65 | 2.04 | 2/51 (3.9) | 2/53 (3.8) | 13/51 (25.5) | 21/53 (39.6) | No significant differences |

Abbreviations: NR, not reported; SD, standard deviation.

^a Time of assessment: 7-day in Ribera and Grillo, 14-day in Thwaites, 6-weeks in Watanakunakorn, NR in Abrams and Rajashekaraiyah.

^b Assessment at 4 days in Ribera, at 72h after starting antibiotic treatment in Grillo.

^c Time of assessment: 90-day in Forsblom and Cheng, 6-months in Ribera and Rieg.

^d Nephrotoxicity in Watanakunakorn, Abrams, Korzeniowski, Ribera, Park and Cheng; antibiotic-modifying adverse events in Thwaites; *C. difficile* infection, allergic reaction or liver enzyme elevation in Ruotsalainen.

^e For studies that reported the duration of bacteraemia as a median [inter-quartile range (IRQ) or range], we estimated the mean as devised by Wan et al [14].

Supplementary Figures

Figure S1. Risk of bias for observational studies.

| | Confounding bias | Selection bias | Classification bias | Missing data | Outcome bias | Reporting bias | Overall assessment of bias |
|--|------------------|----------------|---------------------|--------------|--------------|----------------|----------------------------|
| Watanakunakorn, 1977 | ● | ● | ● | ● | ● | ● | ● |
| Rajashekaraiah, 1980 | ● | ● | ● | ● | ● | ● | ● |
| Ruotsalainen, 2006 (post-hoc analysis of RCT) | ● | ● | ● | ● | ● | ● | ● |
| Forsblom, 2015 | ● | ● | ● | ● | ● | ● | ● |
| Park, 2017 | ● | ● | ● | ● | ● | ● | ● |
| Grillo, 2019 | ● | ● | ● | ● | ● | ● | ● |
| Rieg, 2020 | ● | ● | ● | ● | ● | ● | ● |

Figure S2. Risk of bias for randomised controlled trials.

| | 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 (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-------------------|---|---|---|---|--|--------------------------------------|------------|
| Abrams 1975 | ? | ? | - | ? | ? | ? | ? |
| Korzeniowski 1982 | + | ? | - | ? | - | ? | ? |
| Ribera 1996 | + | ? | - | ? | + | ? | ? |
| Ruotsalainen 2006 | ? | + | ? | ? | ? | + | - |
| Thwaites 2018 | + | + | ? | + | + | + | ? |
| Cheng 2020 | + | + | + | + | + | + | ? |

Figure S3. Funnel plot for 30-day mortality.

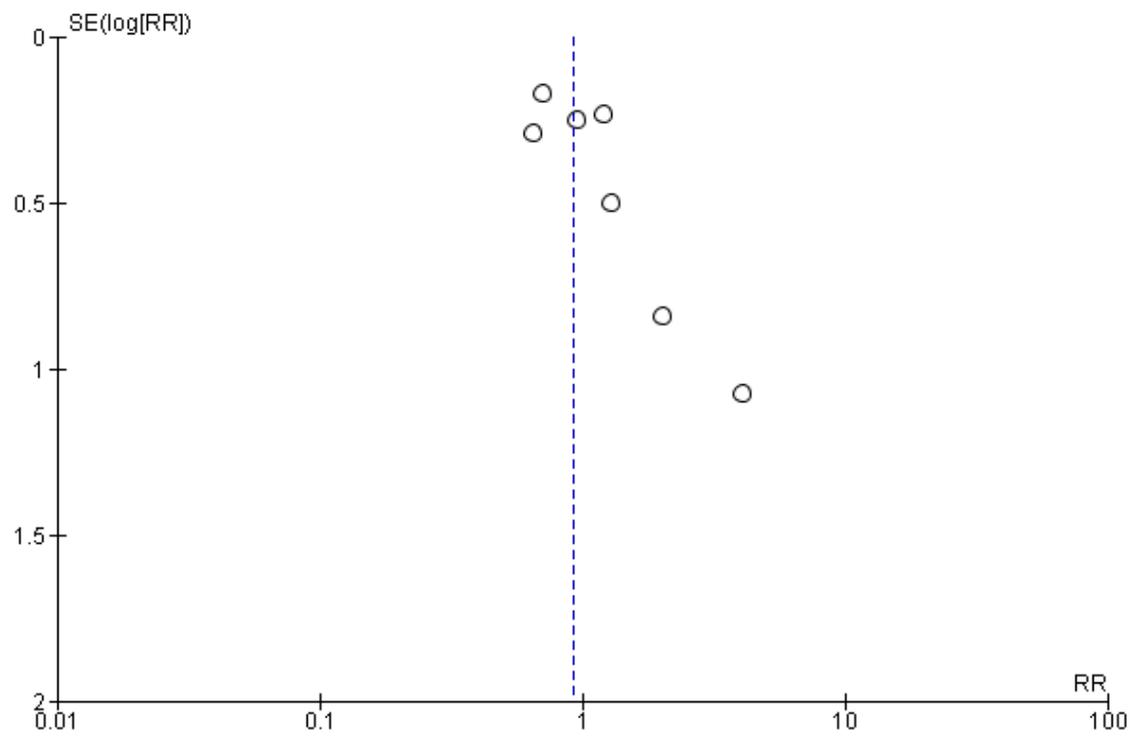


Figure S4. Funnel plot for 90-day mortality.

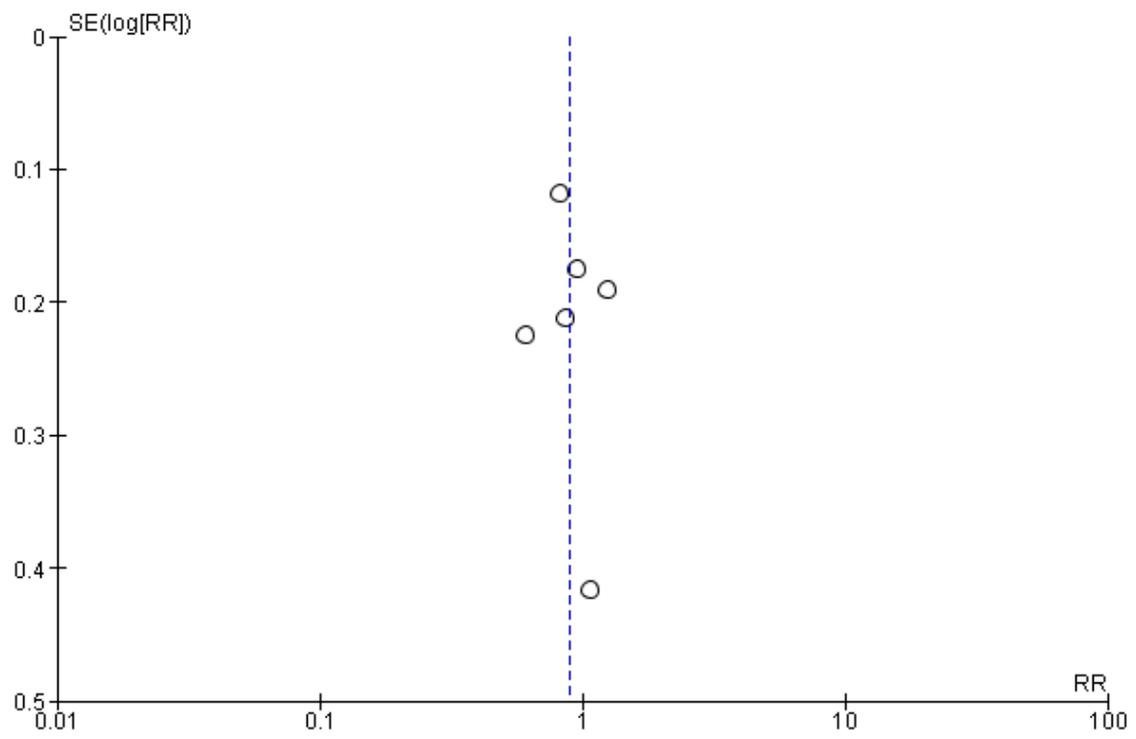
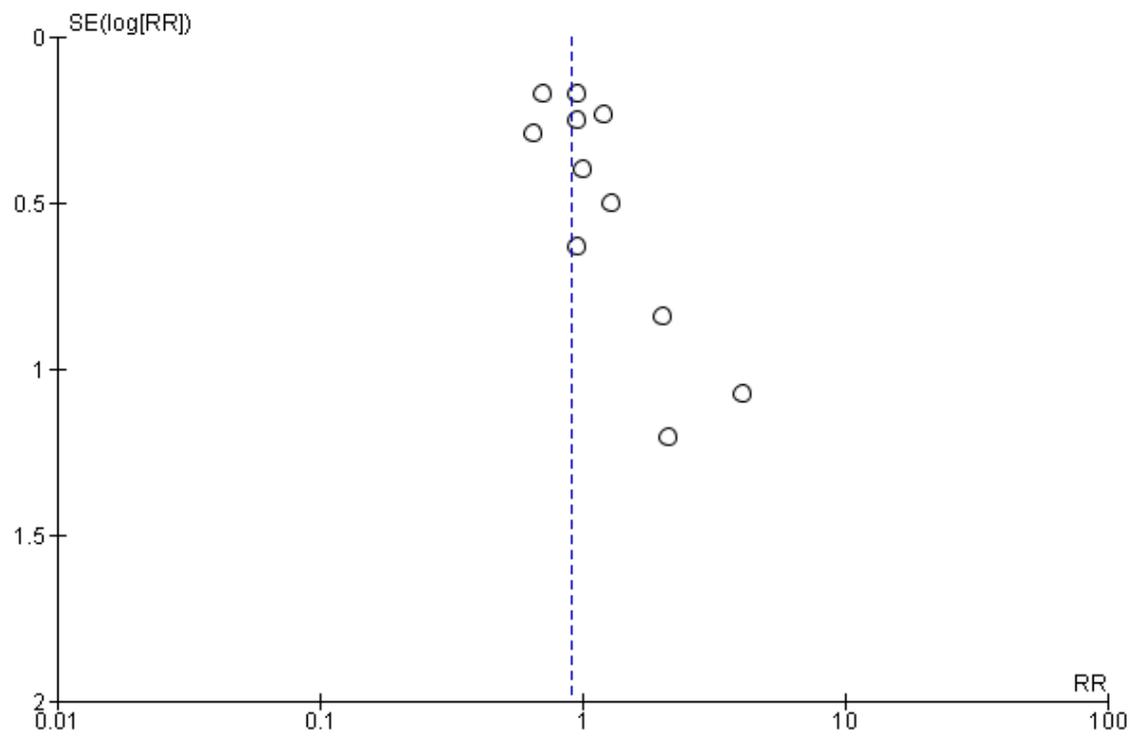


Figure S5. Funnel plot for any-time mortality.



*The Egger test also showed some evidence for publication bias ($p=0.048$)

Figure S6. Funnel plot for relapse or recurrence

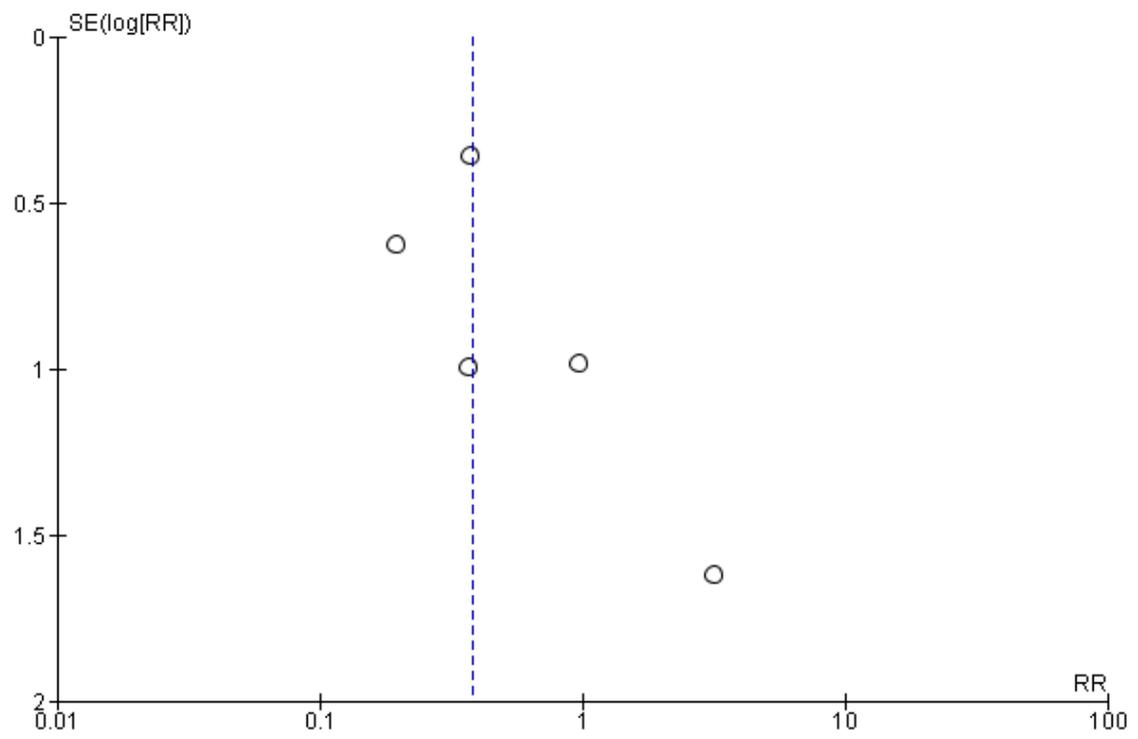
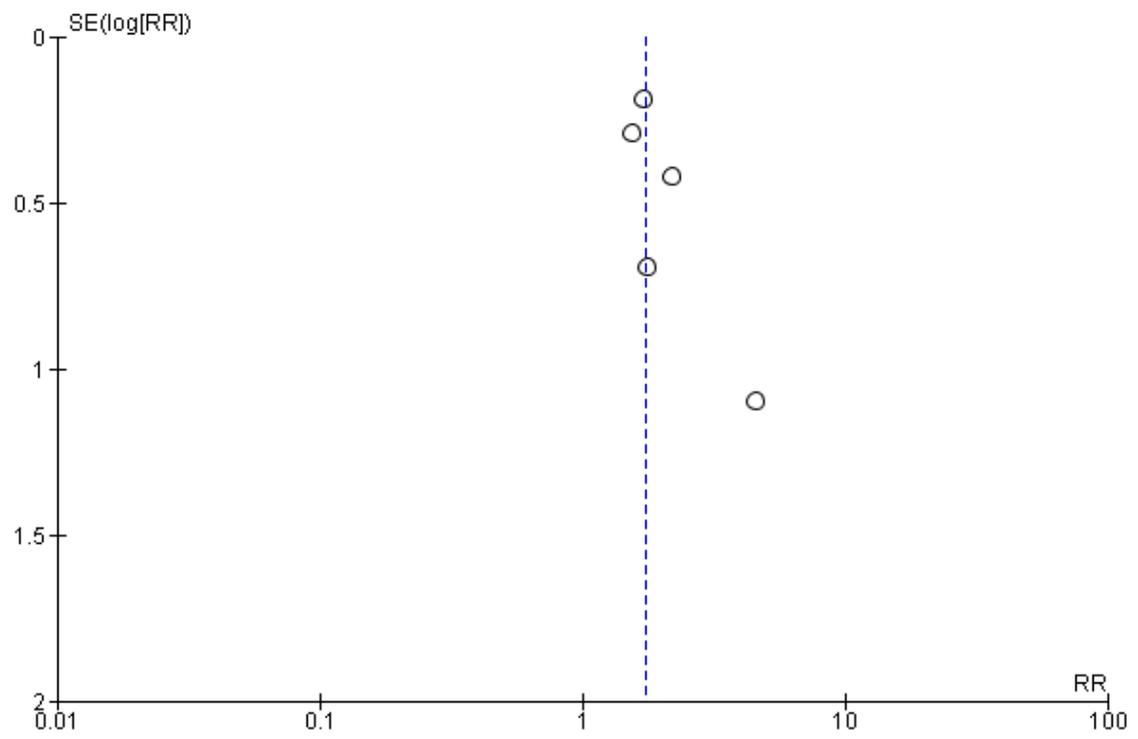


Figure S7. Funnel plot for drug adverse-events



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