Serious MRSA infection: anything new?

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Potential Conflicts of Interest

I have received:

Consulting fees from Abbott Laboratories, Actelion, Astellas, Astra-Zeneca, Bayer, Biomèrieux, Cerexa, Cubist, Da Volterra, The European Tissue Symposium, The Medicines Company, MedImmune, Menarini, Merck, Motif Biosciences, Nabriva, Optimer, Paratek, Pfizer, Phico therapeutics, Qiagen, Roche, Sanofi-Pasteur, Seres, Summit, and Synthetic Biologics;

Lecture fees from Abbott, Alere, Astellas, Astra-Zeneca, Merck, Pfizer & Roche;

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I was a member of the DMC for the ARREST study.

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

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Summary

Background *Staphylococcus aureus* bacteraemia is a common cause of severe community-acquired and hospital-acquired infection worldwide. We tested the hypothesis that adjunctive rifampicin would reduce bacteriologically confirmed treatment failure or disease recurrence, or death, by enhancing early *S aureus* killing, sterilising infected foci and blood faster, and reducing risks of dissemination and metastatic infection.

Methods In this multicentre, randomised, double-blind, placebo-controlled trial, adults (≥18 years) with *S aureus* bacteraemia who had received ≤96 h of active antibiotic therapy were recruited from 29 UK hospitals. Patients were randomly assigned (1:1) via a computer-generated sequential randomisation list to receive 2 weeks of adjunctive

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*See appendix for full list of investigators

Combination antibiotic treatment

- Poor supportive evidence base for superiority vs monotherapy
- In general, 2 is not better than 1 and may be worse (AEs)
- Possible settings for combination treatment
  - High bacterial load
  - High mutational resistance rate e.g. TB, HIV
  - Poor therapeutic options e.g. CREs

S. aureus bloodstream infections (BSIs)

- *S. aureus* BSI is one of the most common and serious community and hospital-acquired bacterial infections
- Potential for *S. aureus* dissemination, with associated mortality of ~20%
- Treatment recommendations for *S. aureus* BSI are not based on sound evidence (~1,600 subjects in RCTs over 50 years)
- Recommended that *S. aureus* BSI is treated with at least 14 days of IV β-lactam antibiotic, or a glycopeptide if MRSA

Tong SY, et al. Clin Microbiol Rev 2015;28:603-61.
Kaasch A et al. J Hosp Infect 2014;68:242-51.
Thwaites GE, et al. Lancet Infect Dis 2011;11:208-22.
Naber CK, et al. Clin Infect Dis 2009;48 Suppl 4:S260-70.
Liu C, et al. Clinical infectious diseases 2011;52:e18-55.

S. aureus bloodstream infections (BSIs)

- Combination antibiotic therapy generally not recommended except in severe MRSA infections (e.g. endocarditis, prosthetic joint infections) …. weak evidence
- Adjunctive rifampicin has long been assumed to improve outcomes in serious *S. aureus* infections
- Good oral bioavailability & cell/tissue/bioflim penetration
- Meta-analysis: 3 RCTs and one cohort study
  - 54 subjects with *S. aureus* BSI treated with adjunctive rifampicin and 44 standard-therapy controls
  - rifampicin associated with reduced all-cause mortality and clinical or bacteriological failure

Norden CW, et al. J Infect Dis 1983;147:352-7.
Forrest GN, et al. Clin Microbiol Rev 2010;23:14-34.
Russell CD, et al. J Med Microbiol 2014;63:841-8.

ARREST trial (ISRCTN37666216; NIHR/HTA funded)

- Does adjunctive rifampicin enhance early killing of *S. aureus*, sterilise infected foci/blood faster, and so reduce the risk of dissemination, metastatic infection and death from *S. aureus* BSI?

Thwaites G et al. Lancet 2018;391:668-678.

ARREST methods (i)

- Adult inpatients (≥18 years) with symptoms and signs of infection, MSSA or MRSA ≥1 blood culture
- ≤96 hours of active antibiotic therapy for current infection (excluding stat doses)
- No evidence of *S. aureus* rifampicin non-susceptibility
- No contraindications to rifampicin
- Ineligible if
  - *S. aureus* was considered a blood culture contaminant
  - mixed with another likely pathogen
  - active tuberculosis suspected
  - If rifampicin considered mandatory

Thwaites G et al. Lancet 2018;391:668-678.

ARREST methods (ii)

- 1:1 randomisation to either 2 weeks of rifampicin or placebo, plus locally determined SoC BSI therapy
- Rifampicin 600 or 900mg daily according to weight, either twice-daily or once-daily dosing, oral or iv, as determined by the attending physician
- Until either 14 days completed or cessation of SoC BSI therapy, whichever earlier
- 12-weeks of assessments
    - Clinical: days 0, 3, 7, 10, 14, then weekly until discharge
    - Blood cultures on days 0, 3 & 7
    - CRP on days 3, 7, 10 &14
    - LFTs on days 3 and 10.
    - Week 12 visit ideally face-to-face.

Thwaites G et al. Lancet 2018;391:668-678.

Study power

- 80% power to detect a 30% relative reduction in bacteriological failure/death from 35% to 25%, an absolute difference of 10% corresponding to a number-needed-to-treat of 10 (two-sided alpha=0.05), assuming 10% lost-to-follow-up by 12 weeks

Thwaites G et al. Lancet 2018;391:668-678.

ARREST results (i)

- 2012-16; 770 participants in 29 UK hospital institutions
- 370 rifampicin vs 388 recipients, after 12 (randomisation error exclusions)
- Baseline characteristics well-balanced
- 65.3% male, median age 65 (IQR 50-76) yrs
- Charlson co-morbidity score 2 (0-3); mean CRP 164 mg/L
- 17.4% nosocomial BSIs; 6.2% MRSA
- Initial focus was deep in 301(39.7%)
- 9.2% subjects were in an intensive care unit

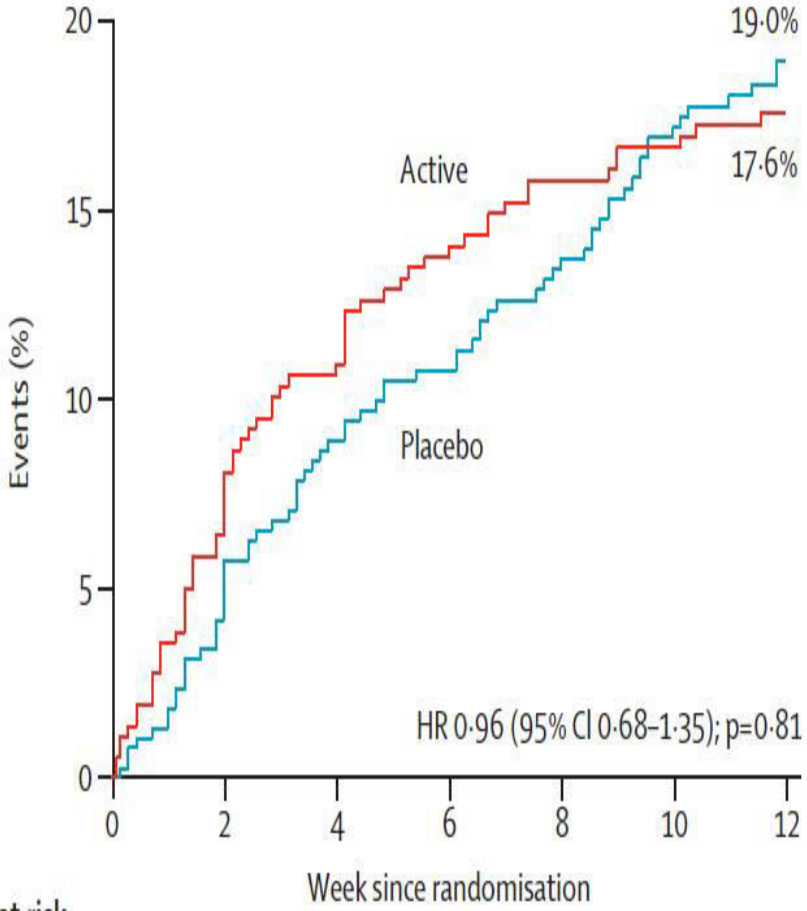
Thwaites G et al. Lancet 2018;391:668-678.

ARREST results: primary outcome

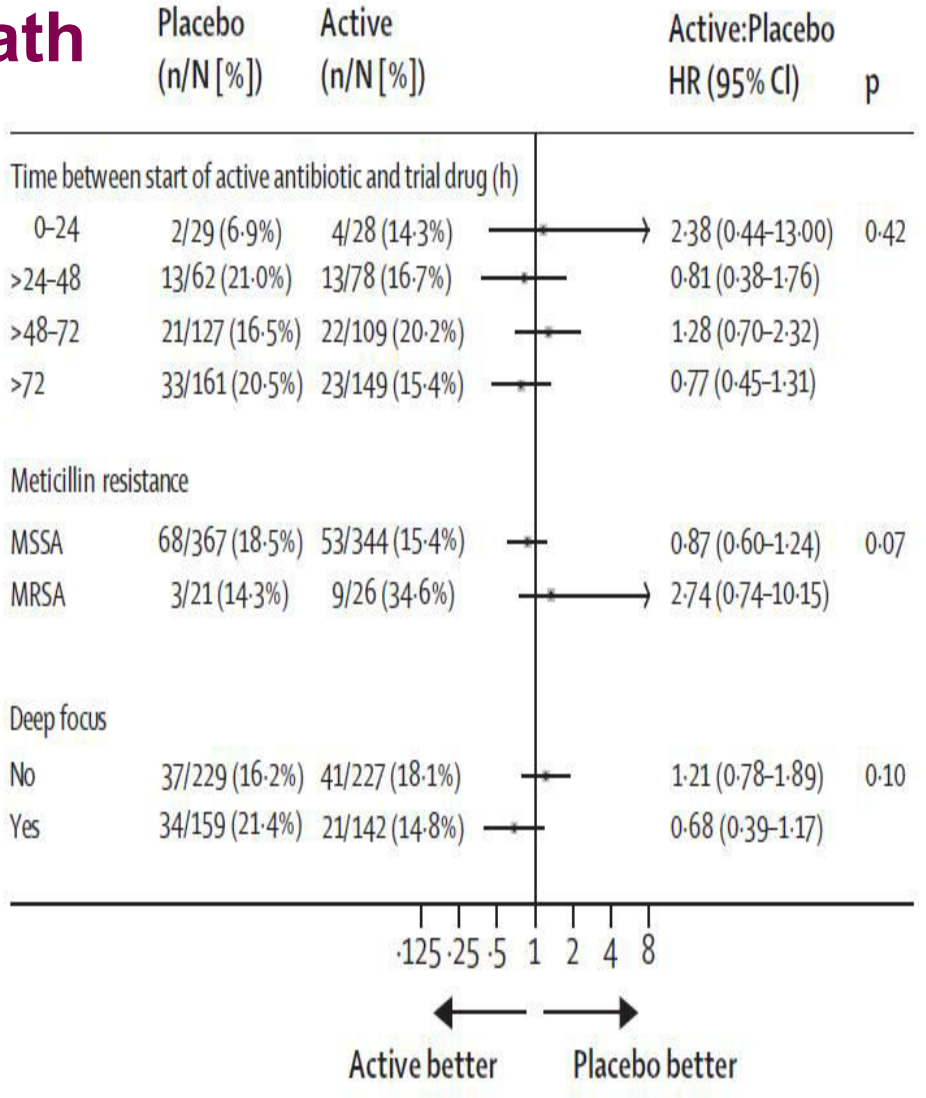
- By 12 weeks, bacteriological failure/recurrence or death occurred in 62 (16.8%) rifampin vs. 71(18.3%) placebo subjects (absolute risk difference = -1.4% (95% CI -7.0%,+4.3%); hazard ratio =0.96 (0.68,1.35) p=0.81
  - 4 (1.1%) vs. 5 (1.3%) failures (p=0.82)
  - 3 (0.8%) vs. 16 (4.1%) bacteriological recurrences (p=0.01)*
  - 55 (14.9%) vs. 50 (12.9%) deaths without bacteriological failure/recurrence (p=0.30)
- *NNT to prevent one bacteriologically-confirmed recurrence was 29

Thwaites G et al. Lancet 2018;391:668-678.

Bacteriologically confirmed treatment failure or disease recurrence, or death



Number at risk (events)												
Placebo	388 (16)	364 (18)	345 (7)	335 (10)	323 (13)	305 (7)	245
Active	370 (23)	331 (15)	314 (11)	302 (7)	289 (3)	280 (3)	222



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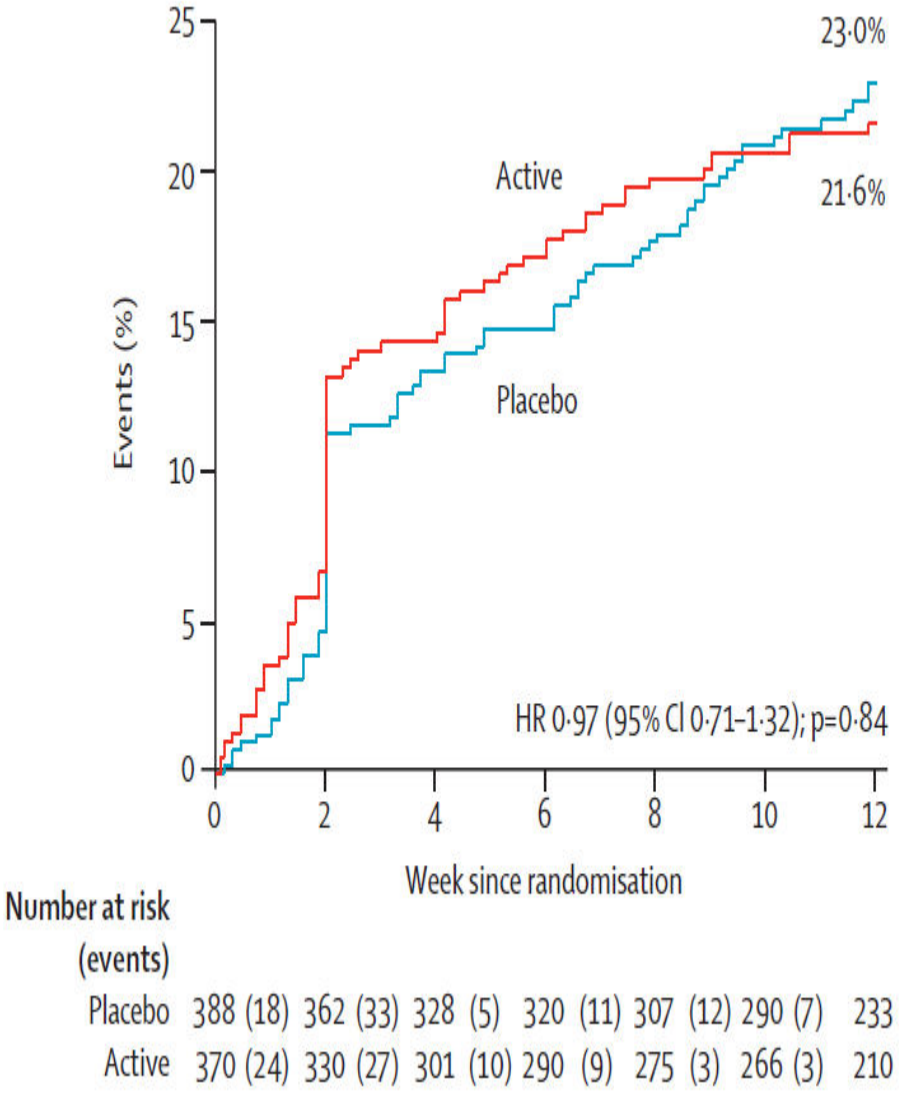
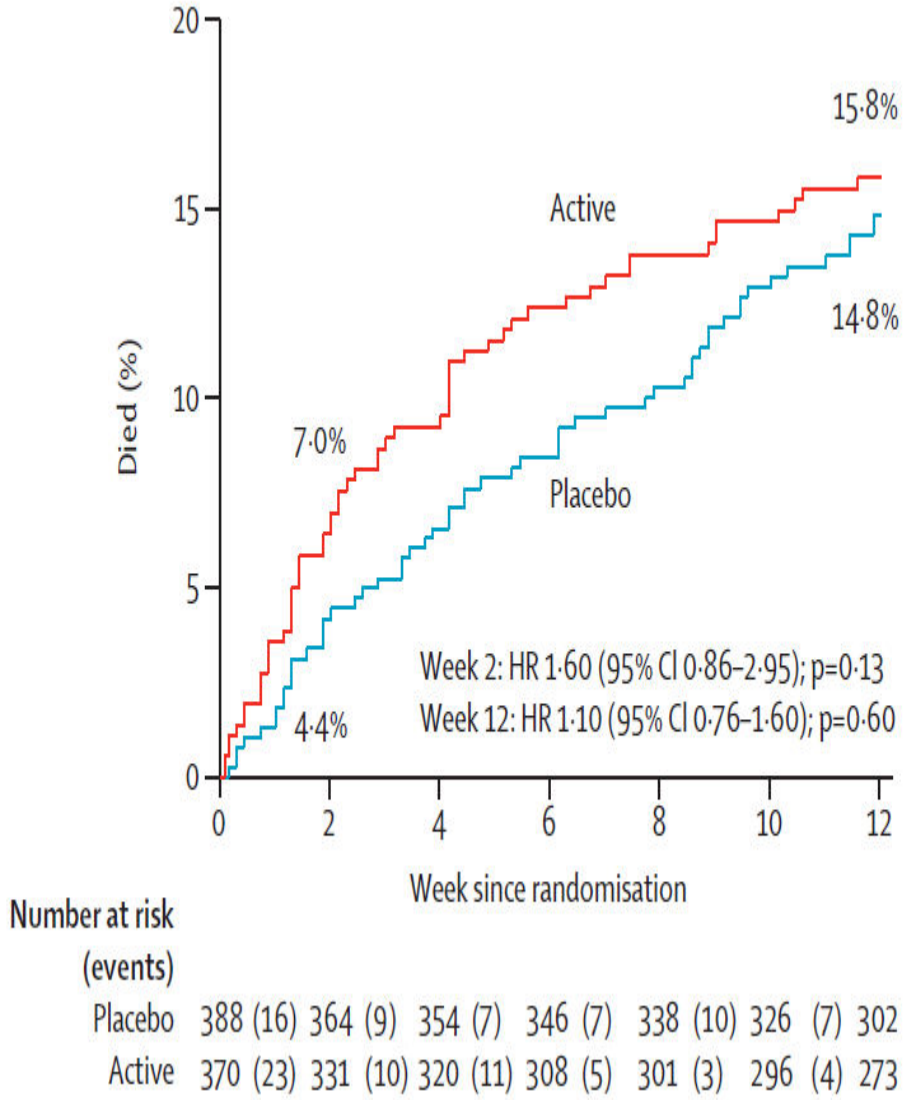
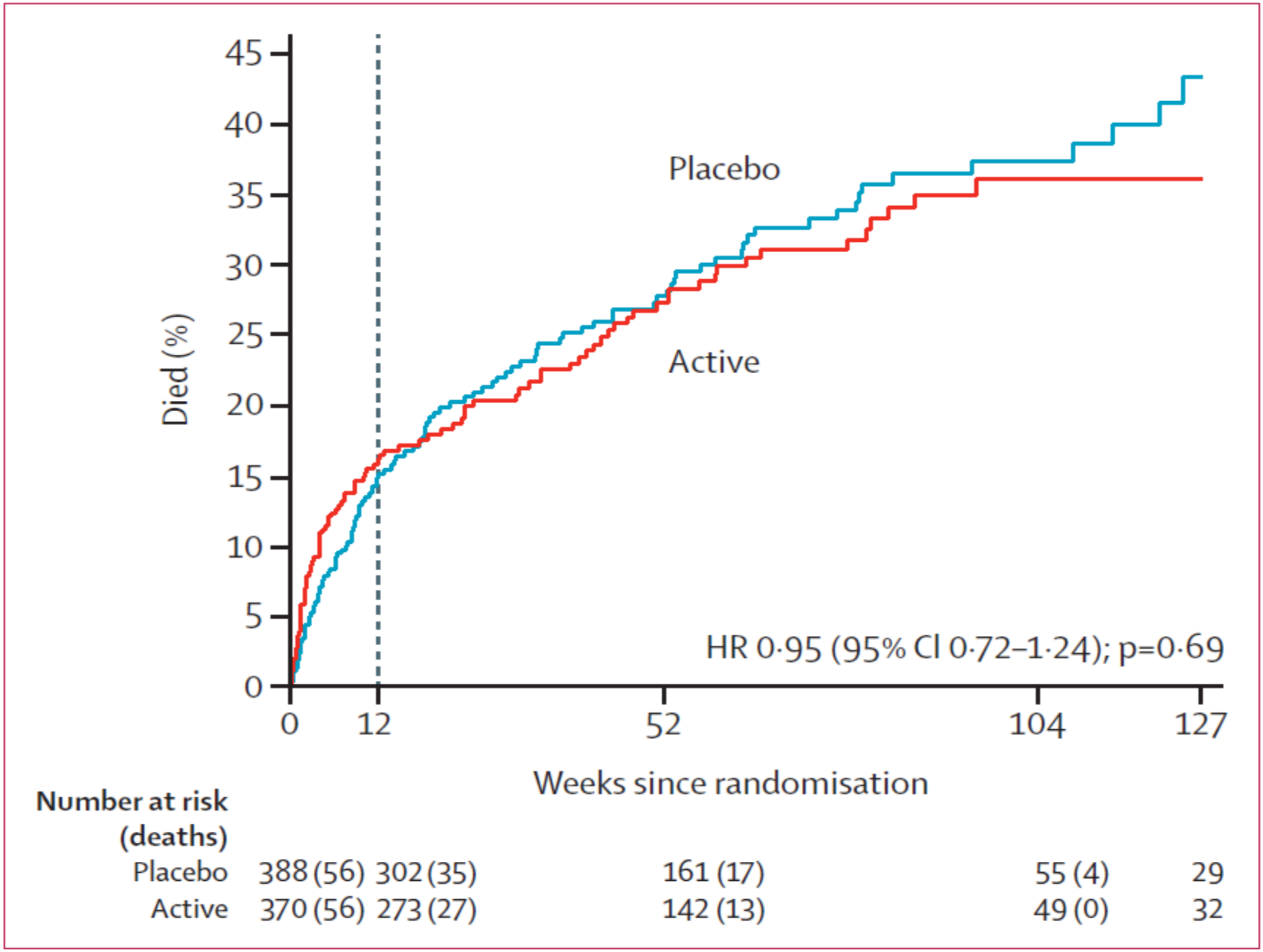
Clinically defined treatment failure or disease recurrence, or death, (left), and mortality (right)





Thwaites G et al. Lancet 2018;391:668-678.



Thwaites G et al. Lancet 2018;391:668-678.

ARREST results: adverse events

- By 12-weeks, 101 (27.3%) rifampicin vs. 94 (24.2%) placebo subjects experienced 112 vs. 116 SAEs (HR=1.21 (95% CI 0.92,1.61) p=0.17)
- 2 rifampicin recipients with pre-existing liver disease had non-fatal hepatic failure
- Bilirubin increased significantly in rifampicin subjects (day 3, $p<0.0001$); no evidence of differences in ALT or alk phos
- Trend towards more renal grade 3/4 AEs in rifampicin recipients (5.1% 2.3%; p=0.053)
- GI disorders (24 vs. 8 subjects, p=0.003) and renal/urinary disorders (8 vs. 1, p=0.02) were more common with rifampicin

Thwaites G et al. Lancet 2018;391:668-678.

Discussion

- MSSA (β-lactam SOC) dominated study
- Median 68 (48–85) hours between starting active antibiotics and trial drug
- No clear evidence of rifampicin enhanced bacterial killing
- Does rifampicin enhance sterilization of deep infection foci and so reduce disease recurrences?
- NNT to prevent recurrence = 26-29 sub-group analyses
- 12-week all-cause mortality (14.8%) was markedly lower than reported in recent large multi-centre study (29.2%)
- AE profile against rifampicin use

Thwaites G et al. Lancet 2018;391:668-678.

Discussion

- Should rifampicin be reserved for TB treatment?

- Using WHO data we found a (non-significant, p=0.07) correlation between locations harbouring increased rifampicin resistance in tuberculosis of native origin and European study countries showing increased rifampicin resistance in *C. difficile*

Freeman J, et al. Clin Microbiol Infect 2015;21:248.e9-248.e16.
World Health Organisation. Global tuberculosis report 2012.

ARREST results (ii)

- Initial focus was deep in 301(39.7%)
  - including 33 (4.4%) with endocarditis
  - 14 (1.8%) with infected prosthesis
- 130 (17.2%) were due to infected central/peripheral lines
- 138 (18.2%) associated with skin/soft tissue infections
- Other focus 6.5%; no focus identified 18.3%

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ARREST results (iii)

- SoC antibiotics (median 29 days) included
  - flucloxacillin in 81.7%)
  - vancomycin or teicoplanin in 50.1%)
- 159 placebo vs.142 rifampicin subjects had a deep focus that was drained/removed in 35(22.0%) vs. 29 (20.4%), respectively
- 22 (2.9%) participants withdrew consent
- At 12-weeks 5.1% had unknown vital status and 8.6% were not assessed for signs/symptoms of *S. aureus* infection (incl. consent withdrawals)

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ARREST results: primary outcome

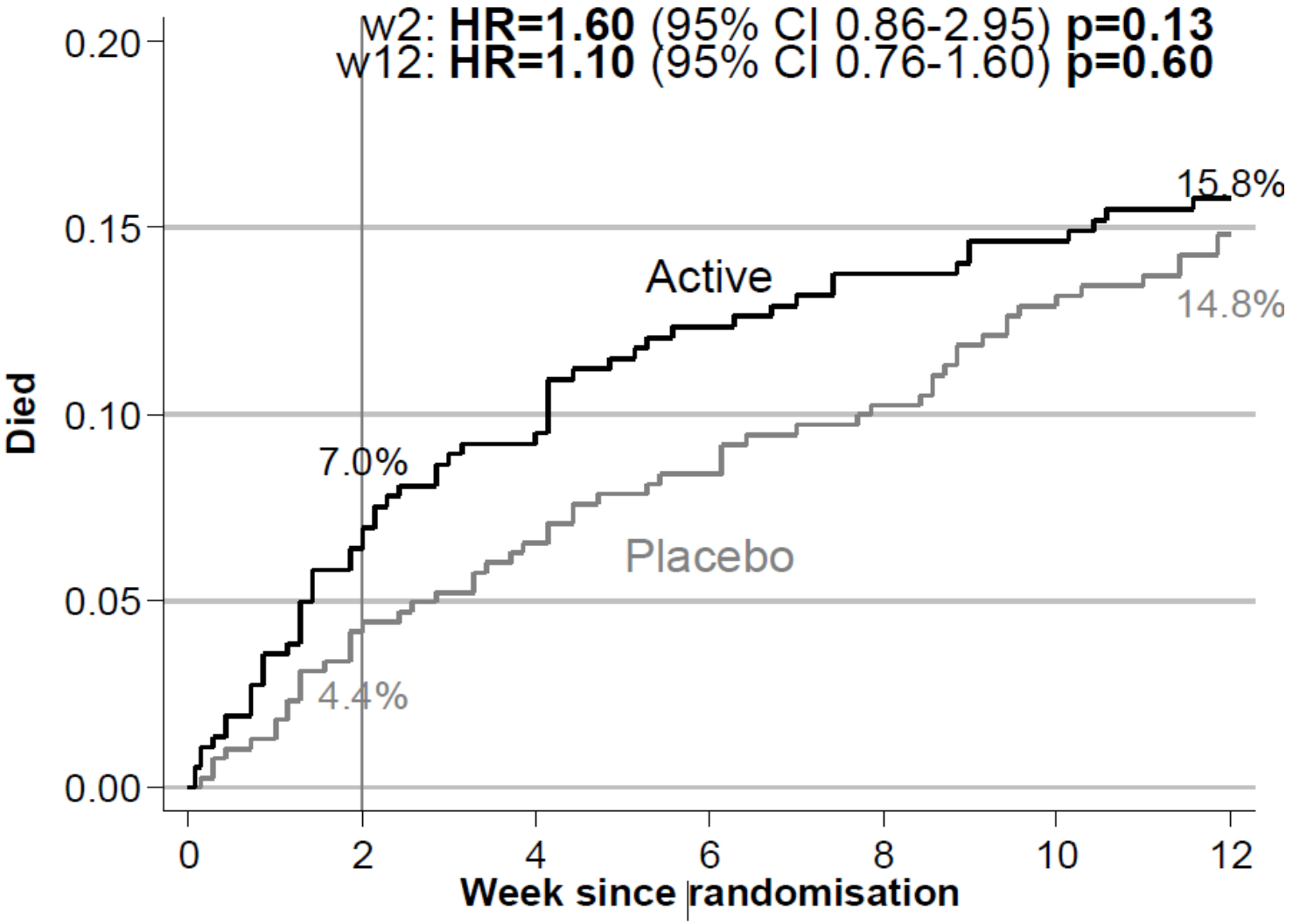
- Subgroup analyses according to
  - time between starting active antibiotics and trial drug
  - methicillin resistance
  - foci of infection (deep versus not deep)

  suggested no heterogeneity in lack of effect of rifampicin
- Significant heterogeneity of rifampicin effect was found across sub-groups defined by initial antibiotic given at randomization, but in none of 16 other subgroup analyses

ARREST results: secondary outcomes

- Rifampicin was associated with a small but significant reduction in clinically-defined disease recurrences
  - 8 (2.2%) versus 22 (5.7%) recurrences
  - competing-risks p=0.01
- NNT to prevent a clinically defined recurrence = 26

All cause mortality



Number at risk (deaths)

Placebo	388	(16)	364	(9)	354	(7)	346	(7)	338	(10)	326	(7)	302
Active	370	(23)	331	(10)	320	(11)	308	(5)	301	(3)	296	(4)	273

ARREST results: secondary outcomes

- There was no evidence that duration of bacteraemia was significantly shorter in those randomized to rifampin
- CRP declined significantly in both groups, but with smaller decreases in rifampicin participants (global p=0.001)
- Two (0.5%) rifampicin recipients developed new rifampicin-resistant *S. aureus* bacteraemia (p=0.24)
- No subjects had rifampicin-resistant *S. aureus* isolated from other sterile sites