Supplementary appendix

Contents:

1. Supplementary Appendix. Methods

Definitions

Persistent bacteremia was defined as MRSA-positive blood cultures at day seven after randomization or later, during antibiotic treatment. Recurrent bacteremia was defined as a subsequent episode of MRSA bacteremia occurring between the EOT and TOC in patients with previous negative blood cultures. Recurrence was considered a relapse when typing results of sequential isolates were identical, defined as 95% similarity and without band differences in pulse field gel electrophoresis (PFGE) [26].

Complicated MRSA bacteremia was defined as evidence of spread of infection, suppurative thrombophlebitis, endocarditis, infection involving a foreign material that could not be removed in less than four days, or persistence of a positive blood culture at 72–96 hours from the start of antimicrobial therapy, evaluated at six weeks after end of therapy. Uncomplicated bacteremia was defined as patients with MRSA bacteremia with no evidence of hematogenous spread of infection at follow-up, plus negative results for blood culture at 72–96 hours from start of antimicrobial therapy. MRSA endocarditis was defined according to modified Duke criteria [27].

References:

26. Tenover FC, Arbeit RD, Goering R V, et al. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J Clin Microbiol **1995**; 33:2233–2239.

27. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–638.

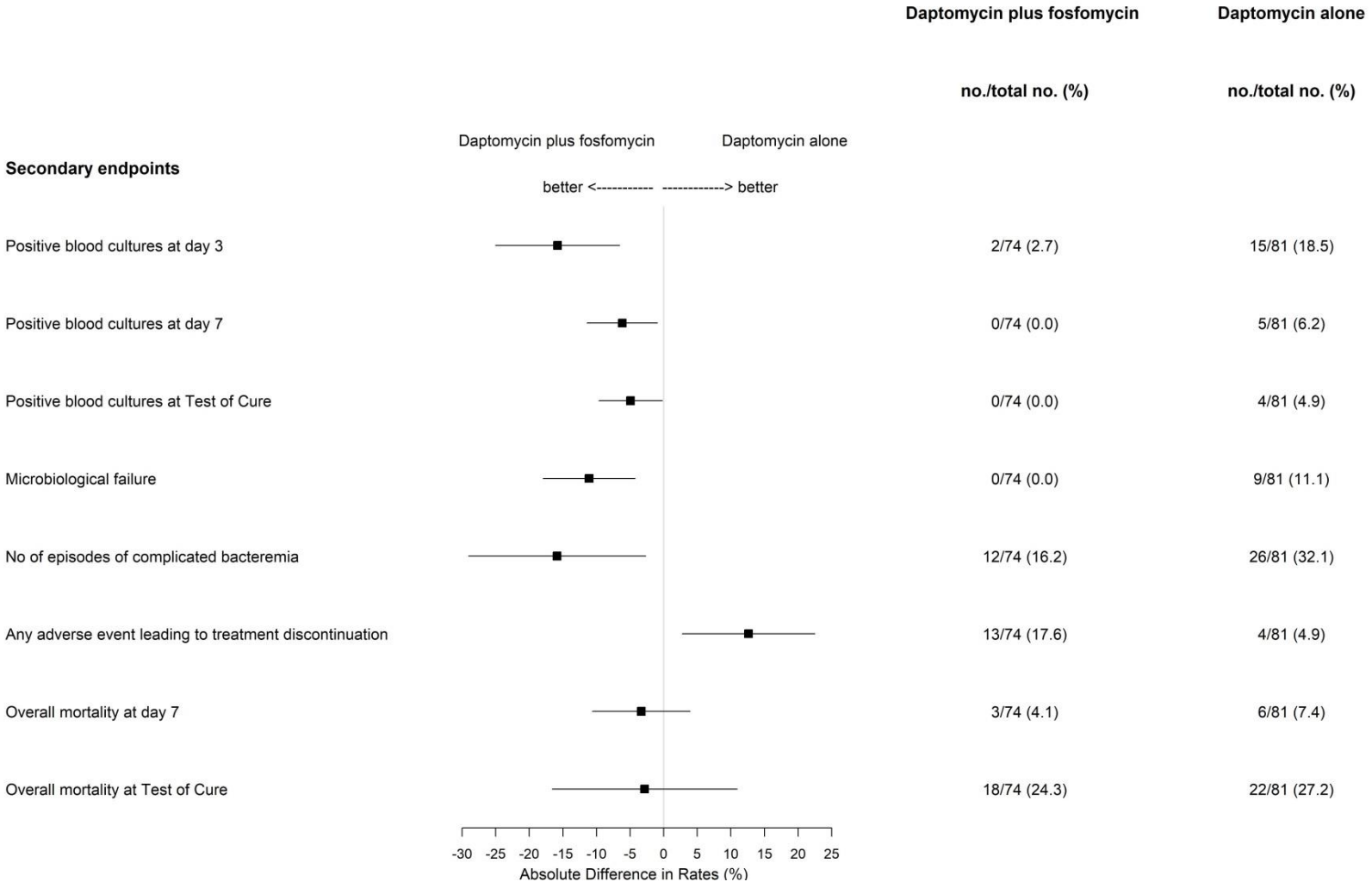
2. Supplementary Appendix. Microbiological Methods

MRSA isolates from blood cultures were identified and tested for antimicrobial susceptibility and frozen at -70ºC until shipped to a central laboratory, which confirmed the identification through matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonik GmbH, Bremen, Germany) and the antimicrobial susceptibility through microdilution (Sensititre Rapmyco®, Thermo Fisher Scientific, Waltham, USA). The antimicrobial susceptibility to daptomycin and fosfomycin was additionally studied by E-test® (Bio-Mérieux, Marcy l'Etoile, France). Data were interpreted according to the European Committee for Antimicrobial Susceptibility Testing (EUCAST) recommendations and criteria [1]. MRSA isolates from patients with persistent or recurrent bacteremia were evaluated with repeated susceptibility testing and available isolates were typed through PFGE.

Reference

1. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 9.0, **2019**. http://www.eucast.org/clinical_breakpoints/

Supplementary Appendix. Figure 3: Secondary endpoints



	Daptomycin plus fosfomycin	Daptomycin alone
	no./total no. (%)	no./total no. (%)
Positive blood cultures at day 3	2/74 (2.7)	15/81 (18.5)
Positive blood cultures at day 7	0/74 (0.0)	5/81 (6.2)
Positive blood cultures at Test of Cure	0/74 (0.0)	4/81 (4.9)
Microbiological failure	0/74 (0.0)	9/81 (11.1)
No of episodes of complicated bacteremia	12/74 (16.2)	26/81 (32.1)
Any adverse event leading to treatment discontinuation	13/74 (17.6)	4/81 (4.9)
Overall mortality at day 7	3/74 (4.1)	6/81 (7.4)
Overall mortality at Test of Cure	18/74 (24.3)	22/81 (27.2)

Supplementary Appendix. Table 5: Adverse events and serious adverse events according to system organ class

	Daptomycin plus fosfomycin No. = 77		**Daptomycin alone** No. = 83		**p-value[a]**
	Patients with event No. (%)	Total events	Patients with event No. (%)	Total events	
Any adverse event	36 (46.8)	51	38 (45.8)	52	0.902
Serious adverse event	23 (29.9)	32	29 (34.9)	40	0.494
Treatment-related serious event	7 (9.1)	9	2 (2.4)	2	0.089
Cardiac failure		5			
Hypokalemia		2			
Hypocalcemia		1			
Creatinine phosphokinase increase		1		2	
Adverse event leading to treatment discontinuation	13 (16.9)	16	4 (4.8)	4	0.013

Mortality due to any cause	18 (23.4)	23 (27.7)	0.530
Serious adverse events according to system organ class[b]			
Cardiac disorders, No. (%)	9 (11.7)	9 (10.8)	
Gastrointestinal disorders, No. (%)	3 (3.9)	1 (1.2)	
General disorders and administration site conditions, No. (%)	4 5.2)	8 (9.6)	
Infections and infestations, No. (%)	4 (5.2)	5 (6.0)	
Injury, poisoning and procedural complications, No. (%)	1 (1.3)	1 (1.2)	
Metabolism and nutrition disorders, No. (%)	7 (9.1)	5 (6.0)	
Nervous system disorders, No. (%)	2 (2.6)	0 (0)	
Renal and urinary disorders, No. (%)	1 (1.3)	5 (6.0)	
Respiratory, thoracic and mediastinal disorders, No. (%)	12 (15.6)	6 (7.2)	
Surgical and medical procedures, No. (%)	0 (0)	2 (2.4)	
Vascular disorders, No. (%)	1 (1.3)	1 (1.2)	

[a] p values refers to comparison between patient with events

[b] Serious adverse events are reported on the basis of conventional International Conference on Harmonization definitions