Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019;380:415-24. DOI: 10.1056/NEJMoa1808312

Supplementary Materials for the POET Trial

The POET investigators

Table of Content

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Charter for the endpoint committee

Medical records for patients who have experienced a possible primary endpoint (judged by the local investigators) will be reviewed by two members of the endpoint committee. They will both register if a primary endpoint is achieved. Prior to this all information concerning the treatment (oral or parenteral) will be deleted from the medical records. If the two members of the committee disagree the third member will decide if the patient experienced an endpoint.

The primary endpoint is a composite endpoint. The endpoint consists of one of the following components, all within 6 months after end of antibiotic treatment:

1. All cause mortality defined as death from any cause.
2. Unplanned cardiac surgery is defined as open chest surgery or percutaneous valve repair. Pacemaker implantation, pericardio- or pleural-drainage is **not** unplanned cardiac surgery.
3. Emboli events are defined as symptoms and clinical finding considered to be caused by an emboli – and confirmed by imaging.
4. Relapse of bacteremia with the primary pathogen is defined as positive blood cultures with the pathogen that caused the endocarditis. Phage typing is not mandatory.

Members of the endpoint committee

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Management of patients with endocarditis with prosthetic heart valves and / or pacemaker

In the POET trial we included patients with left-sided endocarditis, but patients with simultaneous right-sided endocarditis, including Cardiovascular Implantable Electronic Device (CIED) infection (pacemaker or Implantable Cardioverter-Defibrillator (ICD)) were also included.

Patients with CIED infection had their system removed by percutaneous lead extraction if conservative endocarditis therapy was offered, and surgically if endocarditis valve surgery was performed. Additionally, if technically feasible and at the treating physicians discretion, patients who had valve surgery for endocarditis had their CIED surgically removed also if no CIED was diagnosed.

After removal of the device the patients were bridged by epicardial pacemaker leads and / or a percutaneous transvenous lead until a new permanent system was implanted.

A total of 35 patients had a CIED at the time of endocarditis diagnosis (table 1); 14 patients had CIED infection and had the device removed, and 4 patients without documented CIED infection undergoing valve surgery had their device removed. In the remaining 17 cases the device was left in place.

The patients with an un-infected device that was not removed were treated according to the protocol, i.e. no changes in antibiotic therapy were made due to the presence of a device.

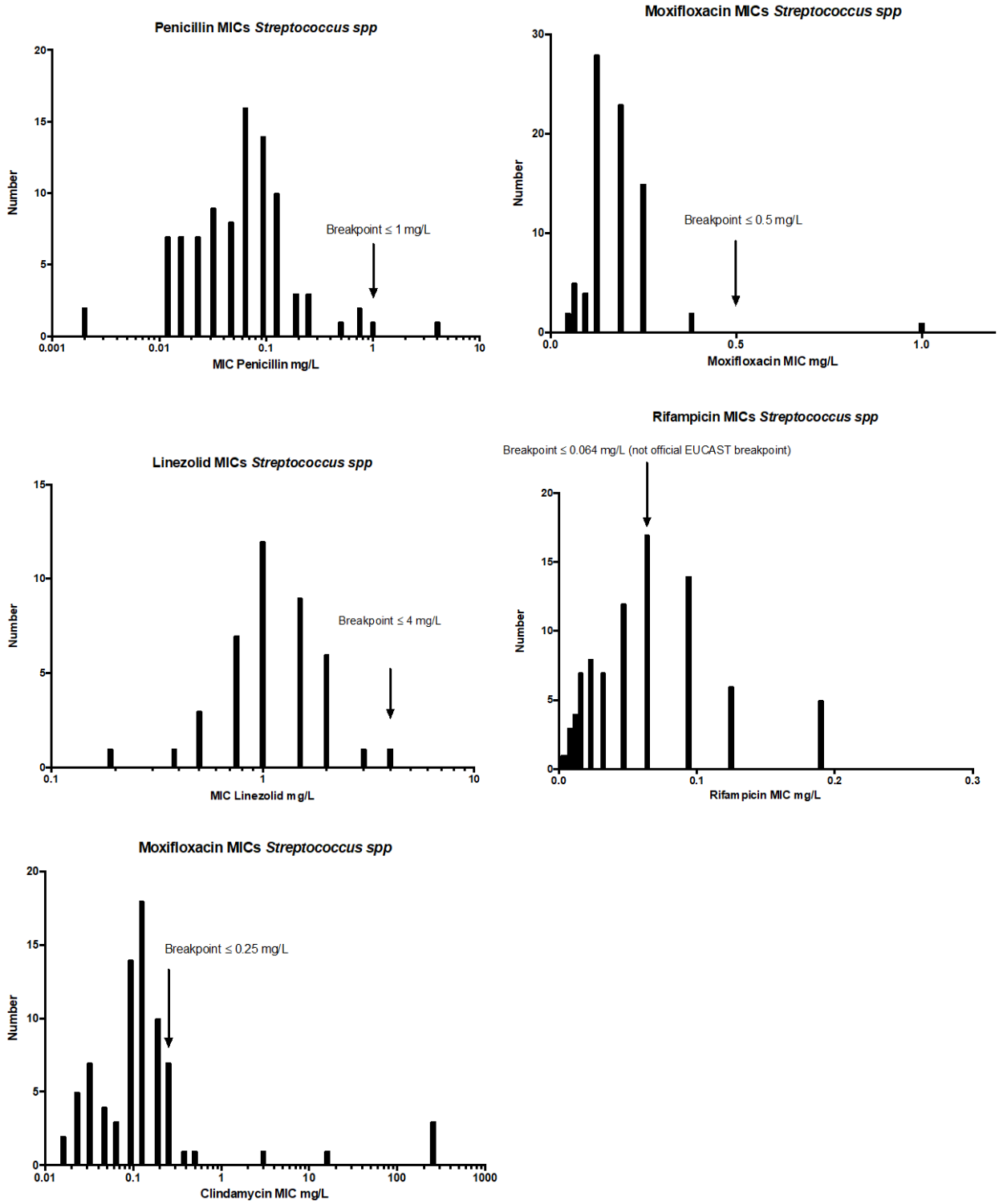
The number of patients with prosthetic heart valves are (n=107) is given in table 1. Twelve patients with prosthetic heart valve infection in the intravenously treated group underwent surgery and 10 patients in the orally treated group underwent surgery (p=0.6). The non-operated patients with a prosthetic heart valve were treated with antibiotics according to the guidelines.

It should be noted that the decisions to remove CIED's or offer surgery to patients with native or with prosthetic valves were not part of the trial, since patients were only included if no (further) surgical interventions were planned.

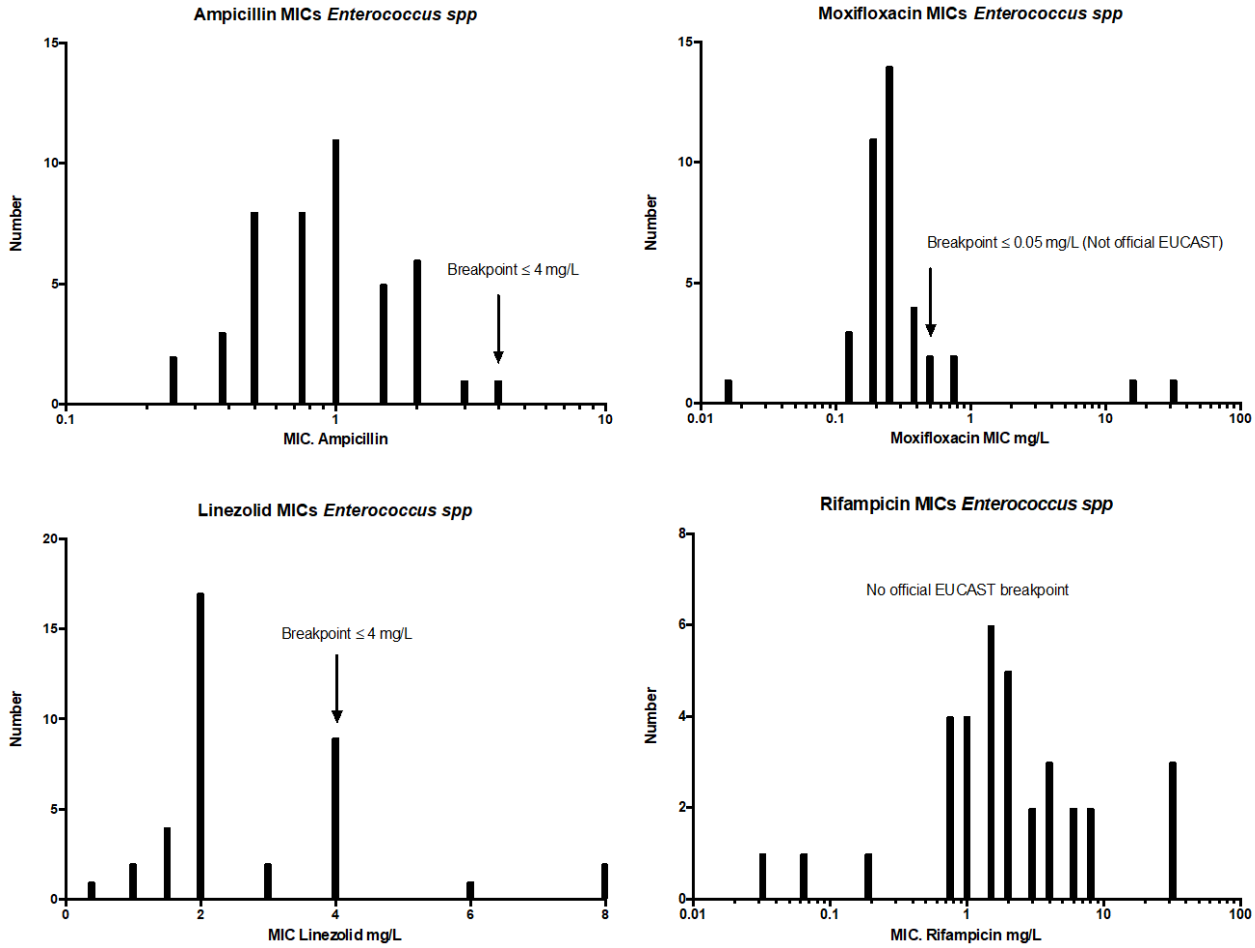
Choice of non-inferiority margin

The non-inferiority margin was chosen based recommendation from the FDA; https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf
First, we considered the clinical acceptable difference in treatment effect. Considering the estimated large gain of oral treatment (hospital resources, economical and patient related) and estimated low risk of fatal outcome due to treatment failure in the orally treated group (inclusion *after* the initial phase, where the vast majority of complications is seen combined with close control of out-patients) we considered a difference of 10% to be clinically acceptable. Secondly, we considered the overall treatment effect. As mortality in untreated patients with infectious endocarditis is close to 100% the treatment effect is very high, which supports the choice of the non-inferiority margin. Finally, practical aspects of realistic recruitment of patients and completion of the trial were also taken into consideration.

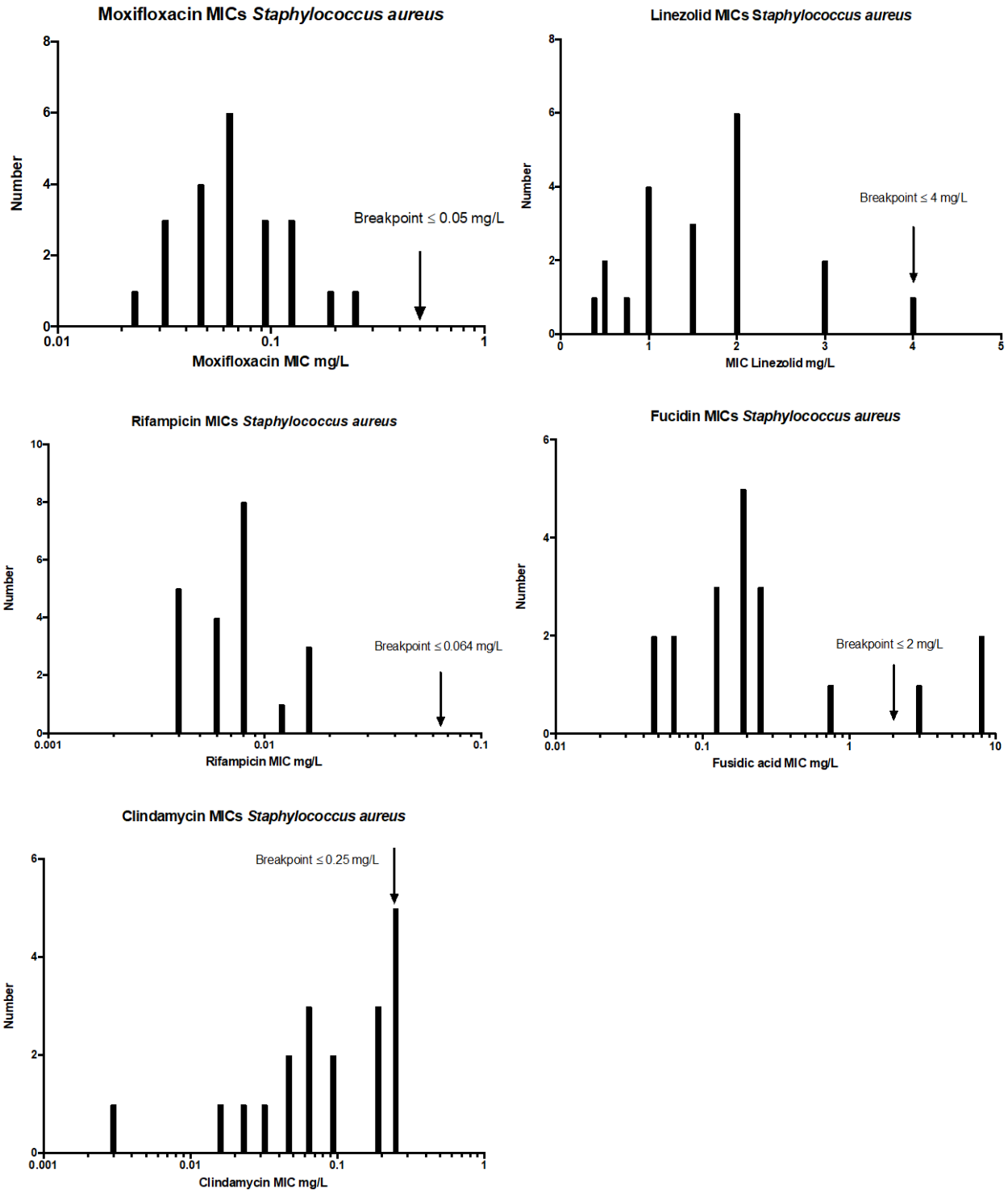
Figure S1



Distribution of MICs for *Streptococcus spp* from the largest center in the study. EUCAST breakpoints at the time of initiation of the study indicated on the figures.

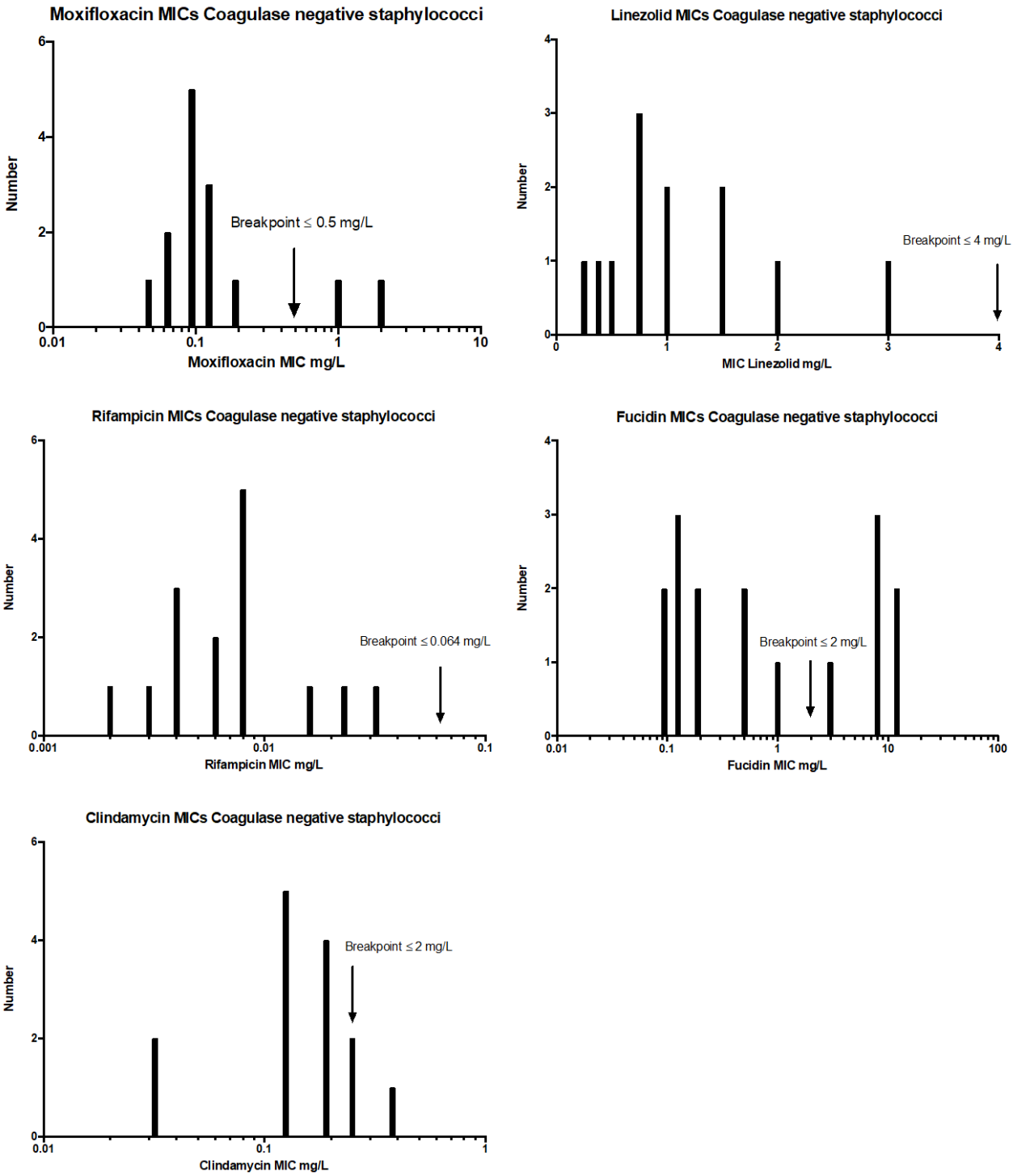


Distribution of MICs for *Enterococcus faecalis* from the largest center in the study. EUCAST breakpoints at the time of initiation of the study indicated on the figures.



Distribution of MICs for *Staphylococcus aureus* from the largest center in the study. EUCAST breakpoints at the time of initiation of the study indicated on the figures.

Penicillin susceptibility is determined by detection of a penicillin zone > 26 mm and a tapered zone edge. Confirmed by □-lactamase induction test (in Denmark often the cloverleaf test).
Of the 35 *S. aureus* isolates identified, 10 were found susceptible to penicillin, all were methicillin susceptible (no MRSA identified).



Distribution of MICs for Coagulase negative staphylococci from the largest center in the study. EUCAST breakpoints at the time of initiation of the study indicated on the figures.
Of the 15 CoNS isolates identified, 7 were found susceptible to penicillin.

Figure S2

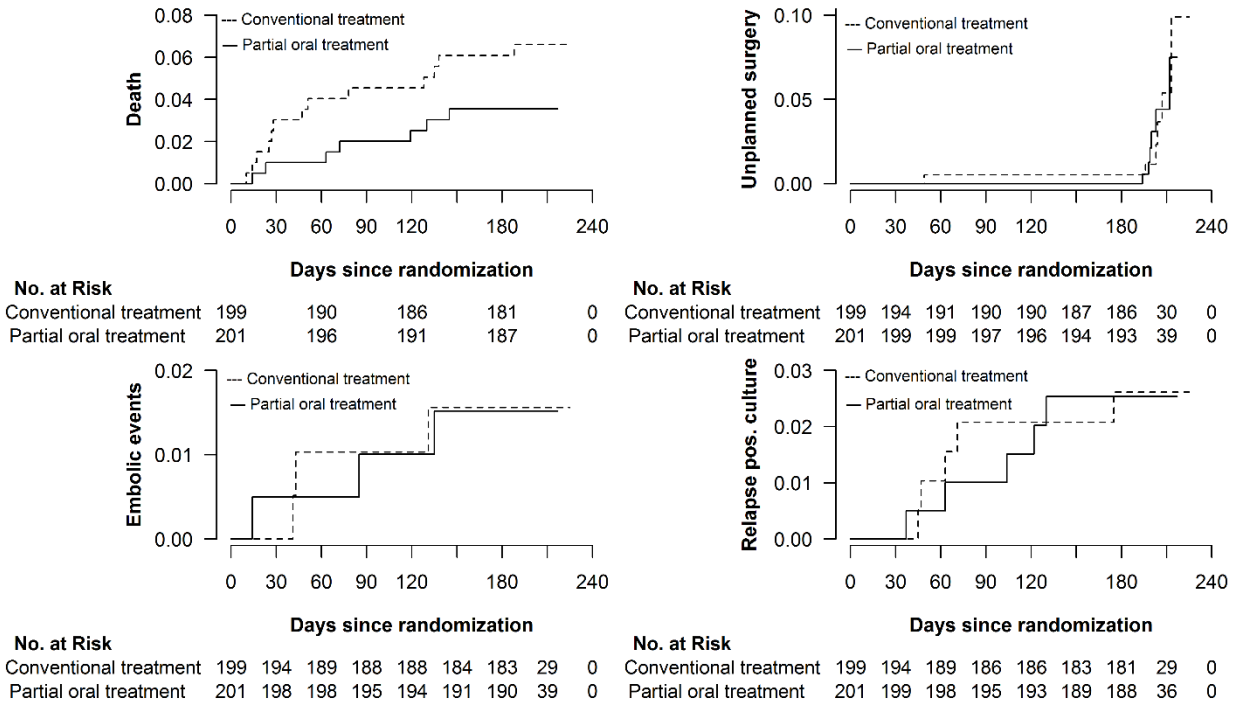
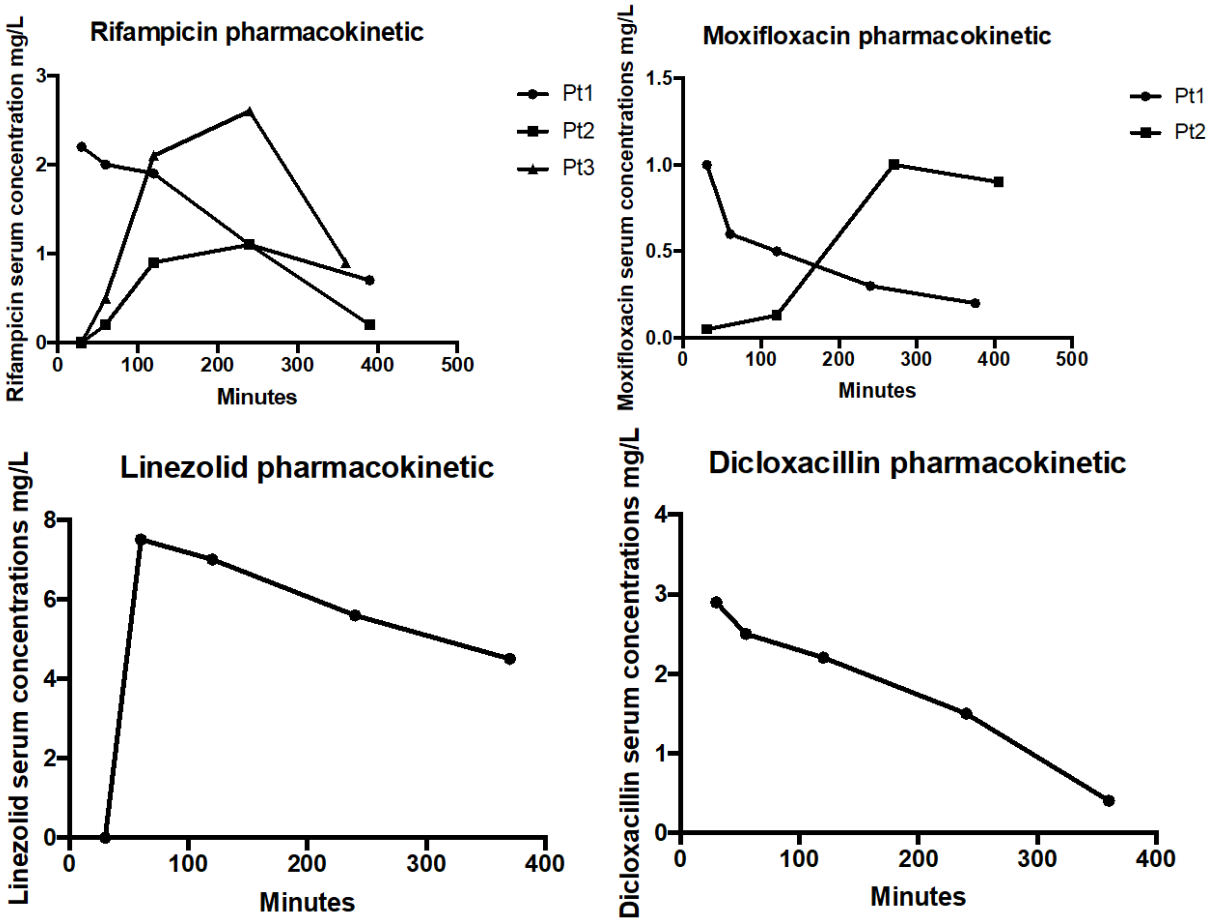
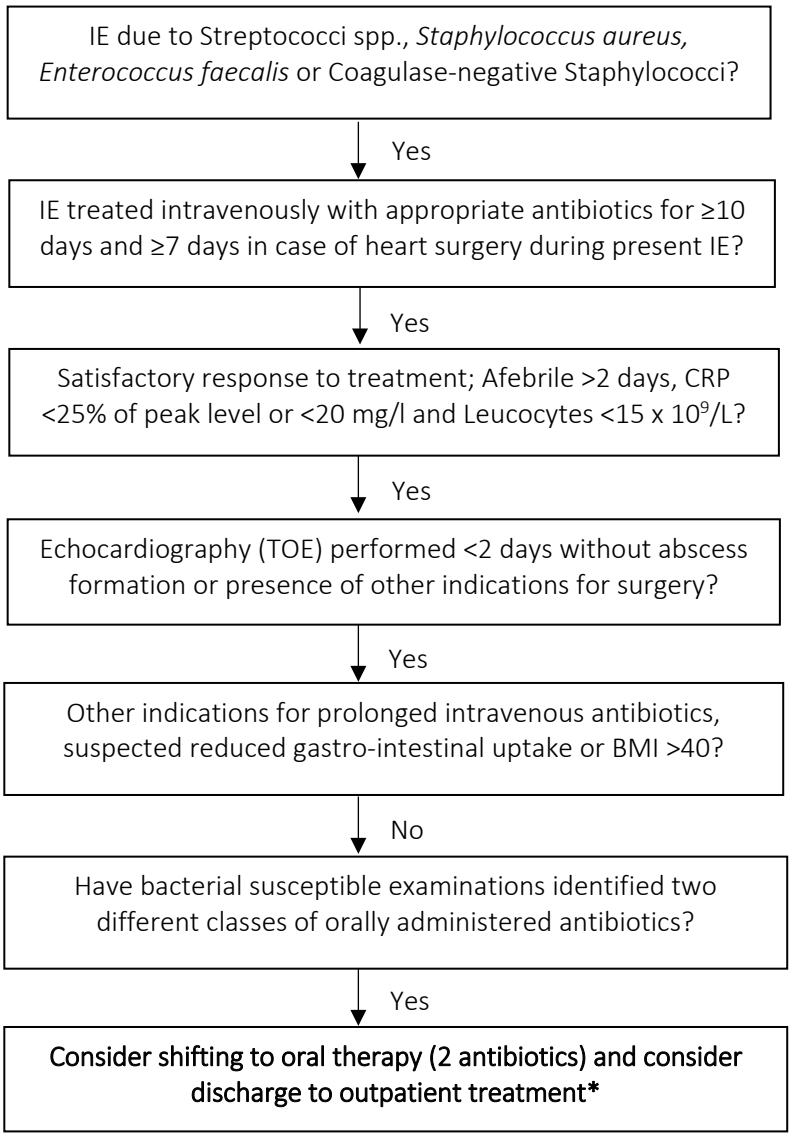

Death
0.08
0.06
0.04
0.02
0.00
--- Conventional treatment
— Partial oral treatment
0 30 60 90 120 180 240
Days since randomization
No. at Risk
Conventional treatment 199 190 186 181 0
Partial oral treatment 201 196 191 187 0
Unplanned surgery
0.10
0.05
0.00
--- Conventional treatment
— Partial oral treatment
0 30 60 90 120 180 240
Days since randomization
No. at Risk
Conventional treatment 199 194 191 190 190 187 186 30 0
Partial oral treatment 201 199 199 197 196 194 193 39 0
Embolic events
0.02
0.01
0.00
--- Conventional treatment
— Partial oral treatment
0 30 60 90 120 180 240
Days since randomization
No. at Risk
Conventional treatment 199 194 189 188 188 184 183 29 0
Partial oral treatment 201 198 198 195 194 191 190 39 0
Relapse pos. culture
0.03
0.02
0.01
0.00
--- Conventional treatment
— Partial oral treatment
0 30 60 90 120 180 240
Days since randomization
No. at Risk
Conventional treatment 199 194 189 186 186 183 181 29 0
Partial oral treatment 201 199 198 195 193 189 188 36 0

Figure S3



First dose pharmacokinetics for orally administered antibiotics in seven patients revealing too low plasma concentration of one of the two orally administered antibiotics. Antibiotic concentrations were measured by HPLC.
Applied cut-off levels for therapeutics plasma concentrations of antibiotics (PK/PD parameters) for the orally administered antibiotics in the trial are listed in Table S3.

Figure S4



Proposal; criteria for shifting from intravenous to oral antibiotic therapy in patients with left-sided endocarditis (IE). TOE; transesophageal echocardiography. *Patients shifted to oral therapy may be discharged to outpatient treatment if OPAT criteria are met.

Table S1

Inclusion and exclusion criteria

Inclusion criteria

- Left-sided endocarditis based on the Duke criteria
- Infected with one of the following microorganisms:
    - ⇒ Streptococci
    - ⇒ *Enterococcus faecalis*
    - ⇒ *Staphylococcus aureus*
    - ⇒ Coagulase-negative staphylococci
- ≥ 18 years
- ≥ 10 days of appropriate parenteral antibiotic treatment overall, and at least 1 week of appropriate parenteral treatment after valve surgery
- T < 38.0 °C > 2 days
- C-reactive protein dropped to less than 25% of peak value or < 20 mg/L, and white blood cell count < 15 x 10^9/L during antibiotic treatment
- No sign of abscess formation revealed by echocardiography
- Transthoracic and transesophageal echocardiography performed within 48 hours of randomization

Exclusion Criteria

- Body mass index > 40
- Concomitant infection requiring intravenous antibiotic therapy
- Inability to give informed consent to participation
- Suspicion of reduced absorption of oral treatment due to abdominal disorder
- Reduced compliance

Table S2
Oral regimens recommended in the POET trial

Penicillin and methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci:

1) Amoxicillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fusidic acid 0.75 g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

1) Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Methicillin resistant coagulase-negative staphylococci

1) Linezolid 0.6 g x 2 and fusidic acid
2) Linezolid 0.6 g x 2 and rifampicin 0.6 g x2

Enterococcus faecalis:

1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
2) Amoxicillin 1 g x 4 and moxifloxacin 0.4 g x 1
3) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
4) Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

Streptococci with a minimal inhibitory concentration for penicillin of <1 mg/L:

1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2

2) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

3) Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x1

Streptococci with a minimal inhibitory concentration for penicillin of ≥1 mg/L:

1) Linezolid 0,6 g x2 and rifampicin 0.6 g x 2

2) Moxifloxacin 0.4 g x 1 and rifampicin 0.6 g x 2

3) Moxifloxacin 0.4 g x 1 and clindamycin 06 g x3

Table S3

Applied cut-off levels for therapeutic plasma concentrations

Antibiotic	**Applied cut-off levels for therapeutic plasma concentration**
Rifampicin	<3 mg/L
Moxifloxacin	<2 mg/L
Linezolid	<8 mg/L
Fusidic acid	< 4 mg/L
Amoxicillin, Streptococcus spp	≤2 mg/L in <50% of the dosing interval
Amoxicillin, E. faecalis	≤8 mg/L in <50% of the dosing interval
Dicloxacillin	≤2 mg/L in <50% of the dosing interval
Clindamycin	<0.5 mg/L

Applied cut-off levels for therapeutics plasma concentrations of antibiotics (PK/PD parameters) for the orally administered antibiotics in the trial. The cut-off levels were based on published data of pharmacokinetics of the included antibiotics. High protein binding (especially dicloxacillin) or high mutation rates (especially in rifampicin-treated patients) were also taken into consideration.
Measurements of plasma concentrations of antibiotics: Venous blood samples were drawn from the central venous catheter or from a peripheral vein in 2 ml EDTA tubes at t= ½, 1, 2, 4, 6 hours after administration of antibiotic. The samples were centrifuged at 3,000 runs per min for 10 min and 1 ml plasma was frozen (-20 ^{0}C) until measurements by high pressure liquid chromatography using Agilent 1290 Infinity UHPLC (Waldbronn, Germany

Table S4
Further details on reasons for non-inclusion

The "other reasons" for not including patients (Fig 1) were: Patients with less than 10 days of antibiotic treatment remaining; lack of appropriate susceptibility testing in time, allergy to potentially offered oral drugs, periods where trial-associated physicians or study nurses (performing blood sampling for pharmacokinetics) were not available; episodes of lack of curriers who could sufficiently fast be able to transport blood samples to the laboratory for drug concentration measurements (one laboratory used for all sites (located at University of Aarhus)); episodes of unavailability of laboratory services for drug measurements.

The meaning of impaired immune response was defined as treatment with immune suppressing medication (prednisolone > 10 mg daily or other) or disease that suppressed the immune system. Of the 25 excluded patients due to immune suppression 10 received medication that suppressed the immune system, 8 had a hematological disease and no information regarding the reason for immune incompetence was available for the remaining 7 patients.

Bacterial findings (including culture negative) in patients excluded due to *Endocarditis caused by other bacteria* appear from table below.

Haemophilus spp	n=5
Cardiobacterium hominis	n=1
Escherichia coli	n=1
Klebsiella spp	n=2
Enterobacter cloacae	n=2
Bartonella sp	n=1
Salmonella spp	n=3
Streptococcus pneumoniae	n=5
Gemella spp	n=2
Granulicatella spp	n=2
Abiotrophica defectiva	n=2
Aerococcus spp	n=4
Lactococcus spp	n=2
Lactobacillus spp	n=2
Corynebacterium spp	n=3
Propionibacterium acnes	n=4
Coagulase-negative staphylococci	n=1
Aspergillus sp	n=1
Candida sp	n=1
Culture negative	n=99
Unknown	n=31

Table S5

Distribution of streptococci species in main and subgroups

Main groups	**Subgroups**
Hemolytic streptococci *(total n=28)*	*S. pyogenes (group A) (n=2)* *S. agalactiae (group B) (n=10)* *S. dysgalactiae (group c or G) (n=16)*
Alpha and non-hemolytic streptococci non specified *(total n= 25)*	
- *S. bovis group (n=19)* *(total n=30)*	*S. gallolyticus (n=10)* *S. infantarius (n=0)* *S. pasteurianus (n=0)* *S. lutetiensis (n=1)*
- *S. salivarius group (n=8)* *(total n=8)*	*S. salivarius (n=8)* *S. vestibularis (n=0)*
- *S. mutans group (n=13)* *(total n=13)*	*S. mutans (n=13)* *S. sobrinus (n=0)* *S. downei (n=0)*
- *S. mitis group (n=40)* *(total n=74)*	*S. mitis (n=40)* *S. oralis (n=3)* *S. infantis (n=0)* *S. parasanguinis (n=2)* *S. sanguinis (n=17)* *S. cristatus (n=0)* *S. gordonii (n=12)*
- *Streptococcus pneumoniae* (distinguished from the *S. mitis* group) *(total n=7)*	
- *S. anginosus (n=10)* *(total n=10)*	*S. anginosus (n=10)* *S. constellatus (n=0)* *S. intermedius (n=0)*
Miscellaneous	*Abiotrophica (n=1)*

Distribution of streptococci species in main and subgroups.

Table S6

Details of the 107 patients with prosthetic heart valve

	Intravenous treatment	Surgically treated prior to randomization	**Oral treatment**	Surgically treated prior to randomization
	n=53	n=12	**n=54**	n=10
Aortic valve position, n (%)	44 (83.0)	8 (18.2)	46 (85.2)	7 (15.2)
Streptococcus spp, n (%)	21 (47.7)	4 (50.0)	16 (34.8)	0
Enterococcus faecalis, n (%)	16 (36.4)	3 (37,5)	19 (41.3)	3 (42.9)
Staphylococcus aureus, n (%)	5 (11.4)	1 (12.5)	5 (10.9)	1 (14.3)
CNS*, n (%)	2 (4.5)	0	6 (13.0)	3 (42.9)
Mitral valve position, n (%)	4 (7.5)	2 (50.0)	4 (7.7)	1 (25.0)
Streptococcus spp, n (%)	3 (75.0)	2 (100.0)	2 (50.0)	0
Enterococcus faecalis, n (%)	1 (25.0)	0	1 (25.0)	0
Staphylococcus aureus, n (%)	0	0	1 (25.0)	1 (100.0)
CNS*, n (%)	0	0	0	0
Aortic and mitral valve position, n (%)	5 (9.4)	2 (40.0)	4 (7.7)	2 (50.0)
Streptococcus spp, n (%)	4 (80.0)	2 (100.0)	1 (25.0)	0
Enterococcus faecalis, n (%)	1 (20.0)	0	1 (25.0)	0
Staphylococcus aureus, n (%)	0	0	1 (25.0)	1 (50.0)
CNS*, n (%)	0	0	1 (25.0)	1 (50.0)
Mechanical prosthesis, n (%)	14 (26.4)	3 (21.4)	12 (22.2)	4 (33.3)
Streptococcus spp, n (%)	5 (35.7)	1 (33.3)	4 (33.3)	0
Enterococcus faecalis, n (%)	5 (35.7)	1 (33.3)	4 (33.3)	1 (25.0)
Staphylococcus aureus, n (%)	3 (21.4)	1 (33.3)	3 (25.0)	2 (50.0)
CNS*, n (%)	1 (7.1)	0	1 (8.3)	1 (25.0)
Biological prosthesis, n (%)	39 (73.6)	9 (23.1)	42 (77.8)	6 (14.3)
Streptococcus spp, n (%)	23 (59.0)	7 (77.8)	15 (35.7)	0
Enterococcus faecalis, n (%)	12 (30.7)	2 (22.2)	17 (40.5)	1 (16.7)
Staphylococcus aureus, n (%)	3 (7.7)	0	4 (9.5)	1 (16.7)
CNS*, n (%)	1 (2.6)	0	6 (14.3)	4 (66.7)
Time since prosthetic valve implantation (years), median (IQR)	5.2 (0.8)	-	5.0 (0.7)	-
Streptococcus spp, median (IQR)	4.2 (0.8 to 7.6)	-	3.5 (1.9 to 6.8)	-
Enterococcus faecalis, median (IQR)	3.2 (0.3 to 10.0)	-	3.5 (0.7 to 9.0)	-
Staphylococcus aureus, median (IQR)	1.3 (0.3 to 5.6)	-	5.1 (2.3 to 14.0)	-
CNS*, median (IQR)	*	-	0.2 (0.2 to 1.8)	-

* only two observations; 0.8 years and 1.7 years. CNS: Coagulase-negative staphylococci.

Table S7

Baseline demographics of patients undergoing heart valve surgery

	Intravenous treatment n=75	**Oral treatment n=77**
Age (years), mean (SD)	62.4 (8.7)	64.6 (8.2)
Gender (female), n (%)	14 (25.3)	14 (20.9)
Temperature (^{0}C), mean (SD)	36.9 (0.47)	37.1 (0.40)
Co-morbidities		
Diabetes, n (%)	6 (8.0)	10 (13.0)
Renal failure, n (%)	5 (6.7)	2 (2.6)
Dialysis, n (%)	2 (2.7)	1 (1.3)
COPD, n (%)	3 (4.0)	3 (3.9)
Liver disease, n (%)	3 (4.0)	1 (1.2)
Cancer, n (%)	4 (5.4)	3 (3.9)
Drug user, n (%)	3 (4.0)	1 (1.3)
Microbiology		
Streptococcus spp, n (%)	39 (52.0)	38 (49.4)
***Enterococcus faecalis*, n (%)**	20 (26.7)	15 (19.5)
***Staphylococcus aureus*, n (%)**	10 (13.3)	16 (20.8)
Coagulase-negative staphylococci, n (%)	6 (8.0)	9 (11.7)
Biochemistry at randomization		
Haemoglobin (mM), mean (SD)	5.9 (0.89)	5.9 (0.78)
Leucocytes (10^9/L), mean (SD)	7.6 (2.1)	7.7 (2.2)
CRP (mg/L), mean (SD)	31.3 (18.6)	26.5 (15.6)
Creatinine, (µM), mean (SD)	106 (72)	102 (92)

Baseline demographics and characteristics of the patients undergoing heart valve surgery for endocarditis during present disease-course.

Table S8

Surgical interventions in patients with endocarditis

Type of surgery	Intravenous treatment n=75	Oral treatment n=77
Aortic valve replacement (bioprosthesis), n (%)	**34 (45.3)**	**32 (41.6)**
Streptococcus spp, n (%)	11 (32.4)	14 (43.8)
Enterococcus faecalis, n (%)	14 (41.2)	9 (28.1)
Staphylococcus aureus, n (%)	6 (17.6)	5 (15.6)
CNS*, n (%)	3 (8.8)	4 (12.5)
Aortic valve replacement (mechanical prosthesis), n (%)	**6 (8.0)**	**14 (18.2)**
Streptococcus spp, n (%)	5 (83.3)	8 (57.1)
Enterococcus faecalis, n (%)	1 (16.7)	3 (21.4)
Staphylococcus aureus, n (%)	0	2 (14.3)
CNS*, n (%)	0	1 (7.1)
Mitral valve replacement (bioprosthesis), n (%)	**17 (22.7)**	**20 (26.0)**
Streptococcus spp, n (%)	8 (47.1)	10 (50.0)
Enterococcus faecalis, n (%)	4 (23.5)	2 (10.0)
Staphylococcus aureus, n (%)	3 (17.6)	6 (30.0)
CNS*, n (%)	2 (11.8)	2 (10.0)
Mitral valve replacement (mechanical prosthesis), n (%)	**3 (4.0)**	**1 (1.3)**
Streptococcus spp, n (%)	3 (100.0)	1 (100.0)
Enterococcus faecalis, n (%)	0	0
Staphylococcus aureus, n (%)	0	0
CNS*, n (%)	0	0
Mitral valve repair, n (%)	**6 (8.0)**	**5 (6.5)**
Streptococcus spp, n (%)	4 (66.7)	2 (40.0)
Enterococcus faecalis, n (%)	1 (16.7)	0
Staphylococcus aureus, n (%)	1 (16.7)	2 (40.0)
CNS*, n (%)	0	1 (20.0)
Aortic and mitral valve replacement (bioprosthesis), n (%)	**4 (5.3)**	**1 (1.3)**
Streptococcus spp, n (%)	3 (75.0)	0
Enterococcus faecalis, n (%)	0	0
Staphylococcus aureus, n (%)	0	0
CNS*, n (%)	1 (25.0)	1 (100.0)
Aortic and mitral valve replacement (mechanical prosthesis), n (%)	**1 (1.3)**	**0**
Streptococcus spp, n (%)	1 (100.0)	0
Enterococcus faecalis, n (%)	0	0
Staphylococcus aureus, n (%)	0	0
CNS*, n (%)	0	0
Aortic valve replacement (bioprosthesis) and mitral valve repair, n (%)	**2 (2.7)**	**3 (3.9)**
Streptococcus spp, n (%)	2 (100.0)	2 (66.7)
Enterococcus faecalis, n (%)	0	1 (33.3)
Staphylococcus aureus, n (%)	0	0
CNS*, n (%)	0	0
Other*, n (%)	**2 (2.7)**	**1 (1.3)**
Streptococcus spp, n (%)	1 (50.0)	1 (100.0)
Enterococcus faecalis, n (%)	0	0
Staphylococcus aureus, n (%)	1 (50.0)	0

CNS*, n (%)	0	0

* One myxoma removal, one mitral valve combined with tricuspid valve repair and one aortic valve replacement (bioprosthesis) combined with mitral valve and tricuspid valve repair.

Time from time to diagnosis to surgery 2 days (IQR 1-9) in intravenously treated patients and 2 days (IQR 1-6) in the orally treated patients.

Time form surgery to randomization 16 days (IQR 13-18) in intravenously treated patients and 17 days (IQR 13-22) in orally treated patients.

Table S9

Details of the 35 patients with an implanted device (pacemaker, CRT or ICD)

	Intravenous treatment n=15	**Pacemaker removed n=7**	**Oral treatment n=20**	**Pacemaker removed n=11**
DDD pacemaker, n (%)	**6 (40.0)**	**3 (50.0)**	**13 (65.0)**	**5 (38.5)**
Streptococcus spp, n (%)	4 (66.7)	2 (66.7)	3 (23.1)	1 (20.0)
Enterococcus faecalis, n (%)	2 (33.3)	1 (33.3)	10 (76.9)	4 (80.0)
Staphylococcus aureus, n (%)	0	0	0	0
CNS, n (%)	0	0	0	0
AAI or VVI pacemaker, n (%)	**4 (26.7)**	**1 (25.0)**	**3 (15.0)**	**2 (66.7)**
Streptococcus spp, n (%)	2 (50.0)	1 (100.0)	0	0
Enterococcus faecalis, n (%)	0	0	2 (66.7)	1 (50.0)
Staphylococcus aureus, n (%)	2 (50.0)	0	1 (33.3)	1 (50.0)
CNS, n (%)	0	0	0	0
ICD or CRT pacemaker, n (%)	**5 (33.3)**	**3 (60.0)**	**4 (20.0)**	**4 (100.0)**
Streptococcus spp, n (%)	4 (80.0)	2 (66.7)	2 (50.0)	1 (25.0)
Enterococcus faecalis, n (%)	1 (20.0)	1 (33.3)	0	0
Staphylococcus aureus, n (%)	0	0	3 (75.0)	3 (75.0)
CNS, n (%)	0	0	0	0
Device infected, n (%)	**6 (40.0)**	**6 (100.0)**	**8 (40.0)**	**8 (100)**
Streptococcus spp, n (%)	4 (66.7)	4 (66.7)	2 (25.0)	2 (25.0)
Enterococcus faecalis, n (%)	2 (33.3)	2 (33.3)	4 (50.0)	4 (50.0)
Staphylococcus aureus, n (%)	0	0	3 (37.5)	3 (37.5)
CNS, n (%)	0	0	0	0
Device not infected, n (%)	**9 (60.0)**	**1 (11.1)**	**12 (60.0)**	**3 (25.0)**
Streptococcus spp, n (%)	6 (66.7)	1 (100.0)	3 (25.0)	0
Enterococcus faecalis, n (%)	1 (11.1)	0	8 (66.7)	2 (66.7)
Staphylococcus aureus, n (%)	2 (22.2)	0	1 (8.3)	1 (33.3)
CNS, n (%)	0	0	0	0
Time since implantation of device, (years) median (IQR)	**2.6 (0.9 to 9.5)**	**-**	**2.3 (0.7 to 5.4)**	**-**
Streptococcus spp, (years) median (IQR)	1.8 (0.8 to 10.7)	-	2.4 (1.5 to 6.9)	-
Enterococcus faecalis, (years) median (IQR)	6.5 (3.1 to 12.6)	-	3.9 (1.0 to 9.9)	-
Staphylococcus aureus, (years) median (IQR)	*	-	0.4 (0.1 to 1.9)	-
CNS, (years) median (IQR)	0	-	0	-

One patient in the oral group had both streptococci and *Staphylococcus aureus.*

*Only two observations; 0.7 years and 1.0 years, CNS: Coagulase-negative staphylococci

Table S10

Antibiotic regimens in the POET trial.

	Oral regimens	Frequency n (%)
Staphylococcus aureus	Dicloxacillin and rifampicin	15 (33)
	Amoxicillin and rifampicin	13 (29)
	Moxifloxacin and rifampicin	3 (7)
	Amoxicillin and fusidic acid	2 (4)
	Dicloxacillin and fusidic acid	2 (4)
	Fusidic acid and linezolid	2 (4)
	Rifampicin and linezolid	2 (4)
	Penicillin and rifampicin	1 (2)
	Amoxicillin and clindamycin	1 (2)
	Ampicillin and rifampicin	1 (2)
	Moxifloxacin and fusidic acid	1 (2)
	Moxifloxacin and linezolid	1 (2)
	Linezolid and clindamycin	1 (2)
Enterococcus faecalis	Amoxicillin and moxifloxacin	24 (47)
	Amoxicillin and linezolid	13 (25)
	Amoxicillin and rifampicin	6 (12)
	Moxifloxacin and linezolid	5 (10)
	Amoxicillin and ciprofloxacin	2 (4)
	Amoxicillin	1 (2)
Streptococci	Amoxicillin and rifampicin	47 (52)
	Amoxicillin and moxifloxacin	12 (13)
	Rifampicin and linezolid	8 (9)
	Moxifloxacin and linezolid	8 (9)
	Amoxicillin and linezolid	7 (8)
	Penicillin	3 (3)
	Ampicillin and moxifloxacin	1 (1)
	Ampicillin and rifampicin	1 (1)
	Dicloxacillin and moxifloxacin	1 (1)
	Moxifloxacin and clindamycin	1 (1)
	Moxifloxacin and vancomycin	1 (1)
Coagulase negative staphylococci	Fusidic acid and linezolid	5 (38)
	Rifampicin and linezolid	4 (31)
	Amoxicillin and linezolid	1 (8)
	Dicloxacillin and rifampicin	1(8)
	Moxifloxacin and linezolid	1(8)
	Rifampicin and Fusidic acid	1(8)

Table S11

Susceptibility to penicillin, ampicillin or methicillin for the bacterial groups included

	Penicillin susceptibility streptococci (MIC < 1 mg/L)	Penicillin susceptibility staphylococci (large and tapered penicillin zone. Penicillinase induction test)	Ampicillin susceptibility (MIC ≤ 4 mg/L)	Methicillin resistance (Cefoxitin or oxacillin screening. Confirmed by mec gene analysis)
*Streptococcus spp**	194 susceptible 2 resistant			
Enterococcus faecalis			96 susceptible 1 resistant	
Staphylococcus aureus		27 susceptible 60 resistant		87 susceptible 0 resistant
Coagulase negative staphylococci		7 susceptible 16 resistant		15 susceptible 8 resistant

*Including 1 isolates of *Abiotrophica defectiva*.
The present table presents the four major bacterial groups included in the study with respect to susceptibility to penicillin, ampicillin or methicillin.

Table S12

Details of the achieved endpoints

	Intravenous treatment	Oral treatment
Causes of death	**12**	**8**
Infection and endocarditis, n (%)	2 (16.7)	2 (25.0)
Infection, not endocarditis, n (%)	2 (16.7)	2 (25.0)
Sudden cardiac death, n (%)	4 (33.3)	0 (0)
Heart failure, n (%)	1 (8.3)	0 (0)
Cerebral haemorrhage, n (%)	1 (8.3)	1 (12.5)
Cancer, n (%)	2 (16.7)	1 (12.5)
Lung disease, (n%)	0 (0)	1 (12.5)
Renal failure, n (%)	0 (0)	1 (12.5)
Reasons for unplanned cardiac surgery	**6**	**6**
Worsening/relapse of infection, n (%)	2 (33.3)	2 (33.3)
Valve dysfunction, no infection, n (%)	3 (50.0)	4 (66.7)
Hematoma in the pericardium, n (%)	1 (16.7)	0 (0)
Type of embolic event	**3**	**3**
Cerebral emboli, n (%)	2 (66.7)	2 (66.7)
Emboli in the eye, n (%)	1 (33.3)	1 (33.3)
Details, patients with relapse of positive blood culture	**5**	**5**
Prosthetic valve, n (%)	2 (40.0)	3 (60.0)
Pacemaker, n (%)	0 (0)	1 (20.0)
Decreased susceptibility, n (%)	0 (0)	0 (0)
Streptococcus spp, n (%)	0 (0)	0 (0)
Enterococcus faecalis, n (%)	3 (60.0)	3 (60.0)
Staphylococcus aureus, n (%)	2 (40.0)	1 (20.0)
Coagulase-negative staphylococci, n (%)	0 (0)	1 (20.0)
Time from randomization to relapse (days), median (IQR)	25 (23-34)	94 (17-103)

Table S13

Breakdown of bacterial species for each of the elements of the composite outcome

	All-cause mortality		Unplanned cardiac surgery		Embolic event		Relapse of positive blood culture	
	IV treatment n=13	Oral treatment n=7	IV treatment n=6	Oral treatment n=6	IV treatment n=3	Oral treatment n=3	IV treatment n=5	Oral treatment n=5
Streptococci	7 (54%)	3 (43%)	2 (33%)	4 (66%)	2 (67%)	2 (67%)	0	0
E faecalis	2 (15%)	1 (14%)	0	0	0	0	3 (60%)	3 (60%)
S aureus	2 (15%)	2 (28%)	3 (50%)	1 (17%)	0	0	2 (40%)	1 (20%)
CNS	2 (15%)	1 (14%)	1 (17%)	1 (17%)	1 (33%)	1 (33%)	0	1 (20%)

IV; Intravenous.

Table S14
Detailed description of side effect in treatment groups

Side effects	Intravenous treatment n=12	Oral treatment n=10
Gastro-intestinal symptoms, n (%)	0 (0)	3 (30.0)
Renal failure, n (%)	0 (0)	1 (10.0)
Hepatic failure, n (%)	0 (0)	1(10.0)
Bone marrow suppression, n (%)	2 (16.7)	4 (40.0)
Allergy, n (%)	10 (83.3)	1 (10.0)

The severity of the listed side effects necessitated shift of antibiotics in all cases. No further grading of side effects was registered. Side effects that did not necessitate shift of antibiotics were not registered.