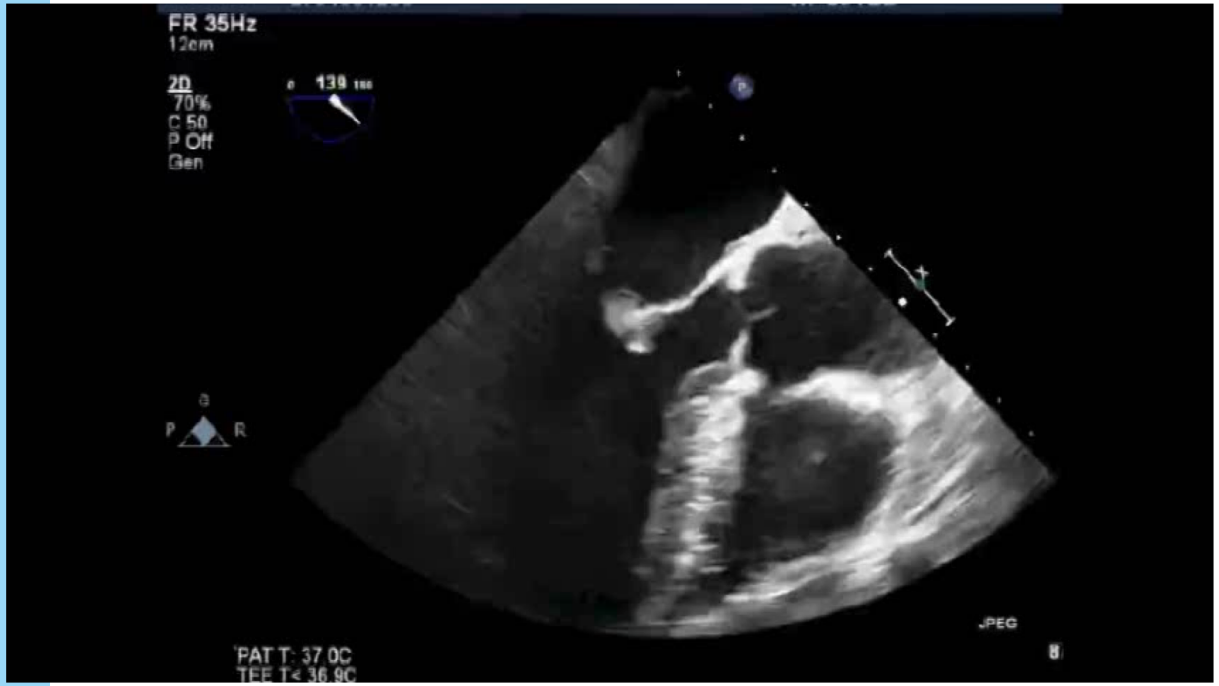
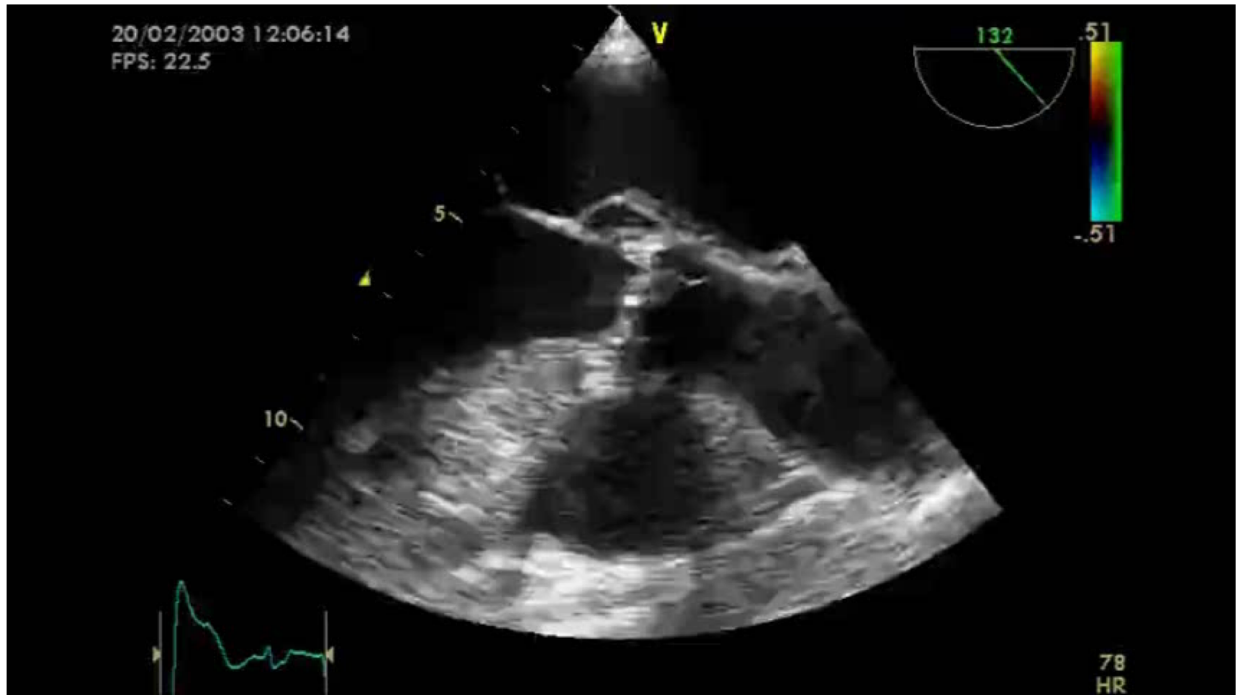
POET

Partial oral treatment of left-sided infectious endocarditis
The POET trial





Kasper Iversen
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On behalf of the POET-investigators

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Declaration of interest

None

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Background

- According to guidelines we treat left-sided infectious endocarditis with intravenous (IV) antibiotics for up to 6 weeks – in-hospital

- Endocarditis is associated with high in-hospital complication- and mortality rates - but mainly in the early phase

- After stabilization the main reason for staying in hospital is to receive iv antibiotics

- Hospital stays *per se* may cause complications

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Intravenous Followed by Oral Antimicrobial Therapy for Staphylococcal Endocarditis

RICHARD H. PARKER, M.D.; and BYRON E. FOSSIECK, Jr., M.D.; Washington, D.C.

N=33

TREATMENT OF RIGHT-SIDED STAPHYLOCOCCUS AUREUS ENDOCARDITIS IN INTRAVENOUS DRUG USERS WITH CIPROFLOXACIN AND RIFAMPICIN

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N = 10

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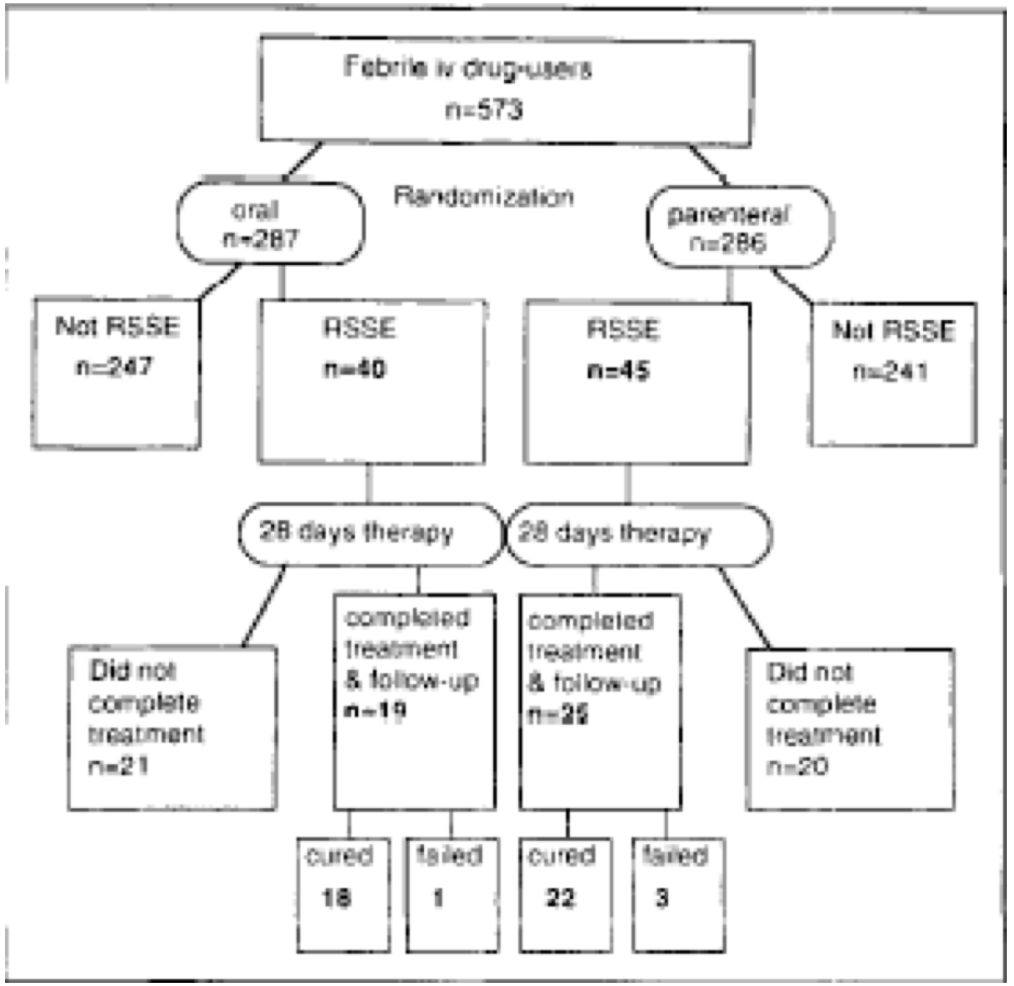

Oral Antibiotic Treatment of Right-sided Staphylococcal Endocarditis in Injection Drug Users: Prospective Randomized Comparison with Parenteral Therapy

Alan W. Heldman, MD, Tina V. Hartert, MD, Stuart C. Ray, MD, Emile G. Daoud, MD, Thomas E. Kowalski, MD, Vincent J. Pompili, MD, Stephen D. Sisson, MD, William C. Tidmore, MD, Keith A. vom Eigen, MD, Steven N. Goodman, MD, PhD, Paul S. Lietman, MD, PhD, Brent G. Petty, MD, Charles Flexner, MD, *Baltimore, Maryland*

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Gender	Age	Microbial pathogen	Valve(s)/material involved	Peroral medication	Treatment duration (Parental/peroral)	Surgery	Outcome
Male	43	β-haemolytic streptocci group g	Prosthetic biological mitral valve	Fucidin and rimactan	13 days/28 days	No	Succes
Male	75	Staphylococcus epidermidis	Aortic and mitral valve	Linezolid and moxifloxacin	17 days/30 days	Yes prosthetic biological mitral and aortic valve	Succes
Male	62	Staphylococcus aureus	Mitral valve	Fucidin and linezolid	17 days/24 days	no	Succes
Male	56	Staphylococcus aureus	Prosthetic biological mitral valve	Fucidin and rimactan	29 days/15 days	no	Succes
Female	74	Streptococcus sangius	Mitral valve	Linezolid and moxifloxacin	15 days /17 days	no	Succes
Male	54	Staphyloccocus aureus	Aortic valve	Rimactan and linezolid	29 days/15 days	Yes prosthetic biological aortic valve	Succes
Male	78	Enterococcus faecalis	Prosthetic biological mitral valve	Linezolid	20 days/10 days	No	Succes
Male	67	Coagulase negative staphylococcus	Pacemaker electrode	Rimactan and linezolid	36 days/16 days	Yes, removal of infected electrode	Succes
Female	65	β-haemolytic streptocci group c	Aortic valve	Rimactan and linezolid	24 days/6 days	Yes, prosthetic biolocigal aortic valve	Succes
Female	44	Staphylococcus lugdunesis	Pacemaker electrode	Penicillin and linezolid	35 days/14 days	Yes, removal of infected electrode	Succes
Male	67	Salmonella	Aortic valve	Ciprofloxacin	42 days/21 days	Yes, prosthetic biolocigal aortic valve	Succes
Male	74	Coagulase-negative staphylococcus	Aortic and mitral valve	Penicillin	40 days/ 5 days	Yes, prosthetic biolocigal aortic and mitral valve	Succes

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Objectives

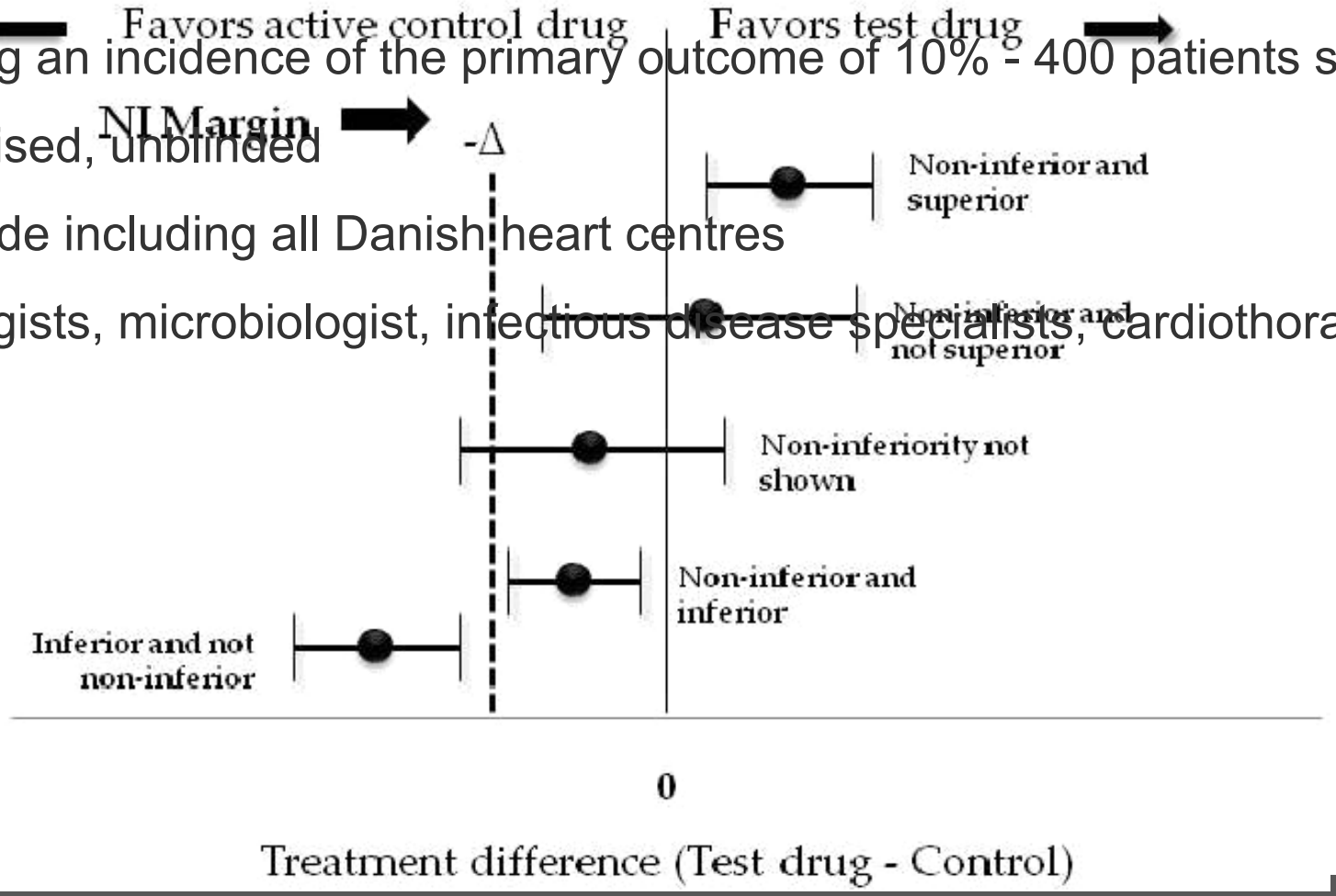
To determine - in stabilised patients with endocarditis - whether

- Orally administered antibiotics and
- Intravenously administered antibiotics

have similar efficacy and safety

Study design

- Non-inferiority trial (delta =10%)
- Assuming an incidence of the primary outcome of 10% - 400 patients should be included
- Randomised, unblinded
- Nationwide including all Danish heart centres
- Cardiologists, microbiologist, infectious disease specialists, cardiothoracic surgeons



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Choice of antibiotics

Intravenous antibiotics: Given according to ESC guidelines

Oral antibiotics regimens: Developed as part of the study;

- Antibiotics with
  - Moderate to high bioavailability
- In all cases two antibiotics;
  - Different drug classes, antimicrobial mechanisms and metabolization
- Minimal inhibitory concentration determinations
- Adjustments acc. to plasma-antibiotics (pharmacokinetics T ½, 1, 2, 4, 6 h)

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

- Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x1

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

- Linezolid 0.6 g x2 and rifampicin 0.6 g x 2
- Moxifloxacin 0.4 g x 1 and rifampicin 0.6 g x 2
- Moxifloxacin 0.4 g x 1 and clindamycin 06 g x3

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Enterococcus faecalis:

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

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

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

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Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

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

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Methicillin resistant coagulase-negative staphylococci

- Linezolid 0.6 g x 2 and fusidic acid
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x2

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Inclusion criteria

- Left-sided endocarditis based on the modified Duke criteria caused by
  - Streptococci or
  - *Enterococcus faecalis or*
  - *Staphylococcus aureus or*
  - Coagulase-negative staphylococci
- ≥10 days of appropriate intravenous antibiotic treatment, and ≥1 week after valve surgery
- T <38.0 °C >2 days
- C-reactive protein fall to ≤25% of peak value or <20 mg/L
- White blood cell count <15 x 10^9/L
- By transesophageal echocardiography ≤48 h prior to randomization: No sign of abscess formation or valve abnormalities requiring surgery

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Exclusion criteria

- Suspicion of reduced absorption of oral treatment due to abdominal disorder
- Body mass index >40 kg/m^2
- Concomitant infection requiring intravenous antibiotic therapy
- Inability to give informed consent to participation
- Reduced compliance

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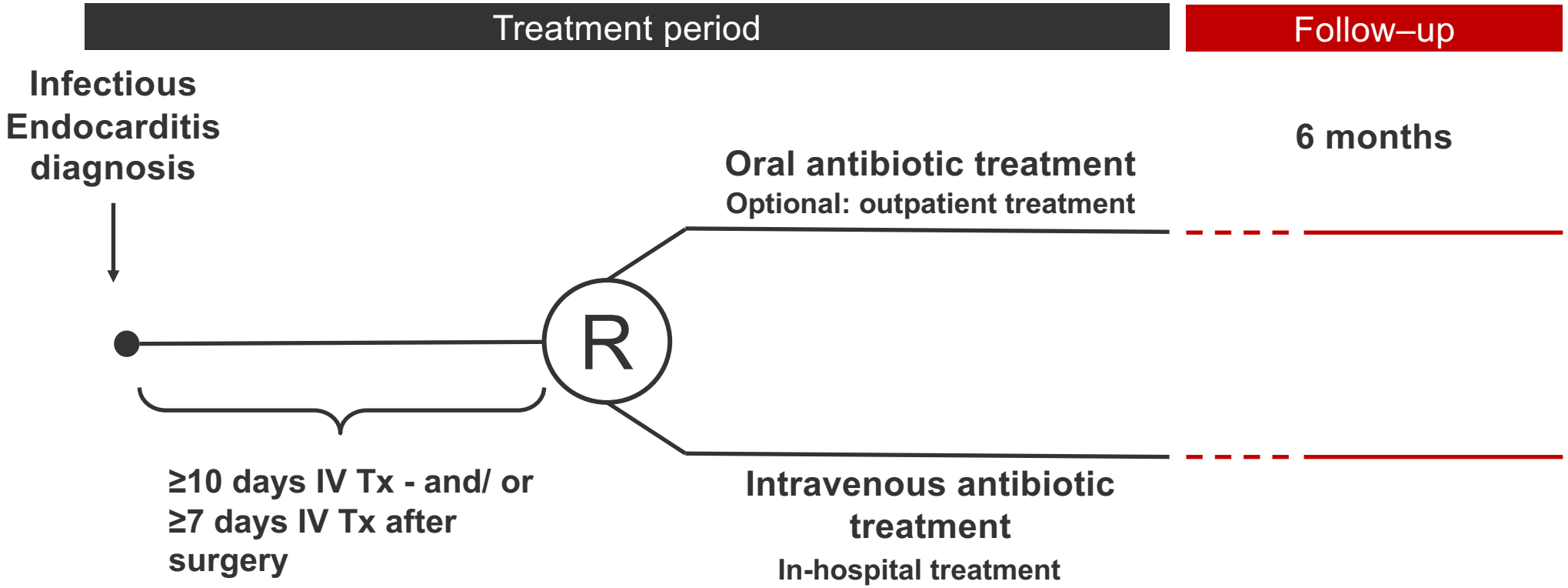
The POET trial design

Investigator initiated, nationwide, randomised, unblinded clinical trial



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Primary endpoint

- A composite endpoint ≤6 months of
  - All cause mortality
  - Unplanned cardiac surgery
  - Embolic events
  - Relapse of bacteremia with the primary pathogen

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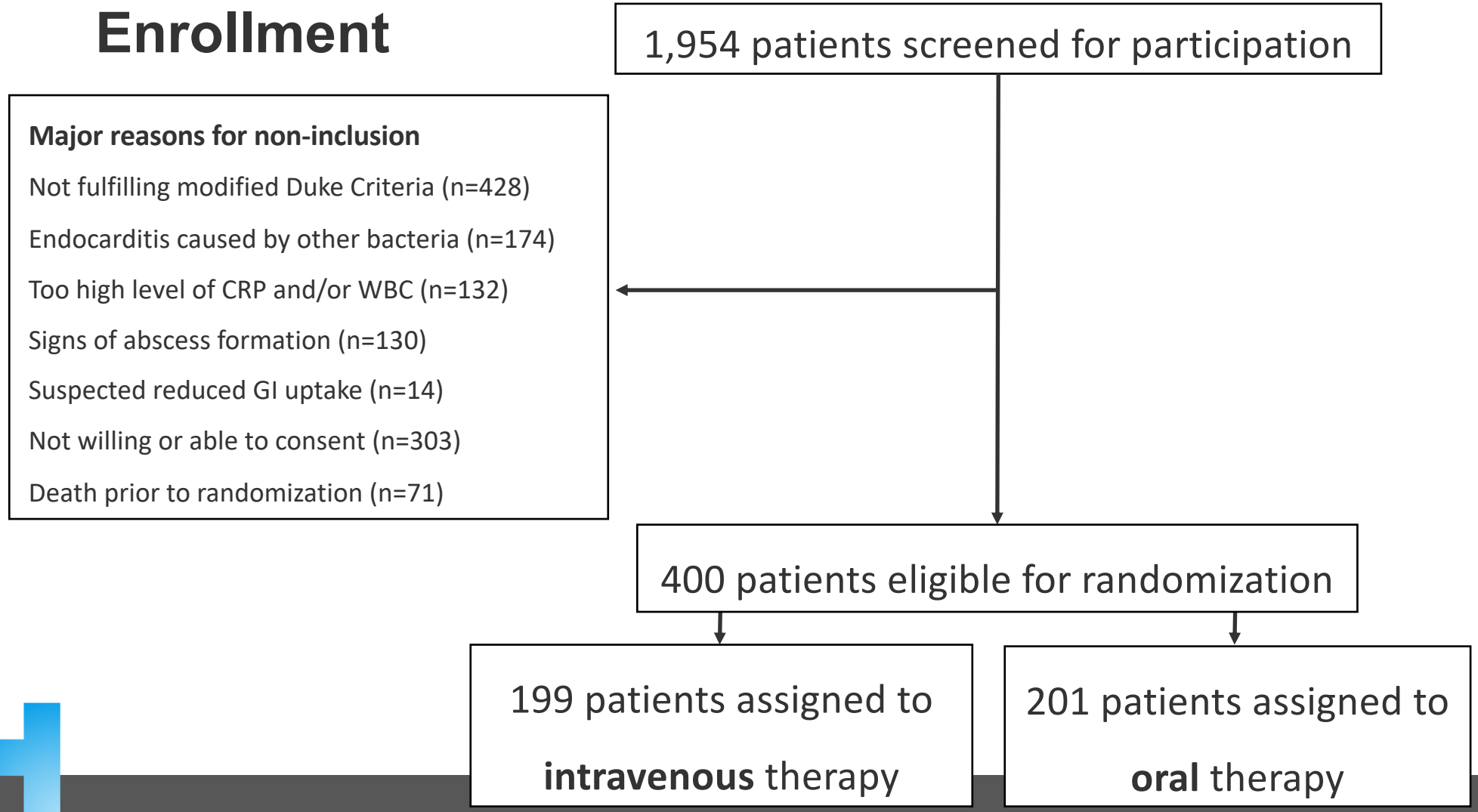
Enrollment



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Baseline characteristics

	Intravenous treatment (n=199)	Oral treatment (n=201)
Age (years), mean (SD)	67.3 (12.0)	67.6 (12.6)
Gender (female), n (%)	50 (25.3)	42 (20.9)
Co-morbidities		
Diabetes, n (%)	36 (18.1)	31 (15.6)
Renal failure, n (%)	25 (12.6)	21 (10.6)
Dialysis, n (%)	13 (6.5)	15 (7.5)
COPD, n (%)	17 (8.5)	9 (4.5)
Cancer, n (%)	14 (7.1)	18 (9.1)
Microbiology		
Streptococcus spp, n (%)	104 (52.3)	92 (45.8)
Enterococcus faecalis, n (%)	46 (23.1)	51 (25.4)
Staphylococcus aureus, n (%)	40 (20.1)	47 (23.4)
Coagulase-negative staphylococci, n (%)	10 (5.0)	13 (6.6)

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Baseline characteristics

	Intravenous treatment (n=199)	Oral treatment (n=201)
Pre-existing cardiac disease or condition		
Prosthetic heart valve	53 (26.6)	54 (27.0)
Other known valve disease	82 (41.4)	90 (44.8)
Cardiac involvement at randomization		
Mitral valve endocarditis	65 (32.7)	72 (35.8)
Aortic valve endocarditis	109 (54.8)	109 (54.2)
Mitral and aortic valve endocarditis	23 (11.6)	20 (10.2)
Valve surgery during present disease-course	75 (37.7)	77 (38.3)

Herlev og Gentofte Hospital

	Oral regimens	Frequency n (%)
Staph 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)

	Oral regimens	Frequency n (%)
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)
CNS	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)

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Primary outcome

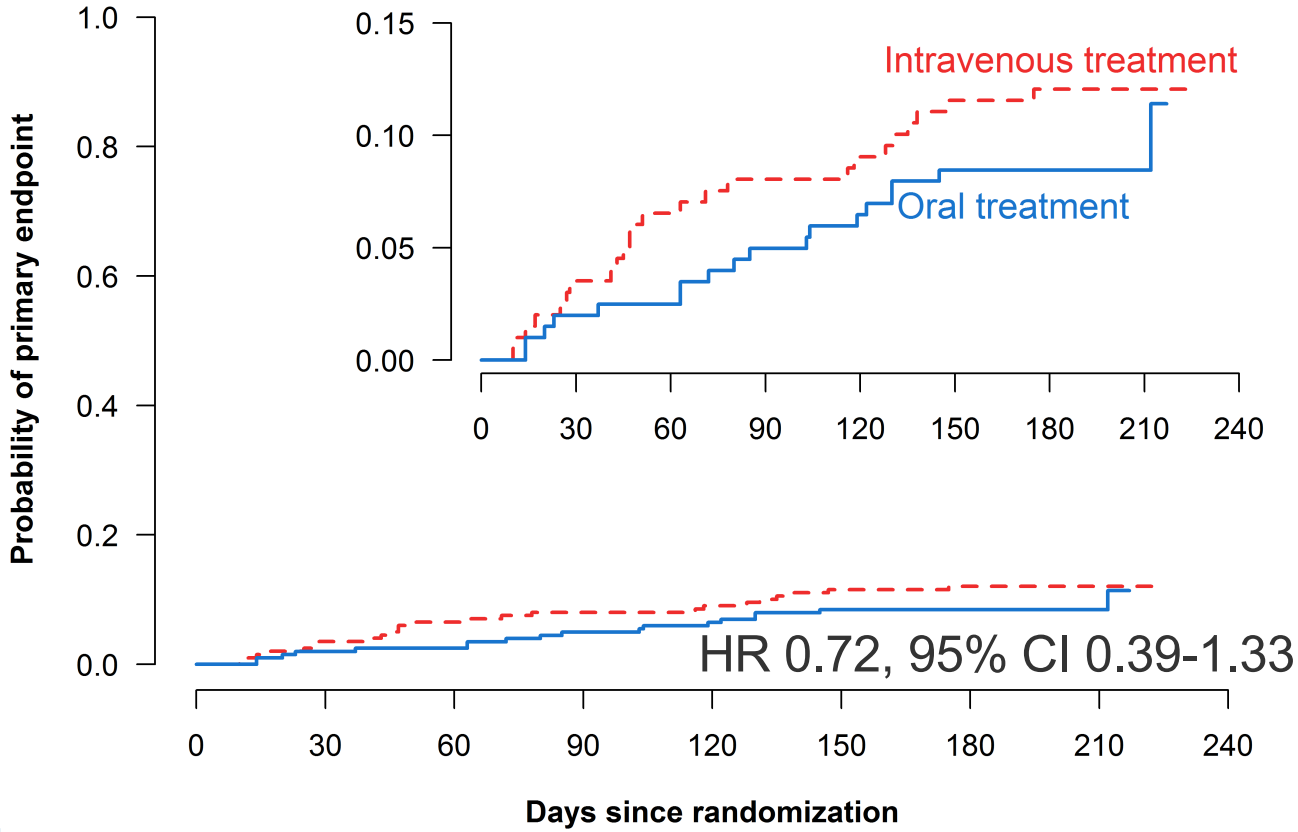
- Occured in 42 patients (10.5%)

	Intravenous treatment n=199	Oral treatment n=201	Difference	95% CI of the difference	HR (95% CI)
Primary outcome, n (%)	24 (12.1)	18 (9.0)	3.1%	-3.4% to 9.6%	0.72 (0.37 to 1.36)

Non-inferiority criteria was met

Primary endpoint

(All cause mortality, unplanned cardiac surgery, embolic events or relapse of bacteremia)



No. at Risk									
Intravenous treatment	199	192	186	183	181	176	174	28	0
Oral treatment	201	197	196	191	188	184	183	36	0

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Secundary outcomes

	Intravenous treatment n=199	Oral treatment n=201	Difference	95% CI of the difference	HR (95% CI)
All-cause mortality, n (%)	13 (6.5)	7 (3.5)	2.9%	-1.7% to 7.8%	0.53 (0.21 to 1.32)
Unplanned cardiac surgery, n (%)	6 (3.0)	6 (3.0)	0.0%	-3.3% to 3.4%	0.99 (0.32 to 3.07)
Embolic event, n (%)	3 (1.5)	3 (1.5)	0.0%	-2.4% -to 2.4%	0.97 (0.20 to 4.82)
Relapse of the positive blood culture, n (%)*	5 (2.5)	5 (2.5)	0.0%	-3.1% to 3.1%	0.97 (0.28 to 3.33)

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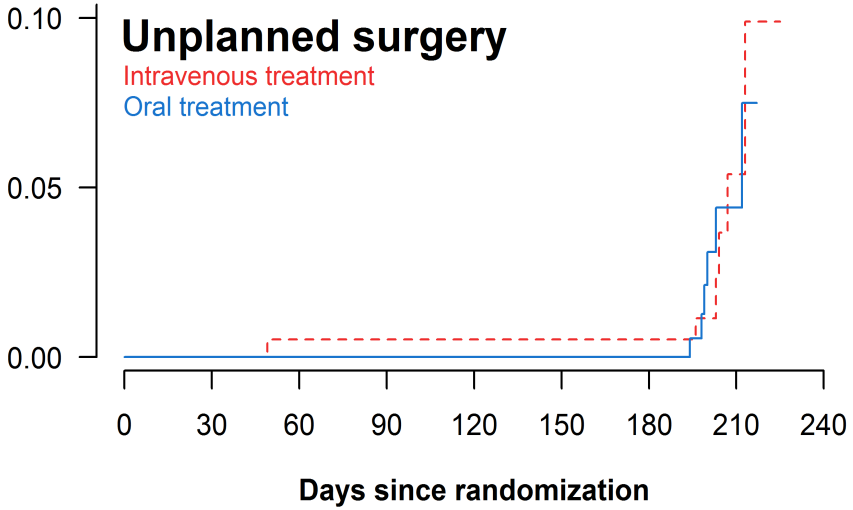
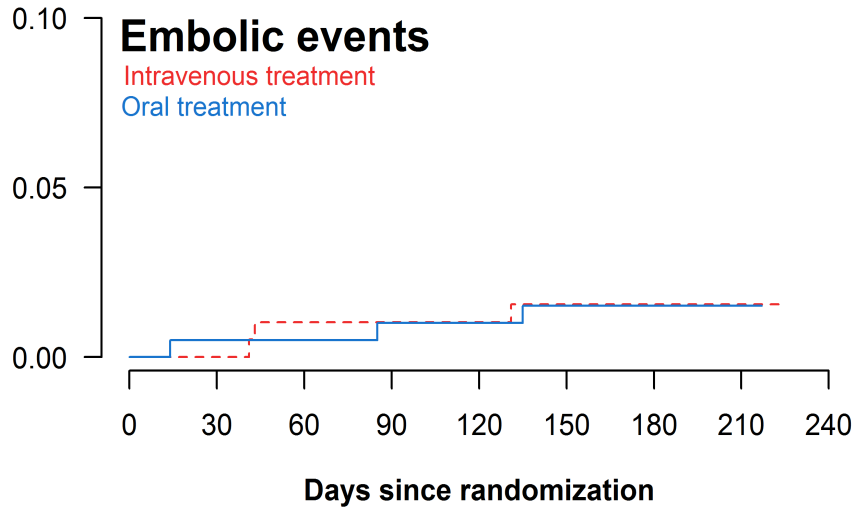
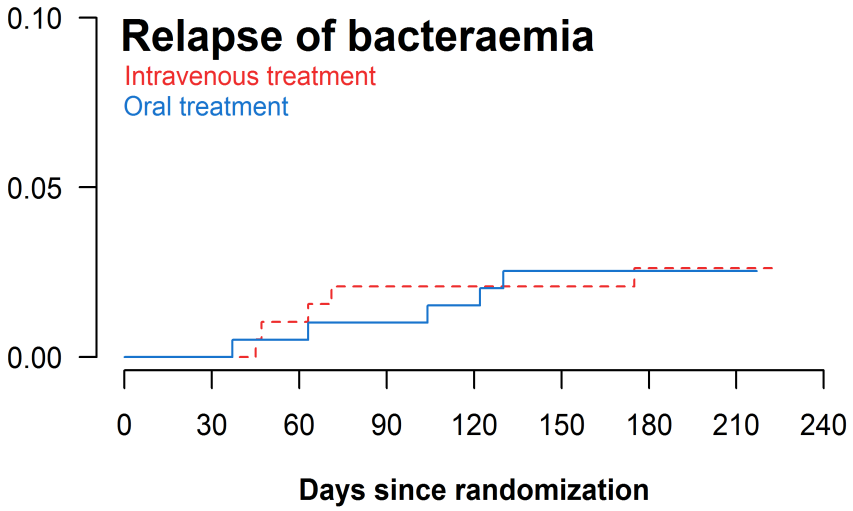
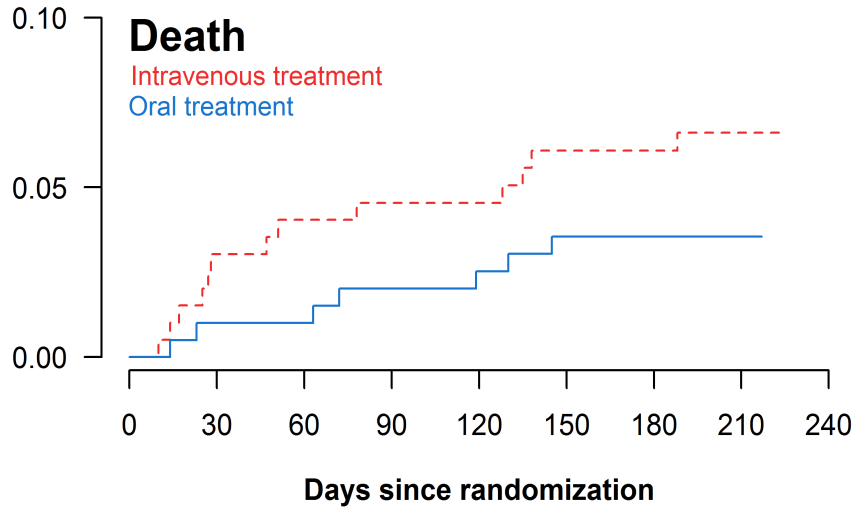
Components of primary endpoint









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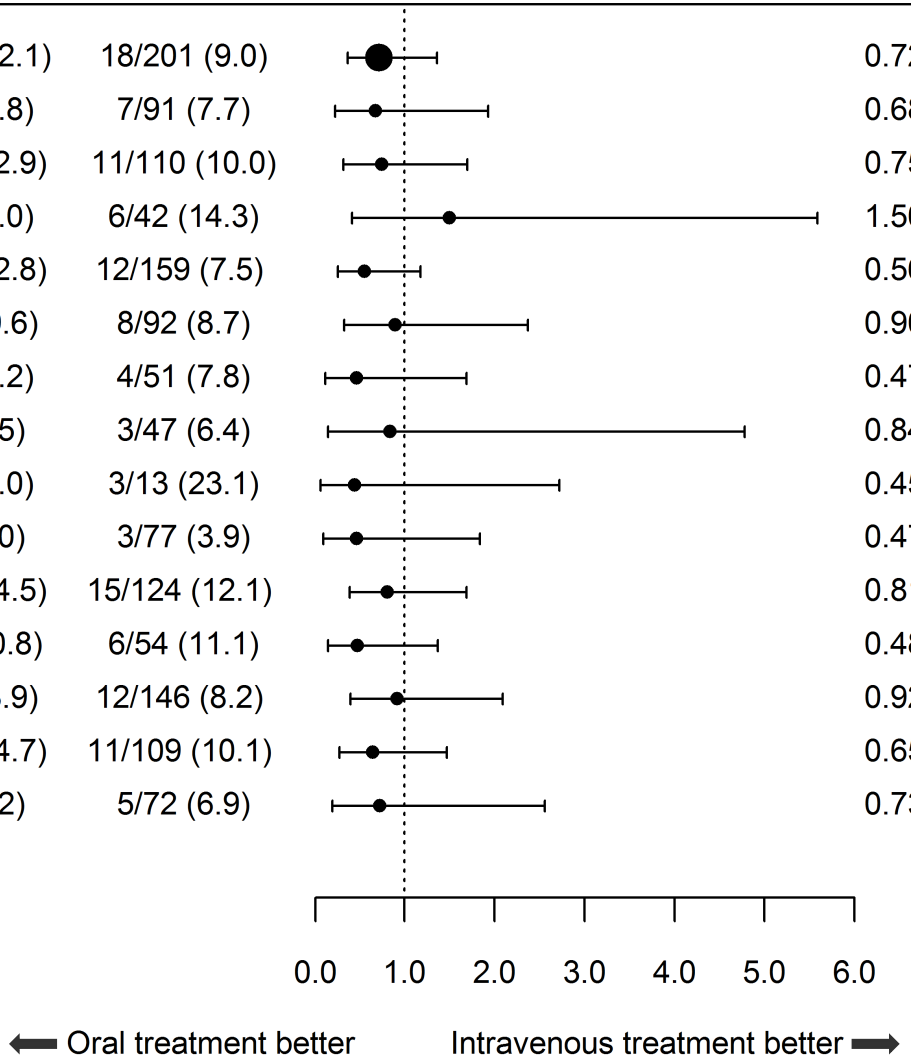
Primary endpoint – prespecified groups

	Prespecified subgroups	Intravenous treatment	Oral treatment	Odds Ratio [95% CI]	P value for interaction
All		24/199 (12.1)	18/201 (9.0)	0.72 [0.37 to 1.36]	
Age	<= 67.5 years	9/83 (10.8)	7/91 (7.7)	0.68 [0.23 to 1.93]	0.34
	> 67.5 years	15/116 (12.9)	11/110 (10.0)	0.75 [0.32 to 1.70]	
Gender	Female	5/50 (10.0)	6/42 (14.3)	1.50 [0.42 to 5.59]	0.19
	Male	19/149 (12.8)	12/159 (7.5)	0.56 [0.26 to 1.18]	
Bacteria	Streptococci	10/104 (9.6)	8/92 (8.7)	0.90 [0.33 to 2.37]	0.94
	E. faecalis	7/46 (15.2)	4/51 (7.8)	0.47 [0.12 to 1.69]	
	S. aureus	3/40 (7.5)	3/47 (6.4)	0.84 [0.15 to 4.78]	
	CNS	4/10 (40.0)	3/13 (23.1)	0.45 [0.07 to 2.72]	
Surgical treatment	Surgical treatment	6/75 (8.0)	3/77 (3.9)	0.47 [0.10 to 1.84]	0.50
	No surgical treatment	18/124 (14.5)	15/124 (12.1)	0.81 [0.39 to 1.69]	
Type of valve	Prosthetic heart valve	11/53 (20.8)	6/54 (11.1)	0.48 [0.15 to 1.37]	0.35
	Native heart valve	13/146 (8.9)	12/146 (8.2)	0.92 [0.40 to 2.09]	
Involved valve	Aortic valve	16/109 (14.7)	11/109 (10.1)	0.65 [0.28 to 1.47]	0.56
	Mitral valve	6/65 (9.2)	5/72 (6.9)	0.73 [0.20 to 2.56]	



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Safety and side-effects

- Sub-therapeutic plasma levels for one orally administered antibiotic in 7 patients
  - Pharmacokinetic results did not necessitate change of antibiotic regimens in any cases

- Side-effects; Intravenous 12 (6%), oral 10 (5%)
  - Allergy (50%), bone marrow suppression (27%) and gastro-intestinal side effects (14%) (ns)

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Outpatient treatment

	Intravenous	Oral	P
Time from IE diagnosis to randomisation*	17 (13-23)	17 (12-24)	0.42
Treatment after randomisation*	19 (14-25)	17 (14-25)	0.48
Length of hospital stays after randomisation*	19 (14-25)	3 (1-10)	<0.001

*In days (median) (IQR)

Conclusions

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- Efficacy and safety of shifting to oral antibiotic treatment was non-inferior to continued intravenous antibiotic treatment in
  - stabilized patients with left-sided endocarditis caused by
  - streptococcus spp, *Enterococcus faecalis, Staphylococcus aureus*, or coagulase-negative staphylococci
  - across co-morbidities, native vs prosthetic valve and surgically vs conservatively Tx

- Oral antibiotics may safely be administered during approximately
  - half of the recommended antibiotic treatment period
  - potentially as outpatient treatment

- More than 50% of patients with endocarditis may be candidates to partial oral antibiotic treatment

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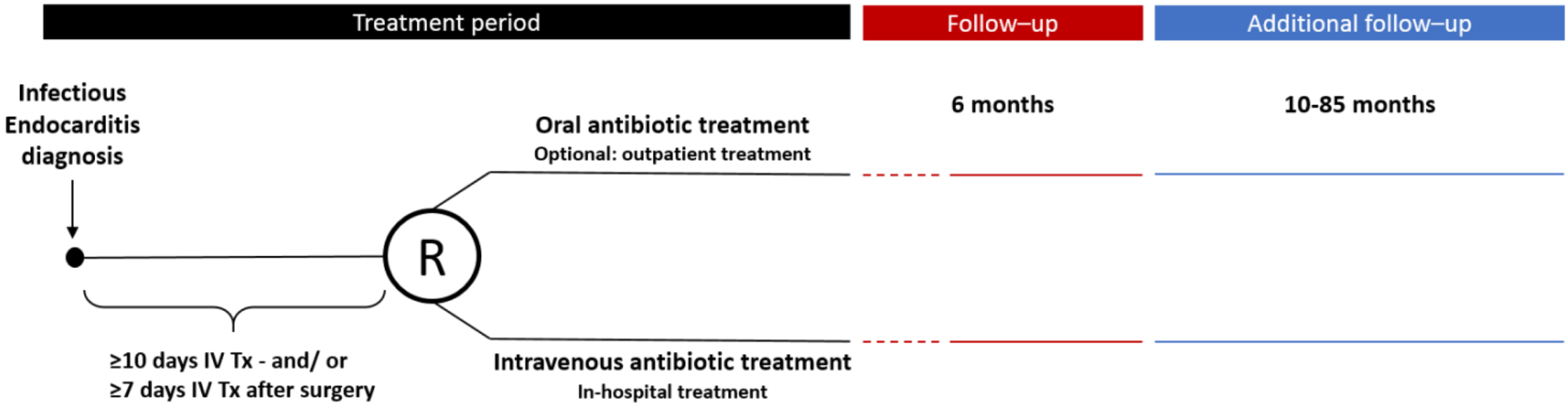
POET follow-up



Long-term follow-up

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- Primary endpoints as applied in the short-term study
- Median follow-up 3.5 years (IQR 2.3-5.1)
- Medical files
- Follow-up; 100%
- All endpoints adjudicated by an independent endpoint committee

Primary endpoint

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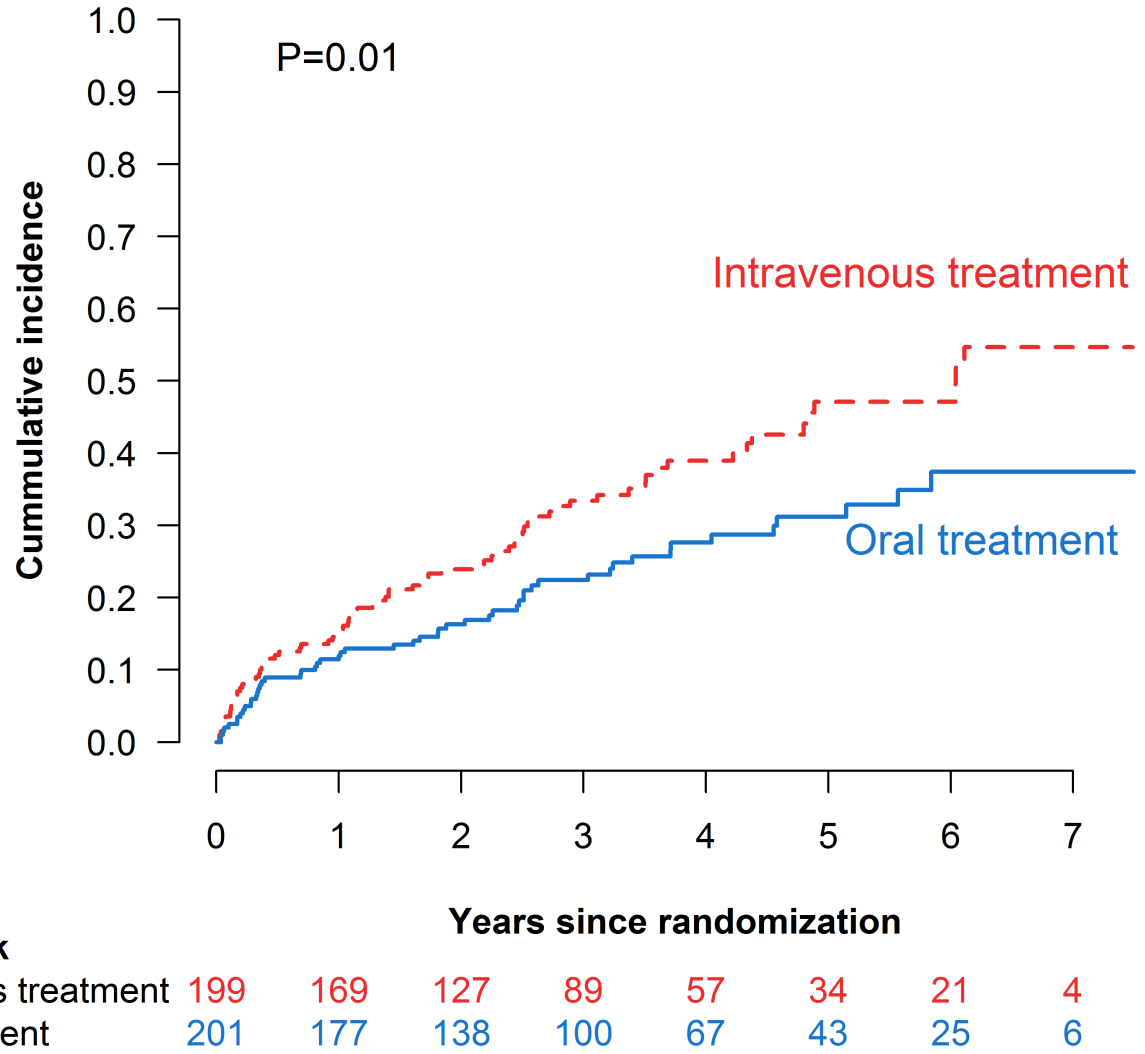
	Intravenous treatment n=199	Oral treatment n=201	HR (95% CI)	P-value
Composite endpoint, n (%)	78 (39.2)	55 (27.4)	0.65 (0.46 to 0.91)	0.01



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Components of the primary endpoint

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	Intravenous treatment n=199	Oral treatment n=201	HR (95% CI)	P-value
All-cause mortality, n (%)	54 (27.1)	33 (16.4)	0.57 (0.37 to 0.87)	0.01
Unplanned cardiac surgery, n (%)	18 (9.0)	12 (6.0)	0.63 (0.30 to 1.30)	0.21
Embolic event, n (%)	6 (3.0)	7 (3.5)	1.14 (0.38 to 3.38)	0.81
Relapse of the positive blood culture, n (%)	11 (5.5)	8 (4.0)	0.69 (0.28 to 1.73)	0.43

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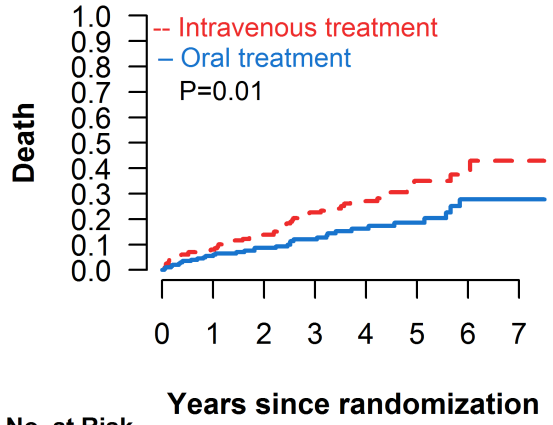
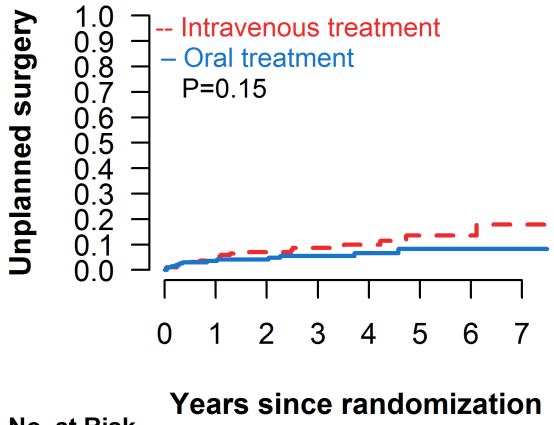


No. at Risk

IV treatment	199	183	144	104	70	42	23	6
Oral treatment	201	190	153	117	78	48	26	6

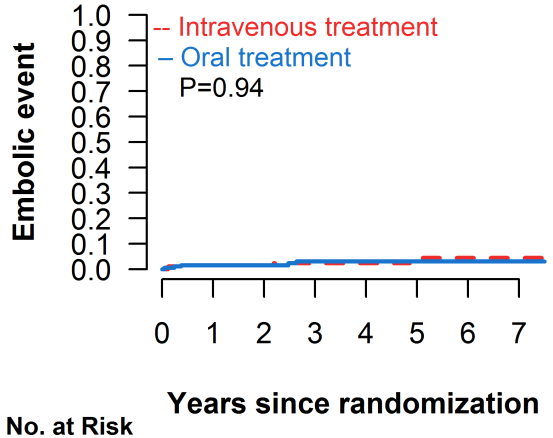
B



No. at Risk

IV treatment	199	175	134	94	61	38	22	5
Oral treatment	201	183	146	109	70	44	25	6

C



No. at Risk

IV treatment	199	180	142	102	68	40	23	6
Oral treatment	201	188	151	114	76	46	26	6

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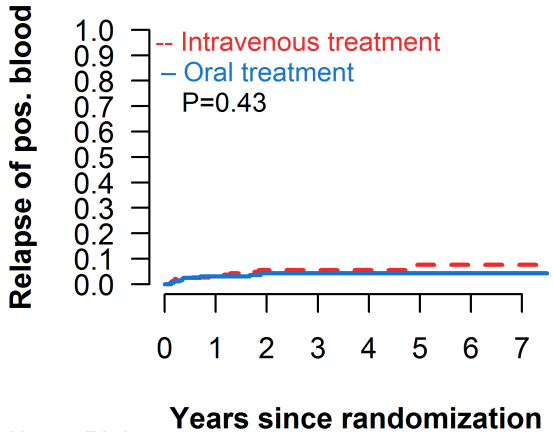

No. at Risk

IV treatment	199	179	138	100	67	39	22	5
Oral treatment	201	185	146	110	77	48	26	6

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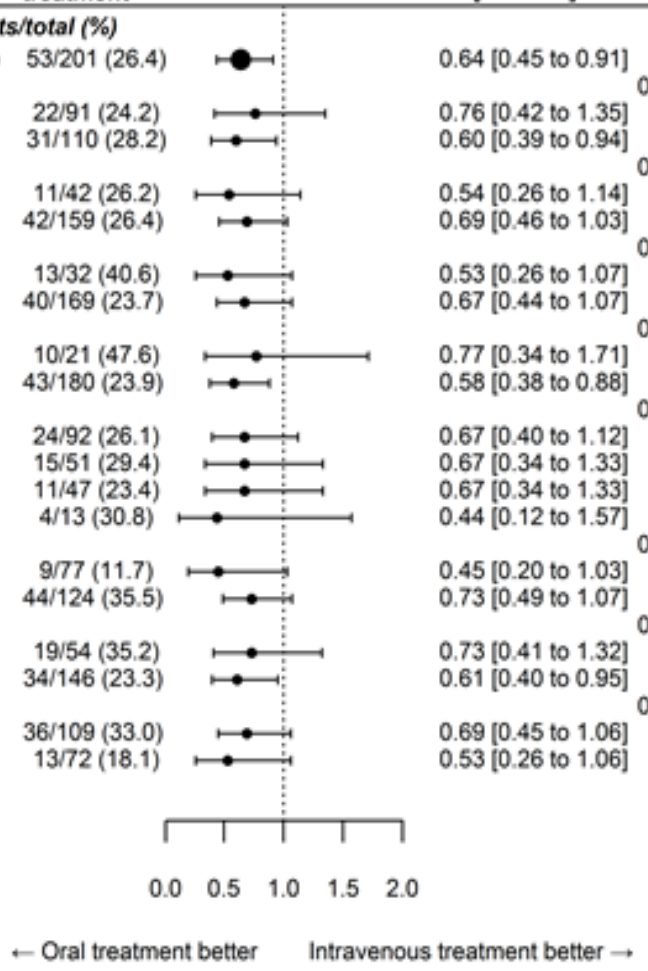
Results – prespecified subgroups – primary outcome

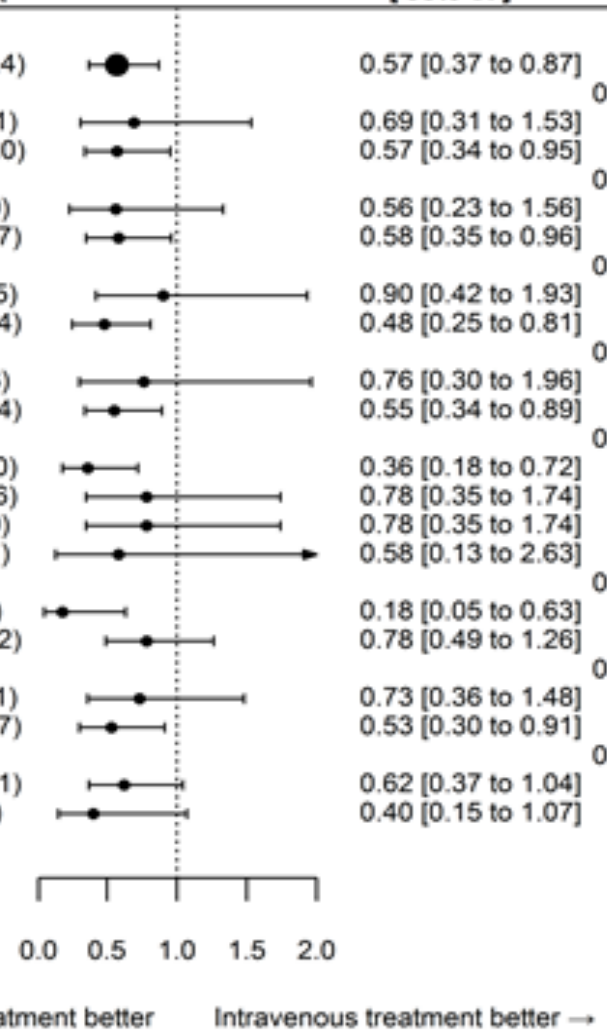
A

Prespecified subgroups	Intravenous treatment	Oral treatment	Hazard Ratio [95% CI]	P-value
	No. events/total (%)			
All patients	76/199 (38.2)	53/201 (26.4)	0.64 [0.45 to 0.91]	
Age				0.35
<= 67.5 years	24/83 (29.9)	22/91 (24.2)	0.76 [0.42 to 1.35]	
> 67.5 years	52/116 (44.8)	31/110 (28.2)	0.60 [0.39 to 0.94]	
Gender				0.49
Female	21/50 (42.0)	11/42 (26.2)	0.54 [0.26 to 1.14]	
Male	55/149 (36.9)	42/159 (26.4)	0.69 [0.46 to 1.03]	
Diabetes				0.74
Yes	22/36 (61.1)	13/32 (40.6)	0.53 [0.26 to 1.07]	
No	54/163 (33.1)	40/169 (23.7)	0.67 [0.44 to 1.07]	
Renal disease				0.74
Yes	15/25 (60.0)	10/21 (47.6)	0.77 [0.34 to 1.71]	
No	61/174 (35.1)	43/180 (23.9)	0.58 [0.38 to 0.88]	
Bacteria				0.97
Streptococci	37/104 (35.6)	24/92 (26.1)	0.67 [0.40 to 1.12]	
E. faecalis	19/46 (41.3)	15/51 (29.4)	0.67 [0.34 to 1.33]	
S. aureus	14/40 (35.0)	11/47 (23.4)	0.67 [0.34 to 1.33]	
CoNS	6/10 (60.0)	4/13 (30.8)	0.44 [0.12 to 1.57]	
Surgical treatment				0.31
Yes	16/75 (21.3)	9/77 (11.7)	0.45 [0.20 to 1.03]	
No	60/124 (48.4)	44/124 (35.5)	0.73 [0.49 to 1.07]	
Type of valve				0.97
Pros. heart valve	27/53 (50.9)	19/54 (35.2)	0.73 [0.41 to 1.32]	
Native heart valve	49/146 (33.6)	34/146 (23.3)	0.61 [0.40 to 0.95]	
Involved valve				0.46
Aortic valve	50/109 (45.9)	36/109 (33.0)	0.69 [0.45 to 1.06]	
Mitral valve	20/65 (30.8)	13/72 (18.1)	0.53 [0.26 to 1.06]	



Results – prespecified subgroups – death

Prespecified subgroups	Intravenous treatment	Oral treatment	Hazard Ratio [95% CI]	P-value
	No. events/total (%)			
All patients	54/199 (27.1)	33/201 (16.4)	0.57 [0.37 to 0.87]	
Age				0.59
<= 67.5 years	13/83 (15.7)	11/91 (12.1)	0.69 [0.31 to 1.53]	
> 67.5 years	41/116 (35.3)	22/110 (20.0)	0.57 [0.34 to 0.95]	
Gender				0.91
Female	15/50 (30.0)	8/42 (19.0)	0.56 [0.23 to 1.56]	
Male	39/149 (26.2)	25/159 (15.7)	0.58 [0.35 to 0.96]	
Diabetes				0.15
Yes	15/36 (57.3)	12/32 (37.5)	0.90 [0.42 to 1.93]	
No	39/163 (23.9)	21/169 (12.4)	0.48 [0.25 to 0.81]	
Renal disease				0.60
Yes	11/25 (44.0)	7/21 (33.3)	0.76 [0.30 to 1.96]	
No	43/174 (24.7)	26/180 (14.4)	0.55 [0.34 to 0.89]	
Bacteria				0.97
Streptococci	29/104 (42.3)	11/92 (12.0)	0.36 [0.18 to 0.72]	
E. faecalis	13/46 (28.3)	11/51 (21.6)	0.78 [0.35 to 1.74]	
S. aureus	8/40 (20.0)	8/47 (17.0)	0.78 [0.35 to 1.74]	
CoNS	4/10 (40.0)	3/13 (23.1)	0.58 [0.13 to 2.63]	
Surgical treatment				0.30
Yes	13/75 (17.3)	3/77 (3.9)	0.18 [0.05 to 0.63]	
No	41/124 (33.1)	30/124 (24.2)	0.78 [0.49 to 1.26]	
Type of valve				0.97
Pros. heart valve	20/53 (37.7)	13/54 (24.1)	0.73 [0.36 to 1.48]	
Native heart valve	34/146 (23.3)	20/146 (13.7)	0.53 [0.30 to 0.91]	
Involved valve				0.35
Aortic valve	37/109 (33.9)	23/109 (21.1)	0.62 [0.37 to 1.04]	
Mitral valve	12/65 (18.5%)	6/72 (0.8)	0.40 [0.15 to 1.07]	



Causes of death

	Intravenous Treatment (n=199)	Oral Treatment (n=201)
All cause	54 (27.1)	33 (16.4)
Infection*, n (%)	14 (7.0)	10 (5.0)
Cardio-vascular, n (%)	21 (10.6)	8 (4.0)
Cancer, n (%)	13 (6.5)	5 (2.5)
Other, n (%)	6 (1.5)	10 (4.5)

POET kriterier: skal opfyldes inden skift fra iv til PO AB

JA
- Sikker endokardit på baggrund af en af følgende bakterier: streptokokker, Staphylococcus aureus, Enterococcus faecalis eller koagulase-negative stafylokokker?

JA
- Behandlet med relevant IV antibiotika ≥10 days og ≥7 days efter hjertekirurgi?

JA
- Tilfredsstillende respons på behandlingen: afebril >2 dage, CRP <25% af højeste målte værdi eller <20 mg/l og Leukocytter <15 x 109/L?

JA
- TEE udført <2 dage uden abscess eller indikation for operation

NEJ
- Anden indikation for forlænget behandling med iv antibiotika, mistænkt nedsat GI optag eller BMI >40

POET
- Overvej at skifte behandlingen fra iv antibiotika til per oral behandling med 2 per orale antibiotika og overvej udskrivelse med ambulant opfølgning

POET

POET criteria

YES
- IE with: streptococci, Staphylococcus aureus, Enterococcus faecalis or CONS?

YES
- IE treated intravenously with appropriate antibiotics for ≥10 days and ≥7 days in case of heart surgery during present IE?

YES
- Satisfactory response to treatment; Afebrile >2 days, CRP <25% of peak level or <20 mg/l and Leucocytes <15 x 10^9/L?

YES
- Echocardiography (TOE) performed <2 days without abscess formation or presence of other indications for surgery?

NO
- Other indications for prolonged intravenous antibiotics, suspected reduced gastro-intestinal uptake or BMI >40?

POET
- **Consider shifting to oral therapy (2 antibiotics) and consider discharge to outpatient treatment**

POET II

Accelererred treatment of endocarditis

POET

Background

Circulation

DECEMBER 1950
VOL. II NO. 6

The Journal of the American Heart Association

The Lewis A. Conner Lecture of the American Heart Association

The Present Status of Treament of Subacute Bacterial Endocarditis

By Arthur L. Bloomfield, M. D.

REGION

Background

- At any rate it must be quite clear **that the essence of the treatment is time**. No agent, **no matter how great its bactericidal effect, can be expected to dislodge cocci from the depths of vegetations in just a few days**; the agent must be present over a long period to aid and abet the natural healing process and to nip off any organisms which stray to accessible surfaces.
- In our early cases **we arbitrarily treated for 60 days'** and as it happened, this turned out to be a fully adequate period**. It is not likely that anything would often be gained by more prolonged therapy.**

POET

Baggrund

- Recently we have wondered whether 60 days may not be too long and Rantz and his associates in our clinic have convinced that 30 days of continuous treatment, provided the daily dose is adequate, yields equally good results. **Periods of therapy short of this must, however, be definitely classed as bad practice.**
- Even in patients with a highly sensitive strain of S. viridans **we use at least 600,000 units daily; the total can conveniently be given in two injections at 12 hour intervals**

REGION

POET

Rationale

- Doses of antibiotics higher than previous
- Often treatment with several drugs
- Relapses are vey rare

POET

	6-week regimen	12-week regimen	Difference in proportion of patients*	95% CI
Intention-to-treat analysis, n	176	175		
Cured	160 (90·9%)	159 (90·9%)	+0·1	−6·2 to 6·3
Cured and alive†	156 (88·6%)	150 (85·7%)	+2·9	−4·2 to 10·1
Cured without further antibiotic treatment‡	142 (80·7%)	141 (80·6%)	+0·1	−8·3 to 8·5
Per-protocol analysis, n	146	137		
Cured	137 (93·8%)	132 (96·4%)	−2·5	−8·2 to 2·9
Cured and alive†	133 (91·1%)	126 (92·0%)	−0·9	−7·7 to 6·0
Cured without further antibiotic treatment‡	NA	NA	NA	NA

Data are number, or number (%) unless otherwise specified. 32 patients (16 in the 6-week group and 16 in the 12-week group) were classified as cases of probable failure of treatment by the independent validation committee. Of 68 protocol violations excluded from the per-protocol population, 18 cases were classified as failure and 50 as cure in the intention-to-treat population. *6-week group minus 12-week group. †Death in cases classified as probable cure by the independent validation committee were classified as failure. ‡Further antibiotic treatment was regarded as a treatment failure. NA=not applicable.

Table 2: Primary outcome analyses of patients with vertebral osteomyelitis according to duration of antibiotic treatment

Louis Bernard et al. Lancet 2015,

PHARMACOTHERAPY accp

Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials

Alexandra M. Hanretty,[1] and Jason C. Gallagher[2]*
[1]St. Christopher's Hospital for Children, Philadelphia, Pennsylvania; [2]Department of Pharmacy Practice, Temple University, Philadelphia, Pennsylvania

REGION H

POET

Objectives

To determine - in stabilised patients with endocarditis - whether

- Accelerated treatment Usual length treatment

have similar efficacy and safety

POET

Inclusion criteria

- Left-sided endocarditis based on the modified Duke criteria caused by
  - Streptococci or
  - *Enterococcus faecalis or*
  - *Staphylococcus aureus*
- <14 days of appropriate intravenous antibiotic treatment
- ≥18 years of age

POET

Exclusion criteria

- Known or presumed immunologic incompetence
- Inability to give informed consent
- Relaps-endocarditis

Participanters

POET

Primary endpoint

- A composite endpoint ≤6 months after randomization of
  - All cause mortality
  - Embolic events
  - Relapse of bacteremia with the primary pathogen

Treatment

- The initial treatment should be given in accordance with present guidelines (including POET guidelines!!)

POET

	Usual treatment	Accelerated treatment
Enterococci uncomplicated	6 weeks	4 weeks
Enterococci complicated^	6 weeks	4 weeks
S aureus uncomplicated	4 weeks	2 weeks
S aureus complicated^	6 weeks	4 weeks
Streptococci uncomplicated	4 weeks	2 weeks
Streptococci complicated^	6 weeks	3 uger
After heart surgery negative cultures	≥2 weeks	≥1 week
After heart surgery positive cultures	As new infection	As new infection

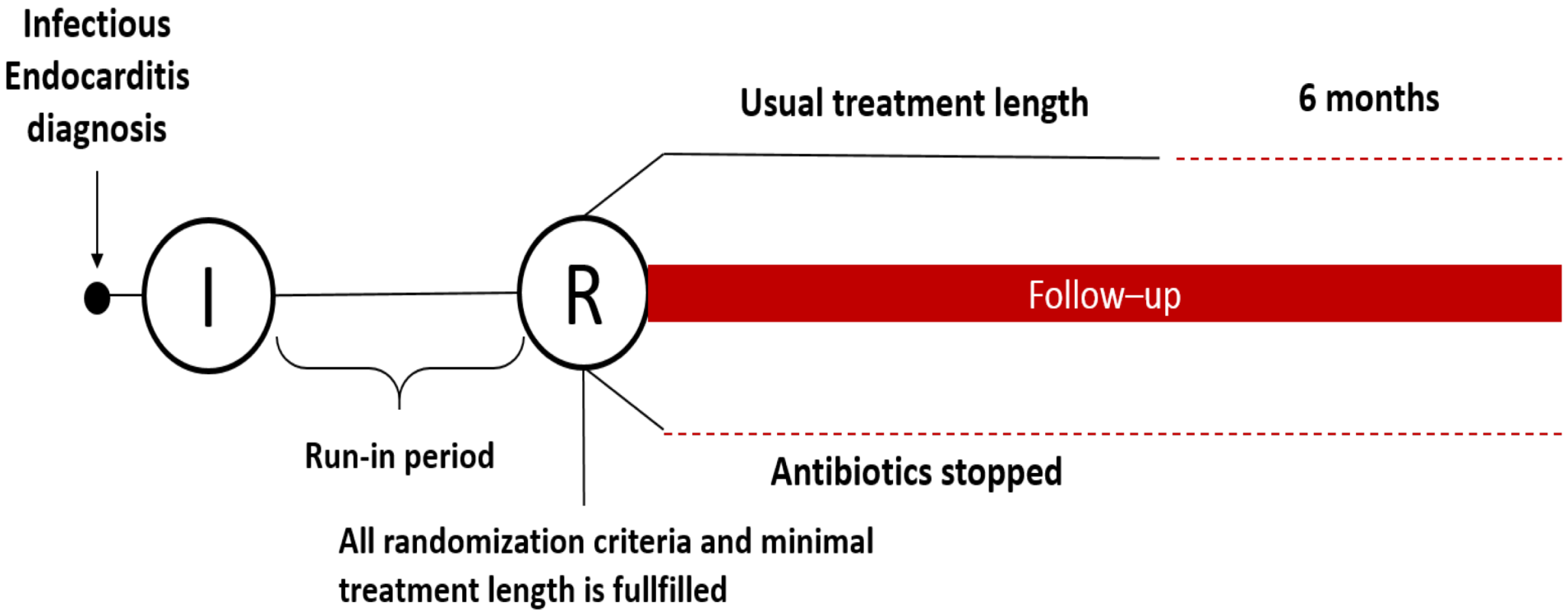
^ Nativ klap, ingen embolisering, ikke operation, ikke immuninkompetent

POET

Criteria for randomization

- No planned cardiac surgery duing the present admission
- Neutrophilic leucocytes < 10 and rise < 15% of the last three measurements **or** neutrophilic leucocytes < 50% of the highest value
- CRP < 40 and rise < 15%
- Procalcitonin < 0.50
- Temperature < 38.0 C in two days
- TEE within 48 hours and no signs of progress of disease

POET


Infectious Endocarditis diagnosis
I
R
Run-in period
Usual treatment length
6 months
Follow–up
Antibiotics stopped
All randomization criteria and minimal treatment length is fullfilled

POET

Follow up

- 1 week – Biochemistry and clinical assesment
- 2 weeks - Biochemistry
- 1 month – Biochemistry and clinical assesment
- 6 weeks - Biochemistry
- 8 weeks - Biochemistry
- 10 weeks - Biochemistry
- 3 months – Biochemistry and clinical assesment
- 6 monts – Biochemistry and clinical assesment

REGION

Sample-size

- Frequency of primary composite endpoint 8%
- Delta 5%
- Sample-size 730

- We aim to include 750 patients (4 years)

- Predefined interrim analysis after 1 year

Status

- 6 patients included

Causes of surgery

Causes of unplanned surgery	Intravenous Treatment (n=199)	Oral Treatment (n=201)
All reasons for surgery, n (%)	18 (9.0)	12 (6.0)
Endocarditis, n (%)	3 (1.5)	2 (1.0)
Aortic stenosis, n (%)	7 (3.5)	3 (1.5)
Aortic or mitral regurgitation, n (%)	7 (3.5)	7 (3.5)
Other, n (%)	1 (0.5)	0 (0)

	Parenteral regimens	n	Oral regimens	n
Staphylococcus aureus	Dicloxcacillin and rifampicin	7	Amoxicillin and rifampicin	13
	Dicloxcacillin	4	Dicloxcacillin and rifampicin	4
	Dicloxcacillin and fusidic acid	4	Moxifloxacin and rifampicin	3
	Cefuroxime and rifampicin	4	Amoxicillin and fusidic acid	2
	Penicillin	3	Dicloxcacillin and fusidic ascd	2
	Linezolid	3	Fusidic acid and linezolid	2
	Cefuroxime and fusidic acid	3	Rifampicin and linezolid	2
	Penicillin and rifampicin	2	Penicillin and rifampicin	1
	Cefuroxime and linezolid	2	Amoxicillin and clindamycin	1
	Moxifloxacin and linezolid	2	Ampicillin and rifampicin	1
	Meropenem and fusidic acid	1	Moxifloxacin and fusidic acid	1
	Cefuroxime	1	Moxifloxacin and linezolid	1
	Moxifloxacin and rifampicin	1	Linezolid and clindamycin	1
	Moxifloxacin and fusidic acid	1		
	Rifampicin and vancomycin	1		
	Fusidic acid and linezolid	1		
	Linezolid and clindamycin	1		
	Vancomycin	1		