Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D.,
Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D.,
Niels E. Bruun, M.D., D.M.Sc., Dan E. Høfsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc.,
Jens J. Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D., Emil L. Fosbøll, M.D., Ph.D.,
Flemming Rosenvinge, M.D., Henrik C. Schønheyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc.,
Christian Torp-Pedersen, M.D., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc., Niels Tønder, M.D., D.M.Sc.,
Claus Moser, M.D., Ph.D., and Henning Bundgaard, M.D., D.M.Sc.

ABSTRACT

BACKGROUND

Patients with infective endocarditis on the left side of the heart are typically treated with intravenous antibiotic agents for up to 6 weeks. Whether a shift from intravenous to oral antibiotics once the patient is in stable condition would result in efficacy and safety similar to those with continued intravenous treatment is unknown.

METHODS

In a randomized, noninferiority, multicenter trial, we assigned 400 adults in stable condition who had endocarditis on the left side of the heart caused by streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci and who were being treated with intravenous antibiotics to continue intravenous treatment (199 patients) or to switch to oral antibiotic treatment (201 patients). In all patients, antibiotic treatment was administered intravenously for at least 10 days. If feasible, patients in the orally treated group were discharged to outpatient treatment. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from the time of randomization until 6 months after antibiotic treatment was completed.

RESULTS

After randomization, antibiotic treatment was completed after a median of 19 days (interquartile range, 14 to 25) in the intravenously treated group and 17 days (interquartile range, 14 to 25) in the orally treated group (P=0.48). The primary composite outcome occurred in 24 patients (12.1%) in the intravenously treated group and in 18 (9.0%) in the orally treated group (between-group difference, 3.1 percentage points; 95% confidence interval, −3.4 to 9.6; P=0.40), which met noninferiority criteria.

CONCLUSIONS

In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. (Funded by the Danish Heart Foundation and others; POET ClinicalTrials.gov number, NCT01375257.)

PATIENTS WITH INFECTIVE ENDOCARDITIS on the left side of the heart are typically treated with intravenously administered antibiotic agents for up to 6 weeks, according to guidelines from the European Society of Cardiology and the American Heart Association.[1,2] During the initial phase after admission, intensive care and close monitoring are often needed. In-hospital mortality is reported to range from 15% to more than 45%, depending on the pathogen and on complicating factors, and half the patients undergo cardiac-valve surgery.[3-5] The majority of complications, including death, are seen during the initial phase.[6-8] For a large proportion of patients, the main reason for staying in the hospital after the initial phase is to complete intravenous antibiotic treatment. Therefore, if oral antibiotic treatment might be safe and efficient, part of the treatment period for patients in stable condition could take place outside hospitals, without the need for an intravenous catheter.

Intravenous treatment during long hospital stays may be associated with an increased risk of complications, whereas a shorter length of hospital stay has been associated with better outcomes in studies of other diseases.[9-11] This forms the basis for recommendations in European and American guidelines for outpatient parenteral treatment of endocarditis in patients fulfilling certain criteria, a regimen commonly used in the United States.[1,2,12,13] However, when outpatient parenteral treatment is given, logistic issues are critical, and education of the patients and staff is necessary to ensure that the patients adhere to the regimen, are adequately monitored for efficacy and adverse effects, and receive paramedic and social support, as well as easy access to medical advice. Oral antibiotic therapy may reduce these challenges and may be an appropriate alternative. However, the clinical evidence for the safety and efficacy of oral antibiotic treatment of endocarditis is limited.[14-18]

In the current trial, we hypothesized that in patients in clinically stable condition who have endocarditis on the left side of the heart, a shift from intravenously to orally administered antibiotic treatment would result in efficacy and safety that would be similar to those with continued intravenous antibiotic treatment.

METHODS

TRIAL DESIGN AND OVERSIGHT

The Partial Oral Treatment of Endocarditis (POET) trial was a nationwide investigator-initiated, multicenter, randomized, unblinded, noninferiority trial performed at cardiac centers in Denmark. The trial design has been published previously.[17] The trial was overseen by an independent data and safety monitoring board. The protocol is available with the full text of this article at NEJM.org. The trial was approved by the regional scientific ethics committee for the Capital Region of Denmark and by the Danish Data Protection Agency and was performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent. All the authors vouch for the completeness and accuracy of the data and analyses presented and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients were adults, 18 years of age or older, in stable condition who were receiving intravenous antibiotic treatment for endocarditis on the left side of the heart (on native or prosthetic valves), who fulfilled the modified Duke criteria,[19] and who had blood cultures that were positive for streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci. Decisions about whether to offer surgery or to remove a pacemaker or an implantable cardioverter–defibrillator were made at multidisciplinary team meetings according to established guidelines and were not a part of the trial. Only patients in stable condition were enrolled (i.e., patients who had had satisfactory clinical responses to initial treatment, including antibiotic treatment administered intravenously for at least 10 days and, among patients who had undergone valve surgery, for at least 7 days after the surgery). In addition, transesophageal echocardiography performed before randomization had to show no signs of abscess formation or valve abnormalities that would require surgery (a full list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix, available at NEJM.org). At the time of randomization, at least 10 days of scheduled antibiotic treatment had to remain. Patients assigned to receive intravenous treatment remained in the hospital until antibiotic treatment was completed. If feasible, patients assigned to receive oral treatment were treated in the outpatient clinics and were seen two to three times per week. Within 1 to 3 days before the completion of the assigned antibiotic treatment, transesophageal echocardiography was performed to confirm that the patient had a suf-

ficient response to treatment. All patients were discharged from the hospital on the day the antibiotic treatment was terminated (determined before randomization); all patients were seen in the outpatient clinic at 1 week and at 1, 3, and 6 months after completion of antibiotic treatment. Enrollment and the assignment of treatment were performed by local investigators with a Web-based case-report-form system.

CHOICE OF ANTIBIOTICS

Intravenous antibiotic treatment was administered in accordance with guidelines of the European Society of Cardiology, with modifications endorsed by the Danish Society of Cardiology.[2,20] The trial investigators developed oral antibiotic treatment regimens as part of the trial (Table S2 in the Supplementary Appendix). Antibiotics for which published data showed moderate to high bioavailability were chosen. The oral regimens were based on pharmacokinetic calculations and expected minimal inhibitory concentrations (MICs) for each bacterial species published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[21] In all cases, susceptibility testing by means of disk diffusion was performed in accordance with EUCAST guidelines. MICs were determined with the use of Etest or VITEK2 (bioMérieux), and the choice of antibiotics for each patient was adjusted accordingly. In all cases, the oral regimens consisted of two antibiotics from different drug classes with different antimicrobial mechanisms of action and different metabolization processes to reduce the risk of de facto monotherapy (e.g., in the case of reduced gastrointestinal uptake or fast metabolization of one drug).

PHARMACOKINETICS

To ensure that patients received sufficient doses of antibiotics, blood samples for the measurement of plasma levels of orally administered antibiotics were obtained on day 1 after the administration of a single dose (30 minutes and 1, 2, 4, and 6 hours after administration) and on day 5, after the administration of multiple doses (with the assumption that a steady state would have been achieved by this time). Samples were also obtained from patients in the intravenously treated group on day 1. Samples were analyzed with the use of high-pressure liquid chromatography. For safety considerations, the first dose and steady-state pharmacokinetics were evalu-

ated (Table S3 in the Supplementary Appendix). Antibiotic doses were adjusted according to pharmacokinetic findings, if necessary.
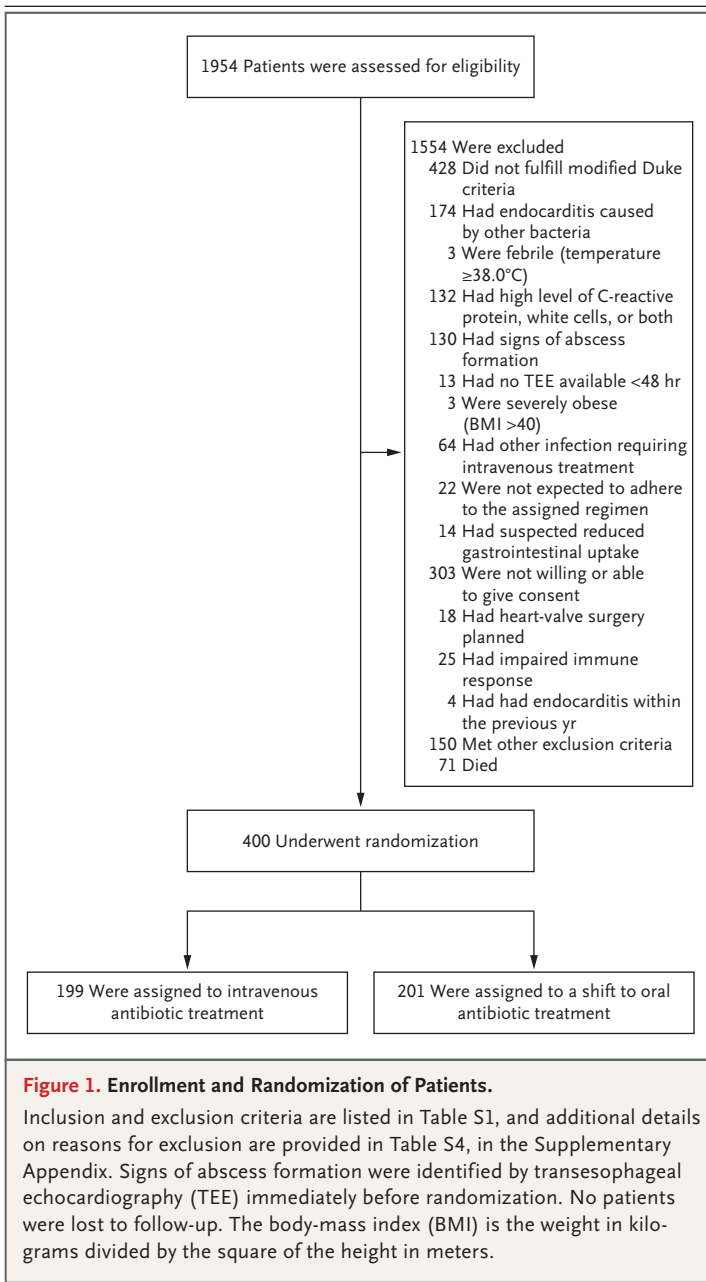
TRIAL PROCEDURES

Participants were randomly assigned in a 1:1 ratio to continued intravenously administered antibiotic treatment or to a shift to orally administered antibiotic treatment. Randomization was performed with the use of a Web-based system, in permuted blocks of 2 to 6, with stratification according to randomization site.

OUTCOMES

The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia with the primary pathogen (detected in blood cultures obtained during follow-up or for clinical reasons) from randomization through 6 months after antibiotic treatment was completed. A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases.

STATISTICAL ANALYSIS

The trial was designed as a noninferiority trial; that is, it was designed to determine, with the use of a noninferiority margin, whether partial oral treatment was noninferior to conventional intravenous treatment. We estimated event rates for the four components of the primary composite outcome from the literature[17]; we estimated the risk of all-cause mortality to be 2 to 5%, the risk of unplanned surgery to be 1 to 3%, the risk of embolic events to be 1 to 2%, and the risk of relapse of bacteremia to be 1 to 3%. Thus, the overall risk of the primary outcome was 5 to 13%. A risk difference (i.e., a noninferiority margin) of 10 percentage points was chosen (see the Supplementary Appendix). Under the assumption of a 10% event rate and a 5% loss to follow-up, we determined that inclusion of 400 patients would be required to provide a power of 90% to confirm noninferiority, with a one-sided confidence interval of 97.5%. Continuous variables are presented as means and standard deviations or medians and interquartile ranges, as appropriate, and were compared with the use of Student's t-test or the Mann–Whitney U test. Categorical variables are expressed

```
┌─────────────────────────────────────────┐
│  1954 Patients were assessed for          │
│  eligibility                              │
└─────────────────────────────────────────┘
                    │
                    │         ┌──────────────────────────────────────┐
                    │         │ 1554 Were excluded                    │
                    │         │   428 Did not fulfill modified Duke   │
                    │         │        criteria                       │
                    │         │   174 Had endocarditis caused         │
                    │         │        by other bacteria              │
                    │         │     3 Were febrile (temperature       │
                    │         │        ≥38.0°C)                       │
                    │         │   132 Had high level of C-reactive    │
                    │         │        protein, white cells, or both  │
                    │         │   130 Had signs of abscess            │
                    │         │        formation                      │
                    ├────────▶│    13 Had no TEE available <48 hr     │
                    │         │     3 Were severely obese             │
                    │         │        (BMI >40)                      │
                    │         │    64 Had other infection requiring   │
                    │         │        intravenous treatment          │
                    │         │    22 Were not expected to adhere     │
                    │         │        to the assigned regimen        │
                    │         │    14 Had suspected reduced           │
                    │         │        gastrointestinal uptake        │
                    │         │   303 Were not willing or able        │
                    │         │        to give consent                │
                    │         │    18 Had heart-valve surgery         │
                    │         │        planned                        │
                    │         │    25 Had impaired immune             │
                    │         │        response                       │
                    │         │     4 Had had endocarditis within     │
                    │         │        the previous yr                │
                    │         │   150 Met other exclusion criteria    │
                    │         │    71 Died                            │
                    │         └──────────────────────────────────────┘
                    ▼
┌─────────────────────────────────────────┐
│  400 Underwent randomization              │
└─────────────────────────────────────────┘
              │               │
      ┌───────┘               └───────┐
      ▼                               ▼
┌──────────────────────┐  ┌──────────────────────┐
│ 199 Were assigned to  │  │ 201 Were assigned to  │
│ intravenous           │  │ a shift to oral       │
│ antibiotic treatment  │  │ antibiotic treatment  │
└──────────────────────┘  └──────────────────────┘
```

Figure 1. Enrollment and Randomization of Patients.

Inclusion and exclusion criteria are listed in Table S1, and additional details on reasons for exclusion are provided in Table S4, in the Supplementary Appendix. Signs of abscess formation were identified by transesophageal echocardiography (TEE) immediately before randomization. No patients were lost to follow-up. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

to the intention-to-treat principle. A per-protocol analysis is also presented for the primary outcome; in the per-protocol analysis, patients who crossed over from their assigned treatment to the other treatment were excluded. Cumulative incidences were calculated for events with competing risk (death) for the outcomes of unplanned cardiac surgery, embolic events, and relapse of bacteremia with the primary pathogen. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed with the use of SPSS software, version 22.0 (IBM), and R software, version 3.3.3 (R Foundation for Statistical Computing).[22-24]

RESULTS

PATIENTS

From July 15, 2011, to August 30, 2017, a total of 1954 patients who were referred to a cardiac center because of suspected endocarditis were screened for inclusion; 400 patients (20%) with endocarditis on the left side of the heart who fulfilled the modified Duke criteria for definite endocarditis were enrolled; 199 patients were randomly assigned to continued conventional intravenous treatment, and 201 patients to a shift to oral treatment (Fig. 1). The most frequent reasons for exclusion were an unconfirmed diagnosis (22%), an unwillingness or inability to give informed consent (16%), or an infection that was caused by other bacteria (9%) (Table S4 in the Supplementary Appendix). Generally, the two groups were well balanced with regard to baseline characteristics (Table 1). The majority of patients were men (77%), and the mean age was 67 years. A total of 139 patients (35%) had at least one major coexisting medical condition. At the time of randomization, the results of routine blood tests were similar in the groups, except that the C-reactive protein level was slightly higher in the intravenously treated group. The most frequently identified pathogen was streptococcus, followed by *S. aureus*, *E. faecalis*, and coagulase-negative staphylococci (Table 1, and Table S5 in the Supplementary Appendix).

The aortic valve was affected in the majority of cases, and in 27% (107 patients), a previously inserted prosthetic valve was affected (details are provided in Table S6 in the Supplementary Appendix). Before randomization, 152 of the 400 enrolled patients (38%) had undergone valve surgery (Ta-

as absolute numbers and frequencies and were compared with the chi-square test, including Yates' correction for continuity. Logistic-regression analysis was used to calculate odds ratios for the primary outcome in prespecified subgroups. Cox regression analysis was used to assess the components of the primary composite outcome to address competing risks (e.g., death). The proportional-hazard assumption was assessed with Schoenfeld residuals. All analyses were performed according

bles S7 and S8 in the Supplementary Appendix), including 22 patients with prosthetic-valve endocarditis (12 patients in the intravenously treated group and 10 in the orally treated group). A total of 35 patients had an implanted cardiac device; 14 patients with pacemaker endocarditis had their pacemaker removed during the current endocarditis disease course (Table S9 in the Supplementary Appendix). There were no significant differences between the two groups regarding the frequency of involvement of the aortic valve, mitral valve, or combined aortic and mitral valve; regarding involvement of the native valve as compared with the prosthetic valve; or regarding the number of patients who underwent valve surgery before randomization (Table 1).

TIMING OF RANDOMIZATION AND LENGTH OF STAY IN THE HOSPITAL

The median time from the diagnosis of endocarditis of the left side of the heart to randomization was 17 days (interquartile range, 13 to 23) in the intravenously treated group and 17 days (interquartile range, 12 to 24) in the orally treated group. After randomization, patients were treated according to the assigned regimen for a median of 19 days (interquartile range, 14 to 25) in the intravenously treated group and 17 days (interquartile range, 14 to 25) in the orally treated group. In the orally treated group, 160 patients (80%) were partially or completely treated as outpatients. After randomization, the median length of stay in the hospital (not a prespecified outcome) was 19 days (interquartile range, 14 to 25) in the intravenously treated group and 3 days (interquartile range, 1 to 10) in the orally treated group (P<0.001).

ANTIBIOTIC TREATMENT

Antibiotic treatment regimens for the 201 patients in the orally treated group who had monomicrobial infections at randomization are listed in Table S10 in the Supplementary Appendix (MICs and breakpoints are provided in Fig. S1, and susceptibility to penicillin and methicillin in Table S11, in the Supplementary Appendix). Four patients crossed over from the orally treated group to the intravenously treated group (1 because of nausea, 1 because of a new incident of bacteremia with a different pathogen, and 2 because of patient preference). No patients crossed over from the intravenously treated group to the orally treated group. From the time of random-

Table 1. Characteristics of the Patients at Baseline.*		
Characteristic	Intravenous Treatment (N = 199)	Oral Treatment (N = 201)
Mean age — yr	67.3±12.0	67.6±12.6
Female sex — no. (%)	50 (25.1)	42 (20.9)
Body temperature — °C	36.9±0.45	37.0±0.44
Coexisting condition or risk factor — no. (%)		
Diabetes	36 (18.1)	31 (15.4)
Renal failure	25 (12.6)	21 (10.4)
Dialysis	13 (6.5)	15 (7.5)
COPD	17 (8.5)	9 (4.5)
Liver disease	7 (3.5)	6 (3.0)
Cancer	14 (7.0)	18 (9.0)
Intravenous drug use	3 (1.5)	2 (1.0)
Pathogen — no. (%)†		
Streptococcus	104 (52.3)	92 (45.8)
Enterococcus faecalis	46 (23.1)	51 (25.4)
Staphylococcus aureus‡	40 (20.1)	47 (23.4)
Coagulase-negative staphylococci	10 (5.0)	13 (6.5)
Laboratory results at randomization		
Hemoglobin — mmol/liter	6.3±1.1	6.5±1.0
Leukocytes — ×10⁻⁹/liter	7.6±3.6	7.2±2.6
C-reactive protein — mg/liter	24.3±18.4	19.9±16.7
Creatinine — μmol/liter	124±112	141±164
Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	53 (26.6)	54 (26.9)
Pacemaker	15 (7.5)	20 (10.0)
Other known valve disease	82 (41.2)	90 (44.8)
Cardiac involvement at randomization — no. (%)§		
Mitral-valve endocarditis	65 (32.7)	72 (35.8)
Aortic-valve endocarditis	109 (54.8)	109 (54.2)
Mitral-valve and aortic-valve endocarditis	23 (11.6)	20 (10.0)
Endocarditis in other locations§	2 (1.0)	0
Pacemaker endocarditis	6 (3.0)	8 (4.0)
Vegetation size >9 mm	7 (3.5)	11 (5.5)
Moderate or severe valve regurgitation	19 (9.5)	23 (11.4)
Valve surgery during current disease course	75 (37.7)	77 (38.3)

* Plus–minus values are means ±SD. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. There were no significant differences between the groups except for the C-reactive protein level, which was slightly higher in the intravenously treated group. COPD denotes chronic obstructive pulmonary disease.
† Patients could have had an infection with more than one pathogen.
‡ No patients had an infection with a methicillin-resistant strain of S. aureus.
§ One patient had an infected ventricular septal defect, and one patient had an infected myxoma in the left atrium.

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N=199)	Oral Treatment (N=201)	Difference	Hazard Ratio (95% CI)
	number (percent)		percentage points (95% CI)	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (–1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (–3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (–2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (–3.1 to 3.1)	0.97 (0.28 to 3.33)

* Six patients, three in each group, had two outcomes.
† For details about relapse of the positive blood culture, see the Supplementary Appendix.

ization until antibiotic therapy was completed, 43 patients (22%) in the intravenously treated group were switched to a different intravenous antibiotic regimen, and 24 (12%) in the orally treated group were switched to a different oral regimen (P<0.01).

PRIMARY OUTCOME

All enrolled patients were followed for 6 months after the antibiotic treatment was completed or until death. No patients were lost to follow-up. The primary composite outcome occurred in a total of 42 patients (10.5%) — in 24 patients (12.1%) in the intravenously treated group and in 18 patients (9.0%) in the orally treated group (odds ratio, 0.72; 95% confidence interval [CI], 0.37 to 1.36). The between-group difference was 3.1 percentage points (95% CI, –3.4 to 9.6; P=0.40) in favor of oral treatment, and the criterion for noninferiority was therefore met. In the per-protocol analysis, the primary composite outcome occurred in 24 of 199 patients (12.1%) in the intravenously treated group and in 18 of 197 patients (9.1%) in the orally treated group (between-group difference, 3.0 percentage points; 95% CI, –3.2 to 9.2). In a sensitivity analysis in which the 4 patients who were switched from oral to intravenous therapy were considered to have had treatment failure, the criterion for noninferiority was still met. In this analysis, the primary outcome occurred in 24 of 199 patients in the intravenously treated group and in 22 of 201 patients in the orally treated group (between-group difference, 1.2 percentage points; 95% CI, –5.6 to 7.5).

The number of events for each component of the primary composite outcome is provided in Table 2 (with additional details in Table S12 in the Supplementary Appendix). The incidences of embolic episodes, unplanned cardiac surgery, and relapse of bacteremia with the primary pathogen were similar in the two groups. There were fewer deaths in the orally treated group than in the intravenously treated group. Cumulative incidence plots for the primary composite outcome and its four components are shown in Figure 2, and in Figure S2 in the Supplementary Appendix. A breakdown of the bacterial species for each component of the primary outcome is provided in Table S13 in the Supplementary Appendix.

The results of the prespecified subgroup analyses of the primary outcome are shown in Figure 3. Homogeneity was seen for all subgroups, and all interactions were nonsignificant.

SAFETY

In seven patients in the orally treated group, the plasma concentration of one of the two administered antibiotics was not at the most effective level, as assessed by peak levels and time above the MIC (rifampicin in the case of three patients, moxifloxacin in two patients, linezolid in one patient, and dicloxacillin in one patient) (Fig. S3 in the Supplementary Appendix). In all seven patients, the plasma concentration of the other simultaneously administered antibiotic was appropriate. The primary outcome did not occur in any of these patients. No antibiotic regimens were changed on the basis of pharmacokinetic findings.

Adverse effects from antibiotics were reported in 22 patients (6%) after randomization — in 12 patients (6%) in the intravenously treated group and in 10 (5%) in the orally treated group

(P=0.66). The most frequently reported adverse effects were allergy (50%), bone marrow suppression (27%), and gastrointestinal effects (14%), with no significant differences between groups (Table S14 in the Supplementary Appendix).

DISCUSSION

In patients with endocarditis on the left side of the heart caused by streptococcus, *E. faecalis*, *S. aureus*, or coagulase-negative staphylococci, who were in clinically stable condition and who had had an adequate response to initial treatment, a shift from initial intravenous to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. The patients in the orally treated group were shifted from intravenous to oral treatment on about day 17, the midpoint of the treatment period. Thus, during half the treatment period, the patients in the orally treated group were eligible for partial or complete outpatient treatment.

The results seemed consistent across prespecified subgroups, including the subgroups defined according to type of valve affected (native valve or prosthetic valve) and according to type of treatment (surgery during the disease course or conservative treatment). It should also be noted that the primary outcome seemed similar across the four different bacterial types. However, the trial was not powered to assess the primary outcome in any of the prespecified subgroups. The high rate of the primary outcome in patients with coagulase-negative staphylococci probably reflects diagnostic delays combined with the fact that it often occurred in older and more frail patients who had serious coexisting conditions.

The rationale for this trial was that in patients with normal gastrointestinal function, the uptake of orally administered antibiotics may allow sufficient plasma concentrations of antibiotics to achieve bacterial killing.[10] As part of the trial, oral regimens were developed, and specific combinations of oral antibiotics were chosen for each regimen (Table S2 in the Supplementary Appendix). The main concern related to the administration of oral antibiotics as compared with intravenous administration is whether the gastrointestinal uptake is sufficient. In this trial, only patients considered to have clinically normal gastrointestinal uptake were enrolled. The regimens that were developed for the trial in-
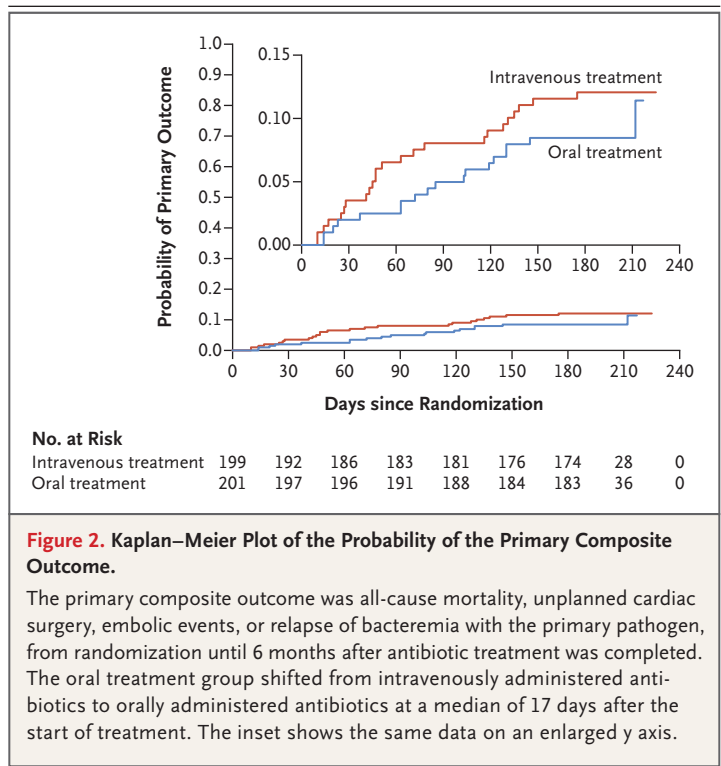
Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.

The primary composite outcome was all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from randomization until 6 months after antibiotic treatment was completed. The oral treatment group shifted from intravenously administered antibiotics to orally administered antibiotics at a median of 17 days after the start of treatment. The inset shows the same data on an enlarged y axis.

cluded antibiotics generally known to have moderate to high bioavailability, and the antibiotics were carefully selected for each patient (Table S10 in the Supplementary Appendix). To address the risk of subtherapeutic antibiotic levels related to potentially reduced gastrointestinal uptake, as well as the risk of variations in pharmacokinetics of the orally administered antibiotics, all oral regimens included two antibiotics from different drug classes and with different antibacterial effects and different metabolization processes. In addition, pharmacokinetic measurements were performed. It was not necessary to change antibiotic therapy in any of the patients on the basis of pharmacokinetic findings. Therefore, we do not consider pharmacokinetics to be a factor when offering oral antibiotic therapy if the currently applied randomization criteria are met and two antibiotics with good bioavailability are prescribed (both carefully selected on the basis of bacterial identification and antimicrobial susceptibility testing) and the patient's gastrointestinal uptake is considered to be normal.

Recommendations for the duration of antibiotic therapy and for in-hospital intravenous administration in patients with endocarditis are based mainly on observational studies.[25,26] Lon-
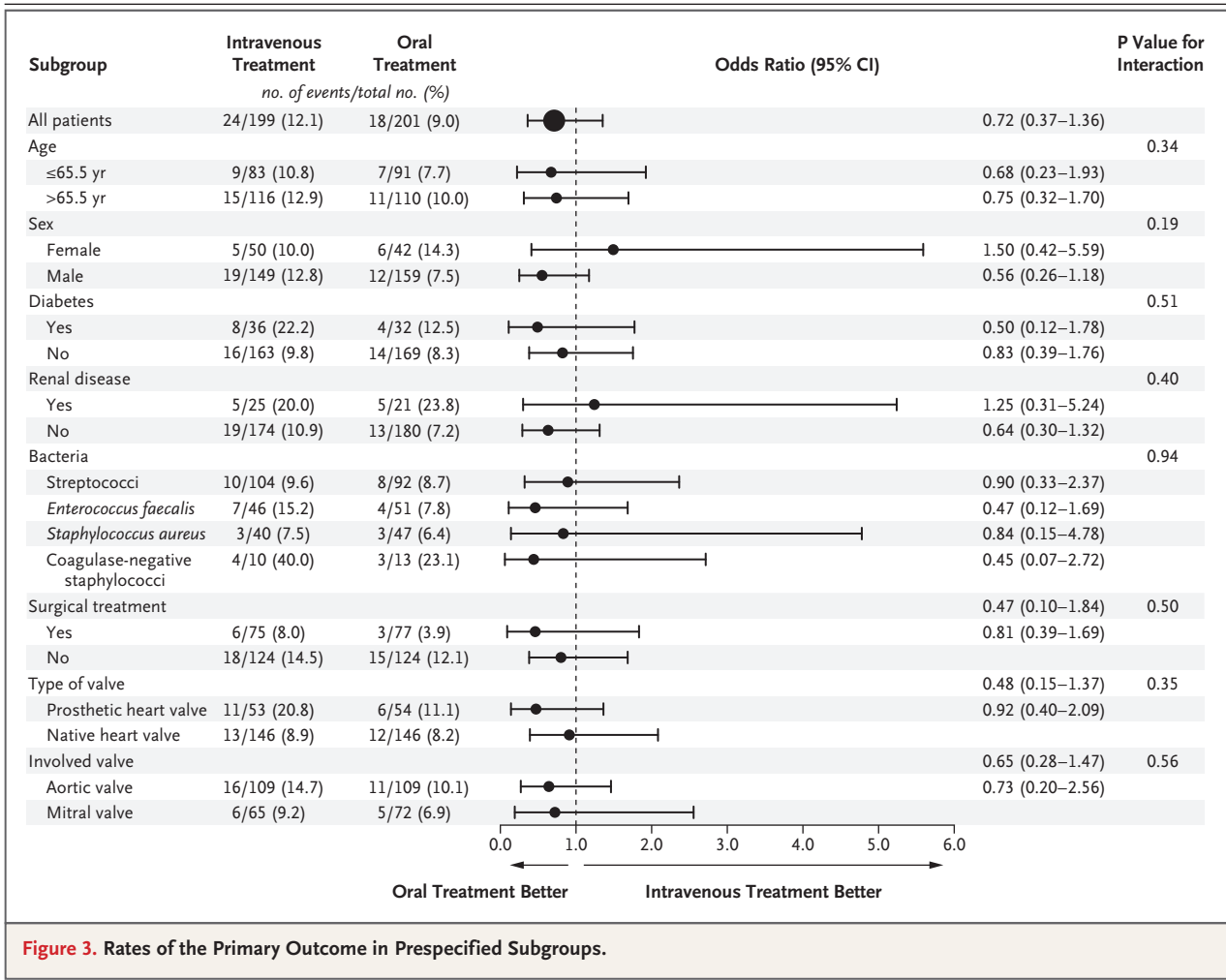
Subgroup	Intravenous Treatment	Oral Treatment	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All patients	24/199 (12.1)	18/201 (9.0)	0.72 (0.37–1.36)	
Age				0.34
≤65.5 yr	9/83 (10.8)	7/91 (7.7)	0.68 (0.23–1.93)	
>65.5 yr	15/116 (12.9)	11/110 (10.0)	0.75 (0.32–1.70)	
Sex				0.19
Female	5/50 (10.0)	6/42 (14.3)	1.50 (0.42–5.59)	
Male	19/149 (12.8)	12/159 (7.5)	0.56 (0.26–1.18)	
Diabetes				0.51
Yes	8/36 (22.2)	4/32 (12.5)	0.50 (0.12–1.78)	
No	16/163 (9.8)	14/169 (8.3)	0.83 (0.39–1.76)	
Renal disease				0.40
Yes	5/25 (20.0)	5/21 (23.8)	1.25 (0.31–5.24)	
No	19/174 (10.9)	13/180 (7.2)	0.64 (0.30–1.32)	
Bacteria				0.94
Streptococci	10/104 (9.6)	8/92 (8.7)	0.90 (0.33–2.37)	
Enterococcus faecalis	7/46 (15.2)	4/51 (7.8)	0.47 (0.12–1.69)	
Staphylococcus aureus	3/40 (7.5)	3/47 (6.4)	0.84 (0.15–4.78)	
Coagulase-negative staphylococci	4/10 (40.0)	3/13 (23.1)	0.45 (0.07–2.72)	
Surgical treatment			0.47 (0.10–1.84)	0.50
Yes	6/75 (8.0)	3/77 (3.9)	0.81 (0.39–1.69)	
No	18/124 (14.5)	15/124 (12.1)		
Type of valve			0.48 (0.15–1.37)	0.35
Prosthetic heart valve	11/53 (20.8)	6/54 (11.1)	0.92 (0.40–2.09)	
Native heart valve	13/146 (8.9)	12/146 (8.2)		
Involved valve			0.65 (0.28–1.47)	0.56
Aortic valve	16/109 (14.7)	11/109 (10.1)	0.73 (0.20–2.56)	
Mitral valve	6/65 (9.2)	5/72 (6.9)		

Oral Treatment Better ← | → Intravenous Treatment Better

Figure 3. Rates of the Primary Outcome in Prespecified Subgroups.

ger hospital stays may be a psychological and a physical burden,[27-30] whereas shortened stays have been associated with better outcomes in studies of other diseases[9-11] and may reduce costs. Oral antibiotic therapy may also minimize the challenges associated with outpatient parenteral treatment,[1,2,12,13] including logistics, monitoring, and risks of complications associated with intravenous catheters (e.g., bleeding, local and systemic infections, and venous thrombosis).

Several observational studies[16-18] and a systematic review by Al-Omari et al.[14] have addressed the safety and efficacy of a shift from intravenous to oral therapy in the treatment of endocarditis. Generally, it has been shown that partial oral treatment has an acceptable cure rate in selected cases of endocarditis on the right side of the heart, whereas the literature on oral treatment for endocarditis on the left side of the heart is

sparse. In a small study involving patients with endocarditis on the left side of the heart (12 patients with a median age of 66 years, of whom 75% were men), we reported that a shift to oral therapy was efficient and safe.[17]

Our trial has several limitations. Only patients with endocarditis on the left side of the heart were enrolled; however, it should be noted that patients with simultaneous infection of a cardiovascular implantable electronic device or endocarditis on the right side of the heart were not excluded. Only patients with endocarditis caused by certain bacterial species were eligible, and the results may not apply to the remaining 25 to 30% of patients who have endocarditis caused by other bacteria or to patients with culture-negative endocarditis. In addition, only five intravenous drug users were enrolled, only 22% of the enrolled patients had *S. aureus*, and, although it was not a

criterion for exclusion, no patients with methi-cillin-resistant *S. aureus* or other antibiotic-resistant phenotypes were enrolled. Referral bias may have affected our findings, because some patients — most likely elderly patients who are fragile and have serious coexisting conditions — may not have been referred to one of the participating centers. The criteria for inclusion in the trial were strict, and clinicians should use these criteria in the decision to shift a patient from intravenous to oral therapy (see Fig. S4 in the Supplementary Appendix). In geographic areas with higher rates of antibiotic resistance, these criteria would also be applicable, since they are based on antibiotic treatment guided by state-of-the-art susceptibility testing. However, the smaller number of effective antibiotics that can be used in areas with a higher degree of antibacterial resistance may represent a limitation.

An additional limitation is that the discharge of patients who were receiving oral treatment to outpatient treatment was not mandatory and was decided according to the patient's preference and the discretion of the treating physician.

Therefore, the duration of outpatient treatment may have been underestimated. Only 20% of the screened population underwent randomization. Considering the reasons for exclusion (Fig. 1), it seems likely that a larger fraction of patients with endocarditis on the left side of the heart may be candidates for partial oral therapy.

In conclusion, in patients who had endocarditis on the left side of the heart caused by streptococcus, *E. faecalis*, *S. aureus*, or coagulase-negative staphylococci and who were in stable condition, a shift from intravenously administered to orally administered antibiotic treatment was noninferior to continued intravenous antibiotic treatment.

APPENDIX

The authors' affiliations are as follows: the Department of Cardiology, Herlev-Gentofte University Hospital (K.I., M.S., C.F.K.), Department of Cardiology, the Heart Center, Rigshospitalet, Copenhagen University Hospital (N.I., D.E.H., E.L.F., L.K., H.B.), the Departments of Infectious Diseases (J.H.-L.) and Clinical Microbiology (C.M.), Rigshospitalet, the Department of Cardiology, Hillerød Hospital (N.T.), and the Department of Clinical Microbiology, Slagelse Hospital and Institute of Clinical Medicine (J.J.C.), University of Copenhagen, Copenhagen, the Departments of Cardiology (S.U.G.) and Clinical Microbiology (F.R.), Odense University Hospital, Odense, the Departments of Cardiology (T.M.) and Cardiology and Epidemiology and Biostatistics (C.T.-P.), Aalborg University Hospital, the Department of Clinical Microbiology, Aalborg University Hospital, Aalborg University (H.C.S.), and the Department of Health Science and Technology, Aalborg University (C.T.-P.), Aalborg, the Department of Cardiology, Zealand University Hospital, Roskilde (H.E.), the Department of Cardiology, Aarhus University Hospital, Aarhus (K.T.J.), the Department of Cardiology, University Hospital of Copenhagen, Gentofte (N.E.B.), and the Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Copenhagen (K.F.) — all in Denmark.

REFERENCES

1. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-86.
2. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.
3. Delahaye F, Alla F, Béguinot I, et al. In-hospital mortality of infective endocar-

ditis: prognostic factors and evolution over an 8-year period. Scand J Infect Dis 2007;39:849-57.
4. Mistiaen WP. What are the main predictors of in-hospital mortality in patients with infective endocarditis: a review. Scand Cardiovasc J 2018;52:58-68.
5. Sy RW, Kritharides L. Health care exposure and age in infective endocarditis: results of a contemporary population-based profile of 1536 patients in Australia. Eur Heart J 2010;31:1890-7.
6. Dickerman SA, Abrutyn E, Barsic B, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J 2007; 154:1086-94.

7. Martín-Dávila P, Navas E, Fortún J, et al. Analysis of mortality and risk factors associated with native valve endocarditis in drug users: the importance of vegetation size. Am Heart J 2005;150:1099-106.
8. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463-73.
9. Kehlet H. Fast-track colorectal surgery. Lancet 2008;371:791-3.
10. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg 2007;245:867-72.

11. Wind J, Polle SW, Fung Kon Jin PH, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg 2006;93:800-9.

12. Andrews MM, von Reyn CF. Patient selection criteria and management guidelines for outpatient parenteral antibiotic therapy for native valve infective endocarditis. Clin Infect Dis 2001;33:203-9.

13. Lacroix A, Revest M, Patrat-Delon S, et al. Outpatient parenteral antimicrobial therapy for infective endocarditis: a cost-effective strategy. Med Mal Infect 2014; 44:327-30.

14. Al-Omari A, Cameron DW, Lee C, Corrales-Medina VF. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. BMC Infect Dis 2014;14:140.

15. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med 1996;101:68-76.

16. Dworkin RJ, Lee BL, Sande MA, Chambers HF. Treatment of right-sided Staphylococcus aureus endocarditis in intravenous drug users with ciprofloxacin and rifampicin. Lancet 1989;2:1071-3.

17. Iversen K, Høst N, Bruun NE, et al. Partial oral treatment of endocarditis. Am Heart J 2013;165:116-22.

18. Mzabi A, Kernéis S, Richaud C, Podglajen I, Fernandez-Gerlinger MP, Mainardi JL. Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non-severely ill patients. Clin Microbiol Infect 2016;22:607-12.

19. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.

20. Infectious endocarditis. Danish guidelines. 2017. (In Danish) (http://www.nbv .cardio.dk/endocarditis).

21. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) home page. 2017 (http://eucast.org).

22. Gerds TA. Prodlim: product-limit estimation for censored event history analysis. 2017 (https://rdrr.io/cran/prodlim/).

23. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2017.

24. Viechtbauer W. Conducting meta-analysis in R with the metafor package. J Stat Softw 2010;36(3):1-48.

25. Thomas DJ. The present status of penicillin therapy in the treatment of subacute bacterial endocarditis. Med J Aust 1949;1:377-9.

26. Bloomfield AL. The present status of treatment of subacute bacterial endocarditis. Circulation 1950;2:801-10.

27. Berg SK, Preisler P, Pedersen BD. Patients perspective on endocarditis — an intermezzo in life. Eur J Cardiovasc Nurs 2010;9:126-31.

28. Verhagen DW, Hermanides J, Korevaar JC, et al. Health-related quality of life and posttraumatic stress disorder among survivors of left-sided native valve endocarditis. Clin Infect Dis 2009;48:1559-65.

29. de Saint-Hubert M, Schoevaerdts D, Poulain G, Cornette P, Swine C. Risk factors predicting later functional decline in older hospitalized patients. Acta Clin Belg 2009;64:187-94.

30. Isaia G, Maero B, Gatti A, et al. Risk factors of functional decline during hospitalization in the oldest old. Aging Clin Exp Res 2009;21:453-7.

Copyright © 2018 Massachusetts Medical Society.

TRACK THIS ARTICLE'S IMPACT AND REACH

Visit the article page at NEJM.org and click on Metrics for a dashboard
that logs views, citations, media references, and commentary.
www.nejm.org/about-nejm/article-metrics.