ORIGINAL ARTICLE

Response-Tailored or Standard-Duration Antibiotic Treatment for Infective Endocarditis

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ABSTRACT

BACKGROUND

In patients with infective endocarditis on the left side of the heart, the current recommendation of up to 6 weeks of antibiotic therapy is based largely on expert consensus opinion. Whether a clinical response–tailored antibiotic management strategy can shorten treatment duration without compromising safety is unclear.

METHODS

In this international, open-label, randomized trial, we assigned adults in stable condition with infective endocarditis caused by *Staphylococcus aureus*, *Enterococcus faecalis*, or streptococcus species to receive either response-tailored or standard-duration antibiotic therapy. Before randomization, all the patients received at least the prespecified 2 to 4 weeks of therapy and met criteria for clinical stabilization. After randomization, patients in the tailored-therapy group discontinued antibiotics and those in the standard-therapy group continued standard treatment (total duration, 4 to 6 weeks). The primary efficacy end point was days alive without antibiotic treatment for infective endocarditis or bacteremia within 6 months after randomization (tested for superiority). The primary safety end point was a composite of death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization (tested for noninferiority; margin, 7.5 percentage points). Relapse of bacteremia or infective endocarditis was a key secondary end point.

RESULTS

A total of 508 patients underwent randomization, with 255 assigned to response-tailored therapy and 253 to standard-duration therapy. The median time alive without antibiotic treatment was 183 days (interquartile range, 181 to 183) with tailored therapy and 169 days (interquartile range, 166 to 171) with standard therapy (Hodges–Lehmann estimated difference, 13 days; 95% confidence interval [CI], 12 to 13; P<0.001 for superiority). A primary safety end-point event occurred in 21 patients (8.2%) with tailored therapy and in 27 patients (10.7%) with standard therapy (absolute between-group difference, –2.4 percentage points; 95% CI, –7.7 to 2.7; P<0.001 for noninferiority), indicating noninferiority. Relapse occurred in 13 patients (5.1%) with tailored therapy and in 4 patients (1.6%) with standard therapy (P=0.04).

CONCLUSIONS

Among patients with infective endocarditis on the left side of the heart, the use of a response-tailored antibiotic strategy resulted in a longer time alive without antibiotic therapy than standard-duration therapy and met the criterion for noninferiority with respect to safety but was associated with a higher incidence of relapse of bacteremia or infective endocarditis. (Funded by Sygeforsikringen "danmark" and others; POET II ClinicalTrials.gov number, NCT03851575.)

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This article was published on August 28, 2026, at NEJM.org.

DOI: 10.1056/NEJMoa2607887

The management of infective endocarditis usually includes high-dose antibiotic treatment for up to 6 weeks.[1,2] Current recommendations regarding the duration of antibiotic therapy are largely based on expert opinion and historical observations rather than randomized trials.[3] For several infectious diseases, shorter antibiotic regimens have been shown to be effective,[4-6] with several advantages over longer regimens, including fewer side effects, fewer health care–associated infections, a lower risk of antimicrobial resistance, decreased costs, and improved patient recovery and mental health.[7] In principle, the optimal duration of antibiotic therapy is the time it takes for complete eradication of the causative pathogen, but for patients with infective endocarditis, no single marker reliably indicates when bacterial clearance has been achieved. In the Partial Oral Treatment of Endocarditis (POET) trial, which involved patients with infective endocarditis on the left side of the heart, a combination of clinical, biochemical, and imaging criteria ("POET criteria" [based on the clinical stabilization criteria that were required to be met before randomization in the trial]) was used to determine the timing of the shift from intravenous to oral step-down therapy.[8] The switch to oral step-down antibiotic therapy resulted in 16 fewer days of intravenous antibiotic treatment than usual care, was shown to be noninferior to usual care after 6 months, and was associated with improved survival after 5 years of follow-up.[8,9] On the basis of these results, we hypothesized that response-tailored treatment based on the POET criteria for clinical stabilization would result in 2 to 3 fewer weeks of intravenous or oral step-down antibiotic treatment than the standard duration of therapy in patients with infective endocarditis without compromising safety.

Methods

Trial Design and Oversight

The Tailored versus Standard-Duration Antibiotic Treatment for Endocarditis (POET II) trial was a prospective, investigator-initiated, international, open-label, randomized, controlled, superiority trial. The trial design has been published previously,[7] and the trial protocol is available (along with the statistical analysis plan) with the full text of this article at NEJM.org. Trial end points, including relapses, were adjudicated by an independent committee whose members were unaware of the treatment assignments. Additional details are provided in the Supplementary Appendix, available at NEJM.org. An independent data and safety monitoring board oversaw the trial. Data analyses were performed by the investigators. The trial was approved by the ethics committee in each participating country. All the patients provided written informed consent. Additional information regarding the design and oversight of the trial and the responsibilities of the authors is provided in the Supplementary Appendix.

Patients

Adults 18 years of age or older were eligible for enrollment in the trial if they had infective endocarditis of native or prosthetic valves on the left side of the heart, according to modified Duke criteria,[10,11] that was caused by *Staphylococcus aureus*, *Enterococcus faecalis*, or streptococcus species. Patients with previous infective endocarditis that had been caused by the same microorganism within 6 months before randomization and patients with known or presumed immunodeficiency were not eligible.[7] A full list of the inclusion and exclusion criteria is provided in the protocol.

Randomization and Treatment

Patients were randomly assigned in a 1:1 ratio to receive antibiotic therapy according to a response-tailored strategy involving a shortened course of therapy (tailored-therapy group) or in a standard-duration regimen (standard-therapy group). Before randomization, all the patients received antibiotic therapy for at least the prespecified minimum duration of 2 to 4 weeks and met the POET criteria for clinical stabilization. Immediately after randomization, patients in the tailored-therapy group discontinued antibiotic therapy, whereas those in the standard-therapy group continued standard treatment until completion of the applicable total treatment duration of 4 to 6 weeks. The criteria for categorization of infective endocarditis as complicated endocarditis and the prespecified minimum duration of antibiotic therapy were defined for each of the three bacterial species (Tables S1 and S2 in the Supplementary Appendix). Otherwise, antibiotic treatment regimens followed established guidelines

from the European Society of Cardiology,[1,12] and oral step-down therapy[1,8] was allowed; further details are provided in the Supplementary Appendix. Patients could be discharged to an outpatient clinic before or after randomization, according to usual practice. Patients who had been discharged while receiving oral step-down antibiotic treatment were followed at least twice weekly.

After discontinuation of antibiotic treatment, follow-up visits occurred after 1, 2, 4, 6, 8, and 10 weeks and after 3 and 6 months. Randomization was performed with Research Electronic Data Capture (REDCap) software, version 8.10.18. The randomization sequence was generated with the RStudio blockrand package, version 1.2, with randomly varying block sizes of one, two, or three patients per block.[13]

END POINTS

The primary efficacy end point was the number of days alive without antibiotic treatment for infective endocarditis or bacteremia within 6 months after randomization. The primary safety end point was a composite of death from any cause, unplanned cardiac surgery, or symptomatic embolic events as confirmed by imaging within 6 months after randomization. Key secondary end points were the individual components of the primary safety end point and relapse of bacteremia or infective endocarditis with the primary pathogen.

STATISTICAL ANALYSIS

The trial was designed as a superiority trial for the primary efficacy end point and as a noninferiority trial for the primary safety end point. After a prespecified interim analysis of recruitment and overall incidence of events was performed, the primary end point was changed, as described in the Supplementary Appendix. We determined that a sample of 475 patients would provide the trial with at least 99% power, at a two-sided alpha level of 0.05, to detect a between-group difference in the median duration of antibiotic treatment of 7 days. For the primary safety end point, we estimated an incidence of 8%.[8] A risk difference (i.e., a noninferiority margin) of 7.5 percentage points was chosen, and we calculated that inclusion of 450 patients would be needed to provide the trial with 90% power to confirm noninferiority, with a one-sided confidence interval of 97.5%. For each of the three bacterial pathogens, we aimed to include at least 118 patients to provide the trial with 80% power to show noninferiority with a noninferiority margin of 12.5% and a one-sided confidence interval of 97.5%. Any missing data are reported in the relevant tables and figures.

All the analyses were performed according to the intention-to-treat principle. Continuous variables are presented as means and standard deviations or as medians and interquartile ranges, as appropriate. Baseline categorical variables are presented as counts and percentages. Treatment groups were compared with Student's t-test or the Mann–Whitney test for continuous variables after visual inspection of normality. For the Mann–Whitney test, we also used the Hodges–Lehmann location shift to obtain 95% confidence intervals. Categorical variables were compared with the chi-square test and Yates' correction for continuity. Kaplan–Meier estimates were used to describe the probability of a primary safety endpoint event over time.

The difference between the groups with respect to the primary efficacy end point was expressed as both a median difference and a mean difference, with 95% confidence intervals. The differences between the groups with respect to the primary safety end point and relapse of bacteremia or infective endocarditis with the primary pathogen were calculated with the Newcombe method. Logistic-regression analysis was used to calculate odds ratios for the primary end point in prespecified subgroups. For other end points, the widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer treatment effects.

Cox regression analyses were used to assess each component of the composite primary safety end point and accounted for death as a competing risk. The proportional-hazards assumption was assessed with Schoenfeld residuals. A per-protocol analysis of the primary efficacy end point was performed; patients who crossed over from tailored therapy to standard therapy were excluded. Two sensitivity analyses were performed: in one analysis, relapse of bacteremia or infective endocarditis with the primary pathogen was added to the primary safety end point, and in the other analysis, patients who had received treatment for concomitant extracardiac infections were excluded. Cumulative incidences were calculated

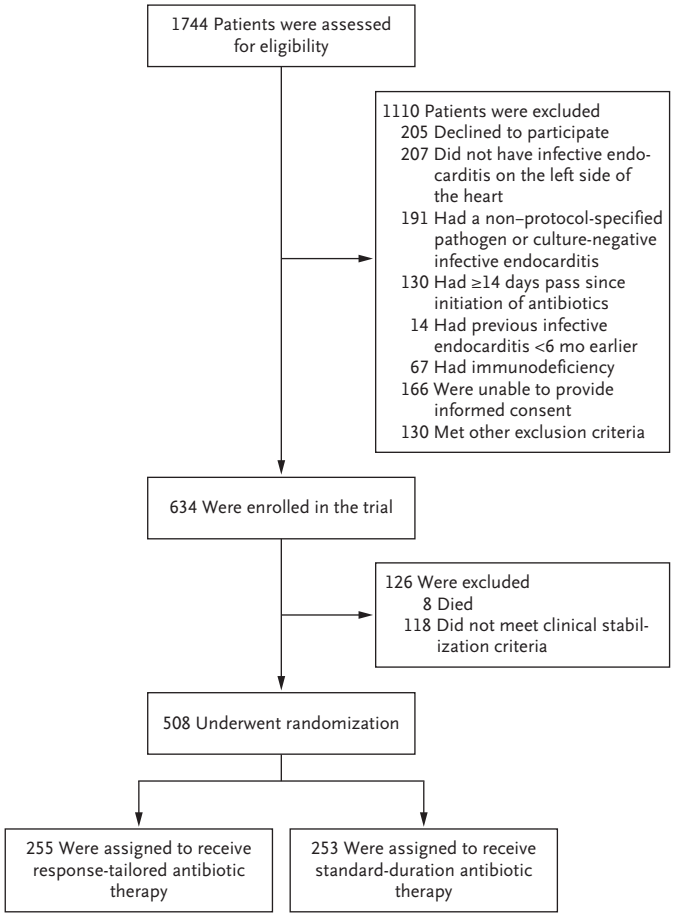

Figure 1. Eligibility, Enrollment, and Randomization.

Patients were randomly assigned to receive a shortened course of antibiotic therapy (for a minimum of 2 to 4 weeks) according to a response-tailored strategy or to receive a standard course of antibiotic therapy.

for events with competing risk for the end points of unplanned cardiac surgery and symptomatic embolic events. P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed with R software, version 3.6.1 (R Foundation for Statistical Computing).[13]

RESULTS

PATIENTS

From February 2019 through October 2025, a total of 1744 patients with suspected infective endocarditis were screened for inclusion at 13 sites in Denmark, Sweden, and the United States. Of these patients, 634 (36.4%) had confirmed infective endocarditis on the left side of the heart and were enrolled consecutively. The most common reasons for exclusion were unwillingness or inability to provide informed consent (33.4%), unconfirmed diagnosis (18.6%), and infective endocarditis with a bacterial pathogen that was not specified in the inclusion criteria (17.2%); 126 patients (19.9%) who had been enrolled either died or did not meet the stabilization criteria before completion of standard antibiotic treatment. Therefore, 508 patients (80.1%) underwent randomization. A total of 255 patients were randomly assigned to receive a shortened course of antibiotic therapy according to a tailored strategy and 253 patients to receive a standard course of antibiotic therapy (Fig. 1 and Fig. S1). No patients were lost to follow-up for the primary efficacy or primary safety end points.

The mean age of the patients was 70 years, and 75.4% were men (Table 1). The aortic valve was affected in 321 patients (63.2%), and 134 patients (26.4%) had prosthetic-valve infective endocarditis (Table S4). Before randomization, 168 patients (33.1%) had undergone cardiac surgery, including 40 patients (23.8%) with prosthetic-valve infective endocarditis (Table S5). The most common type of bacterial pathogen was streptococcus species (in 291 patients [57.3%]), followed by *S. aureus* (in 123 patients [24.2%]) and *E. faecalis* (in 94 patients [18.5%]). Overall, the characteristics of the patients at baseline appeared to be balanced between the two groups (Table 1). A total of 119 patients (23.4%) had complicated endocarditis, and 319 patients (62.8%) received oral step-down antibiotic treatment (Tables S6 and S7).

PRIMARY EFFICACY END POINT

The median time from initiation of appropriate antibiotic treatment to randomization was 24 days (interquartile range, 17 to 30) in the tailored-therapy group and 23 days (interquartile range, 15 to 29) in the standard-therapy group (Table 1). From randomization through the end of follow-up (at 6 months), the median number of days alive without antibiotic therapy for infective endocarditis or bacteremia within 6 months after randomization (the primary efficacy end point) was 183 (interquartile range, 181 to 183) in the tailored-therapy group, as compared with 169 (interquartile range, 166 to 171) in the standard-therapy group (Hodges–Lehmann esti-

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Response-Tailored Therapy (N=255)	Standard-Duration Therapy (N=253)
Age — yr	68.9±13.7	70.2±13.2
Male sex — no. (%)	193 (75.7)	190 (75.1)
Median duration of antibiotic treatment at randomization (IQR) — days	24 (17–30)	23 (15–29)
Coexisting condition or risk factor — no. (%)		
Diabetes	37 (14.5)	53 (20.9)
Renal failure†	28 (11.0)	31 (12.3)
Dialysis	6 (2.4)	8 (3.2)
Chronic obstructive pulmonary disease	20 (7.8)	24 (9.5)
Liver disease	11 (4.3)	8 (3.2)
Active cancer	17 (6.7)	16 (6.3)
Intravenous substance use disorder	5 (2.0)	0
Bacterial pathogen — no. (%)		
Staphylococcus aureus	61 (23.9)	62 (24.5)
Enterococcus faecalis	52 (20.4)	42 (16.6)
Streptococcus species	142 (55.7)	149 (58.9)
Median laboratory value at randomization (IQR)‡		
Hemoglobin — mmol/liter	6.7 (6.0–7.5)	6.8 (6.1–7.7)
Leukocyte count — $\times 10^{-9}$/liter	6.6 (5.2–7.8)	6.6 (5.6–7.8)
C-reactive protein — mg/liter	14.0 (5.1–26.0)	13.0 (4.3–26.0)
Procalcitonin — μg/liter	0.10 (0.06–0.12)	0.10 (0.06–0.11)
Creatinine — μmol/liter	77.0 (64.0–102.5)	83.0 (66.5–110.0)
Body temperature at randomization — °C	36.8±0.4	36.7±0.4
Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	68 (26.7)	66 (26.1)
Pacemaker or implantable cardioverter–defibrillator	18 (7.1)	20 (7.9)
Congenital heart disease	15 (5.9)	13 (5.1)
Cardiac involvement — no. (%)		
Mitral-valve infective endocarditis	127 (49.8)	116 (45.8)
Aortic-valve infective endocarditis	160 (62.7)	161 (63.6)
Vegetation size >9 mm	17 (6.7)	18 (7.1)
Moderate-to-severe valve insufficiency	47 (18.4)	49 (19.4)
Valve surgery during current disease course	84 (32.9)	84 (33.2)

* Plus–minus values are means ±SD. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. IQR denotes interquartile range.

† Chronic kidney disease had been diagnosed previously or was diagnosed during the current disease course by the treating physician.

‡ Laboratory results were missing for 11 patients in the tailored-therapy group and for 12 patients in the standard-therapy group overall. Data were missing for hemoglobin for 2 patients in the tailored-therapy group and for 6 patients in the standard-therapy group; for procalcitonin for 9 and 10 patients, respectively; and for C-reactive protein, leukocyte count, and creatinine for 1 patient in the tailored-therapy group and for 5 patients in the standard-therapy group. Medians were calculated on the basis of patients with available data.

Table 2. Efficacy and Safety End Points and Relapse.

End Point	Response-Tailored Therapy (N=255)	Standard-Duration Therapy (N=253)	Hodges–Lehmann Estimate of Difference or Absolute Difference (95% CI)*	Mean Difference or Hazard Ratio (95% CI)†
Primary efficacy end point				
Median no. of days alive without antibiotic therapy for infective endocarditis or bacteremia within 6 months after randomization (IQR)	183 (181 to 183)	169 (166 to 171)	13 (12 to 13)	9.7 (5.2 to 14.2)
Safety end points				
Primary safety end point				
Death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization — no. (%)	21 (8.2)	27 (10.7)	–2.4 (–7.7 to 2.7)	0.77 (0.43 to 1.36)
Other safety end points				
Death from any cause — no. (%)	13 (5.1)	11 (4.3)	0.8 (–3.1 to 4.7)	1.18 (0.53 to 2.63)
Unplanned cardiac surgery — no. (%)	5 (2.0)	10 (4.0)	–2.0 (–5.4 to 1.1)	0.49 (0.17 to 1.45)
Symptomatic embolic events — no. (%)	6 (2.4)	8 (3.2)	–0.8 (–4.1 to 2.3)	0.75 (0.26 to 2.15)
Other key end point				
Relapse of bacteremia or infective endocarditis with primary pathogen — no. (%)	13 (5.1)	4 (1.6)	3.5 (0.4 to 7.1)	3.29 (1.07 to 10.11)

* The Hodges–Lehmann estimate of the difference between the groups is provided for the primary efficacy end point. The absolute differences between the percentages in the two groups are provided for all the other end points and are shown in percentage points. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer a treatment effect.

† The mean difference between the groups is provided for the primary efficacy end point. Hazard ratios are provided for all the other end points. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer a treatment effect.

mate of the between-group difference, 13 days; 95% confidence interval [CI], 12 to 13; P<0.001 for superiority) (Table 2 and Fig. 2A). The median total duration of antibiotic therapy was 26 days (interquartile range, 18 to 30) in the tailored-therapy group and 41 days (interquartile range, 28 to 42) in the standard-therapy group (Hodges–Lehmann estimate of the between-group difference, –13 days; 95% CI, –14 to –11), which corresponded to an absolute difference in the median duration of treatment of 15 days and a relative difference of 36.6% (Table S8).

SAFETY END POINTS

Death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization (the primary safety end point) occurred in 21 patients (8.2%) in the tailored-therapy group and in 27 patients (10.7%) in the standard-therapy group, with an absolute between-group difference of –2.4 percentage points (95% CI, –7.7 to 2.7; P<0.001 for noninferiority) in favor of tailored therapy, which met the criterion for noninferiority (Table 2 and Fig. 2B). The results for the individual components of the primary safety end point are shown in Figure S2. The incidence of death, unplanned cardiac surgery, and symptomatic embolic events and of serious adverse events and overall adverse events appeared to be similar in the two groups (Tables S9 and S10).

BACTERIAL PATHOGENS

The difference between the groups in the incidence of a primary safety end-point event was 3.6 percentage points (95% CI, –10.9 to 3.5) among patients with streptococcal infection and 6.4 percentage points (95% CI, –17.4 to 3.8) among those with *S. aureus* infection, with both results favoring the tailored treatment strategy (Table S11). Among patients with *E. faecalis* infection, the difference was 6.8 percentage points (95% CI, –5.8 to 19.1) in favor of standard-duration therapy. The cumulative incidence of a primary safety end-point event for each bacterial type is provided in Figure S3.

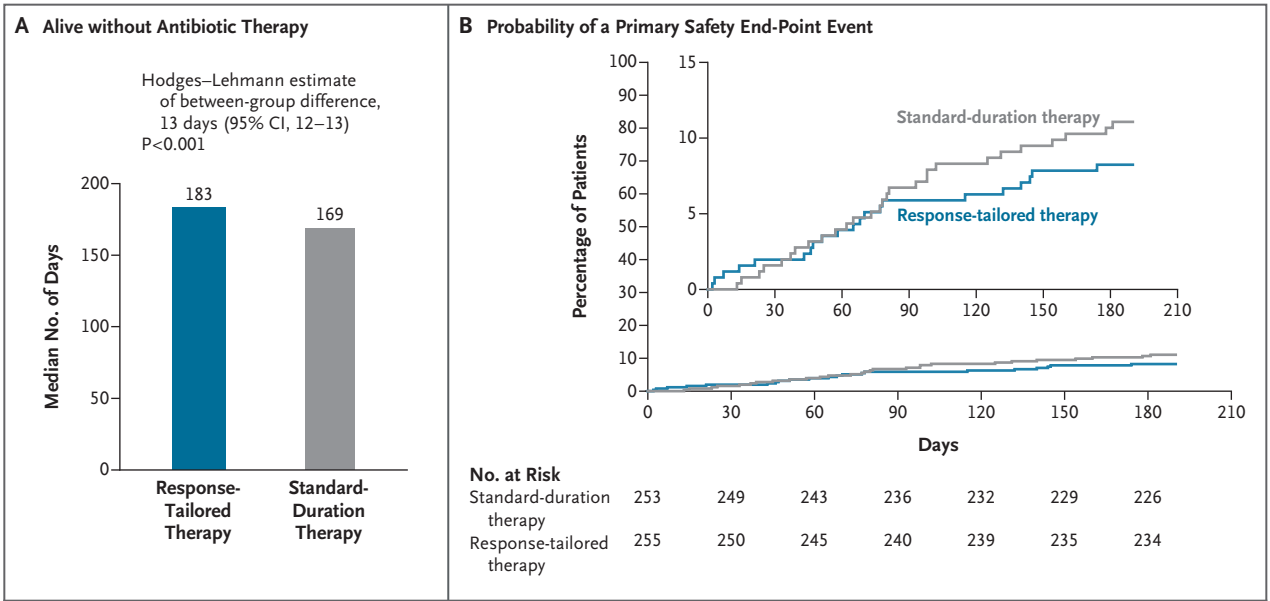

Figure 2. Primary Efficacy and Safety End Points.

Panel A shows the median number of days alive without antibiotic therapy for infective endocarditis or bacteremia within 6 months after randomization (the primary efficacy end point) among patients in the tailored-therapy and standard-therapy groups. Panel B shows the Kaplan–Meier estimates of the probability of a composite of death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization (the primary safety end point). The inset shows the same data on an enlarged y axis.

RELAPSE

Relapse of bacteremia or infective endocarditis with the primary pathogen occurred in 17 of 508 patients (3.3%), including 13 (5.1%) in the tailored-therapy group and 4 (1.6%) in the standard-therapy group (P=0.04) (Table 2 and Fig. S4). The median time to relapse was 28 days (interquartile range, 9 to 92) among patients in the tailored-therapy group and 74 days (interquartile range, 54 to 103) among those in the standard-therapy group. Across both groups, most of the patients with relapse had native-valve infection (11 of 17 patients [64.7%]) and did not undergo surgery (16 of 17 patients [94.1%]); 6 of 134 patients with prosthetic-valve infective endocarditis (4.5%) had relapse, and 1 patient had surgery. Relapse occurred in 6 of 94 patients (6.4%) with infective endocarditis caused by *E. faecalis*, in 4 of 123 patients (3.3%) with infective endocarditis caused by *S. aureus*, and in 7 of 291 patients (2.4%) with infective endocarditis caused by streptococcus species (Table S12).

The sensitivity analyses — one in which relapse was added to the primary safety end point and the other in which patients who had received treatment for concomitant extracardiac infections were excluded — and the per-protocol analysis (in which 2 patients who had crossed over to standard treatment were excluded) yielded findings that were consistent with those of the primary analyses (Tables S13 through S18 and Figs. S5 and S6). The results of the prespecified subgroup analyses of the primary safety end point are shown in Figure 3.

DISCUSSION

In this randomized trial involving patients with infective endocarditis on the left side of the heart that was caused by *S. aureus*, *E. faecalis*, or streptococcus species, the use of a response-tailored strategy led to a duration of time alive without antibiotic therapy within 6 months after randomization that was 13 days longer than the duration with standard therapy. This result was achieved without an apparent higher incidence of death from any cause, unplanned cardiac surgery, or symptomatic embolic events within 6 months after randomization (the primary safety end point). The findings appeared to be consistent across prespecified subgroups, including those defined according to the type of valve in-

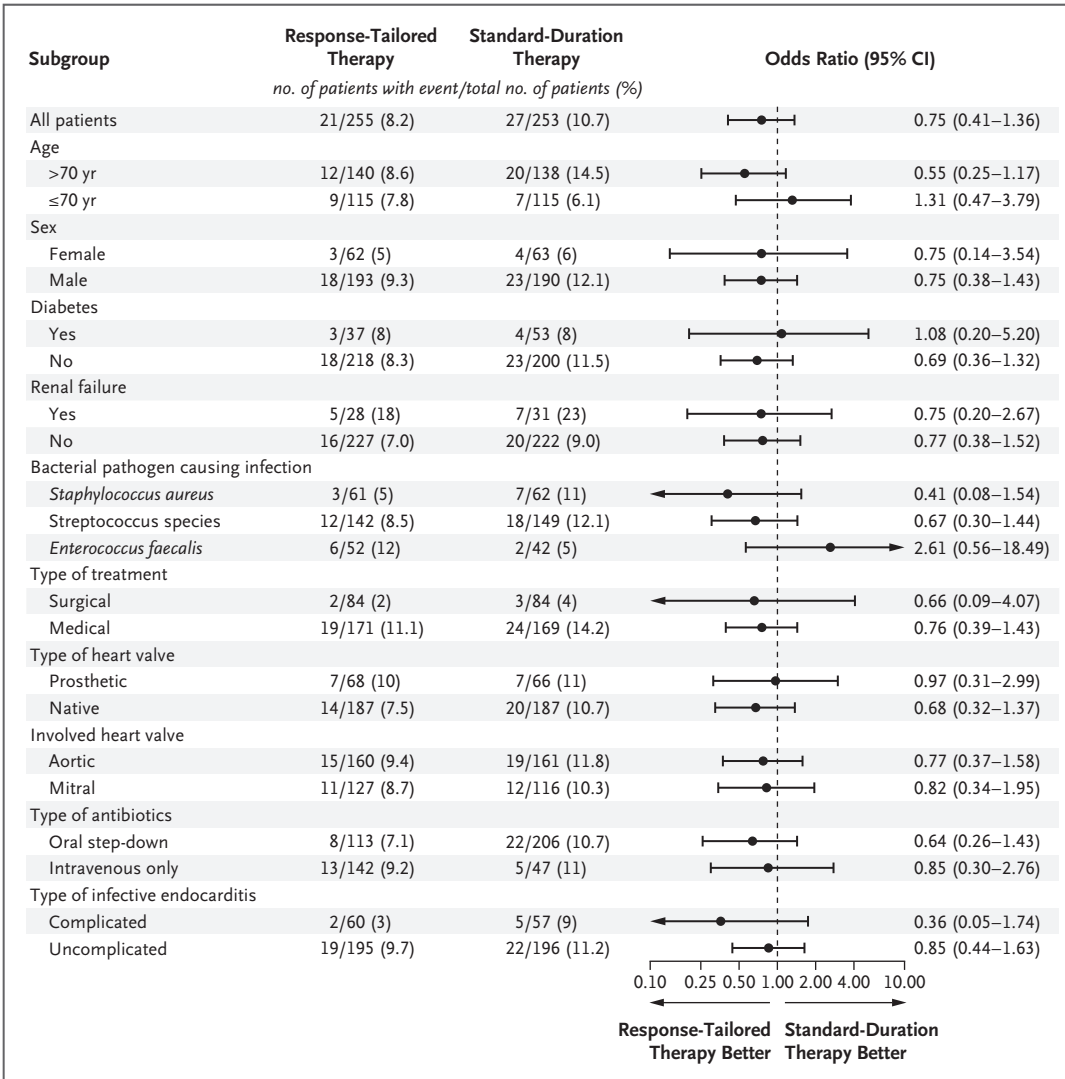

Figure 3. Primary Safety End Point in Prespecified Subgroups.

With respect to the presence of renal failure, chronic kidney disease had been diagnosed previously or was diagnosed during the current disease course by the treating physician. Patients could have had infective endocarditis that involved both the aortic valve and the mitral valve. Arrows on the confidence interval bars indicate that the upper or lower boundary of the confidence interval is off the scale. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.

volved in infective endocarditis (native or prosthetic), treatment (medical or surgical), and certain concurrent conditions. The shorter duration of antibiotic therapy, by 15 days, with response-tailored therapy corresponded to approximately one third of the duration of standard antibiotic treatment.

The main concern related to a shorter duration of antibiotic therapy is relapse of infection. The incidence of relapse of bacteremia or infective endocarditis with the primary pathogen was low but was found to be significantly higher in the tailored-therapy group than in the standard-therapy group. In both groups, relapses were associated with safety end points, but most relapses were assessed as uncomplicated and managed with reinitiation of antibiotic therapy. Of note, no overall difference in the primary safety end point was observed between the two groups. The 5.1% incidence of relapse with the primary

pathogen that was seen in the tailored-therapy group was within the range of relapse incidence of 2 to 9% that has been described in the literature[14-16] and in the European Society of Cardiology guidelines.[1]

Considering the potential benefits of a reduction in antibiotic exposure, an increase in the risk of relapse could be deemed acceptable if it is not associated with major clinical complications. In prespecified subgroup analyses of the primary safety end point according to bacterial pathogen, noninferiority criteria for response-tailored therapy were met for patients with infective endocarditis caused by streptococcus species or *S. aureus*. The incidences of the primary safety end-point events and relapse were highest among patients with infective endocarditis caused by *E. faecalis*. Among patients with relapse of enterococcal infection, a primary safety end-point event occurred in 2 of 6 patients. The results of the sensitivity analysis in which relapse was included in the primary safety end point were reassuring for patients with infective endocarditis caused by streptococcus species or *S. aureus*, but more events appeared to occur among patients with infective endocarditis caused by *E. faecalis* in the tailored-therapy group. The recruitment of patients with infective endocarditis due to *E. faecalis* was terminated before the planned sample size was reached, and the confidence intervals remained wide; no firm conclusions could be drawn for this subgroup.

The incidence of death observed in the tailored-therapy group in this trial (5.1%) was similar to the approximately 5% incidence reported in the POET trial,[8] which included a broadly similar patient population, but was lower than that seen in the phase 4 POETry study (12%).[17] The POETry study included patients who had infective endocarditis on the left side of the heart that was caused by the same types of bacterial pathogens that had caused infective endocarditis in the patients in our trial and who survived until the end of antibiotic treatment.

The patients included in our trial were not representative of an all-comer population of patients who had infective endocarditis but, rather, were representative of a population of patients who had infective endocarditis on the left side of the heart that was caused by one of the three most common pathogens and who survived the acute phase of disease and met the stabilization criteria. This subgroup of patients has previously been estimated to comprise approximately half of all patients with infective endocarditis.[8,17] The findings of the POET II trial are generalizable for this subgroup of patients with infective endocarditis (Tables S19 and S20).

The rationale for this trial builds on evidence from other types of bacterial infections, in which shorter antibiotic regimens have been found to be more effective and safe than the standard duration of treatment.[5,6,18] A shorter course of antibiotic therapy may reduce the risk of adverse drug effects, health care–associated complications, antimicrobial resistance, and costs and may improve quality of life by reducing the physical and psychological toll associated with prolonged antibiotic treatment and hospitalizations.[19-21] In this trial, the individualized treatment duration, which was based on the prespecified POET criteria (including clinical, biochemical, and imaging characteristics), extends the concept of response-guided antibiotic management.

Our trial has several limitations. Only patients with infective endocarditis caused by *S. aureus*, *E. faecalis*, or streptococcus species were included, so the findings may not be generalizable to infection with more rare pathogens. However, the pathogens included in our trial are responsible for approximately 70% of all infective endocarditis cases.[22-25] The trial included only patients with infective endocarditis on the left side of the heart; however, it should be noted that patients who had concurrent infective endocarditis on the right side of the heart or concurrent infection involving a cardiovascular implantable electronic device were not excluded. Only five patients (1.0%) had intravenous substance use disorder and most of the patients were enrolled in Denmark; because of these aspects of the trial population, the results may not be generalizable to other patient populations, geographic areas, or health care systems. In total, 36.4% of the screened population was enrolled, and 19.9% of these patients did not undergo randomization because they died or did not meet the stabilization criteria. Approximately half the patients with infective endocarditis on the left side of the heart that was caused by one of the three specified pathogens were excluded from the trial because they did not provide informed consent, which suggests that a large proportion of patients

with infective endocarditis may be eligible for tailored therapy.

Among patients with infective endocarditis on the left side of the heart that was caused by the pathogens commonly associated with the disease, the use of a response-tailored strategy that allowed early discontinuation of antibiotic therapy resulted in a greater number of days alive without antibiotic treatment or bacteremia during the 6 months after randomization than a standard duration of therapy. Moreover, no apparent between-group difference was observed in the incidence of death from any cause, unplanned cardiac surgery, or symptomatic embolic events that were confirmed by imaging within 6 months after randomization. However, the incidence of relapse of bacteremia or infective endocarditis was significantly higher with the response-tailored strategy.

Supported by unrestricted grants from Sygeforsikringen "danmark," Danmarks Frie Forskningsfond, Thora og Viggo Groves Mindelegat, Regionernes Medicinpulje, Arvid Nilssons Fond, Hjertecentrets Forskningsudvalg, Rigshospitalets Forskningsfond, Augustinus Fonden, Carl og Ellen Hertz's legat, and the William Demant Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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