univerzitetni klinični center ljubljana
*University Medical Centre Ljubljana*

# Infekcijska klinika bere

## Izobraževalni seminar, 11.10.2018






Doc. dr. Daša Stupica, dr. med.

JAMA | Original Investigation

# Effect of Algorithm-Based Therapy vs Usual Care on Clinical Success and Serious Adverse Events in Patients with Staphylococcal Bacteremia
## A Randomized Clinical Trial

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# Izhodišče in namen raziskave

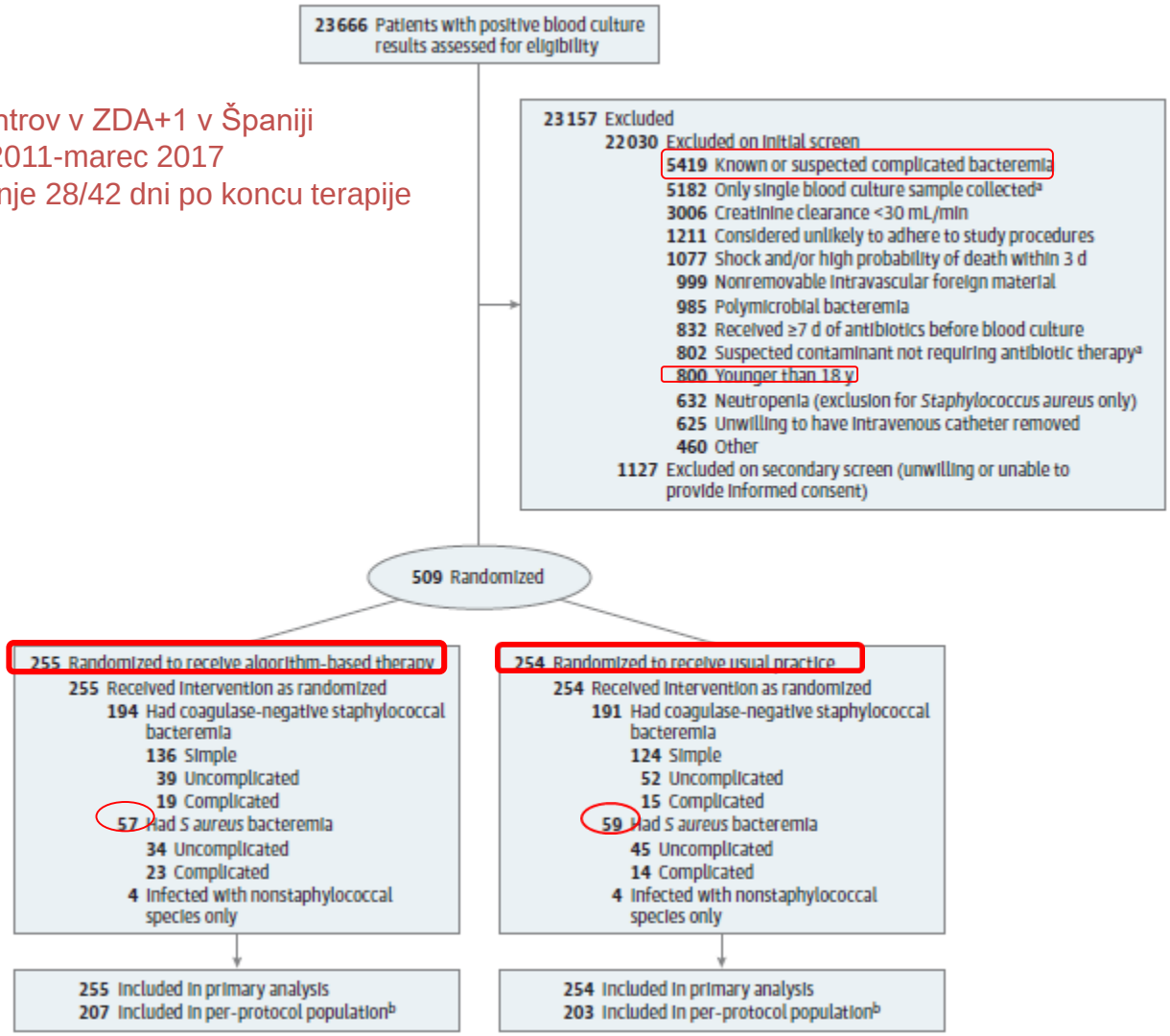
**IMPORTANCE** The appropriate duration of antibiotics for staphylococcal bacteremia is unknown.

**OBJECTIVE** To test whether an algorithm that defines treatment duration for staphylococcal bacteremia vs standard of care provides noninferior efficacy without increasing severe adverse events.

JAMA

- 16 centrov v ZDA+1 v Španiji
- April 2011-marec 2017
- Sledenje 28/42 dni po koncu terapije

**Figure. Flow of Participants Through the Staphylococcal Bacteremia Trial**




[a] Prior to an amendment allowing inclusion of these patients.

[b] Details for reasons for exclusion from the per-protocol population are provided in eTable 8 in Supplement 2.

**Algoritem obravnave**

- Kontrolne HK na 24-48 ur
- Izbira antibiotika
- Trajanje zdravljenja
- UZ srca pri *S.aureus*

**Table 1. Clinical Classification of Bacteremia and Duration of Algorithm-Based Therapy**

| Definition | Duration of Therapy (Range), d |
|---|---|
| ***Staphylococcus aureus* Bacteremia** | |
| Uncomplicated | 14 (±2) |
| Intravascular catheter source of infection (if present) removed within 5 d | |
| Negative follow-up blood culture 24-72 h after initial positive culture | |
| Defervescence within 72 h of initial positive culture | |
| Echocardiogram without evidence of endocarditis | |
| No symptoms or signs of metastatic infection | |
| No indwelling intravascular prosthetic devices | |
| Complicated | 28-42 (±2) |
| Positive follow-up blood culture for *S aureus*, OR | |
| Persistent fever, OR | |
| Echocardiography with evidence of endocarditis, OR | |
| Symptoms or signs of metastatic infection | |
| **Coagulase-negative Staphylococcal Bacteremia** | |
| Simple | 0-3 (+1)[a] |
| Single blood culture positive for coagulase-negative staphylococci | |
| Negative follow-up blood culture | |
| No signs or symptoms of local infection at a catheter site | |
| No symptoms or signs of metastatic infection | |
| No indwelling intravascular prosthetic devices | |
| Uncomplicated | 5 (±1) |
| ≥2 blood cultures positive for coagulase-negative staphylococci drawn ≤24 h apart, OR | |
| Single blood culture positive for coagulase-negative staphylococci, PLUS symptoms or signs of infection at a catheter site | |
| Complicated | 7-28 (±2) |
| ≥2 blood cultures positive for coagulase-negative staphylococci from samples drawn >24 h apart, OR | |
| Echocardiography with evidence of endocarditis, OR | |
| Symptoms or signs of metastatic infection | |

[a] For patients with simple coagulase-negative staphylococcal bacteremia, treatment was discontinued on randomization to algorithm-based therapy. Thus, if clinicians suspected that the positive culture result was attributable to contamination and had not initiated therapy, those patients did not receive any study antibiotic therapy.

Table 2. Characteristics of Patients in the Intention-to-Treat Population

| Characteristic | Algorithm-Based Therapy (N = 255) | Usual Practice (N = 254) |
|---|---|---|
| Age, median (range), y | 58 (19-91) | 60 (18-94) |
| Men, No. (%) | 146 (57.3) | 137 (53.9) |
| Race, No. (%)[a] | | |
| White | 175 (68.6) | 174 (68.5) |
| Black or African American | 63 (24.7) | 60 (23.6) |
| Other[b] | 17 (6.7) | 20 (7.9) |
| Ethnicity, No. (%) | | |
| Hispanic or Latino | 21 (8.2) | 23 (9.1) |
| Not Hispanic or Latino | 234 (91.8) | 231 (90.9) |
| Body mass index, median (range)[c] | 27.6 (11.1-63.5) | 27.4 (13.5-71.0) |
| Creatinine clearance (MDRD equation), median (range), mL/min/1.73m$^2$ | 82.7 (12.1-873.6) | 88.0 (9.7-834.9) |
| Risk factor, No. (%) | | |
| Immunosuppressed condition[d] | 75 (29.4) | 72 (28.3) |
| Diabetes mellitus | 63 (24.7) | 72 (28.3) |
| Chronic liver disease | 25 (9.8) | 20 (7.9) |
| Surgery within previous 30 d | 24 (9.4) | 20 (7.9) |
| Trauma within previous 30 d | 9 (3.5) | 12 (4.7) |
| Injection drug use | 9 (3.5) | 12 (4.7) |
| Preexisting valvular heart disease | 9 (3.5) | 9 (3.5) |
| Chronic renal insufficiency | 8 (3.1) | 5 (2.0) |
| History of *S aureus* infection within the past year | 7 (2.7) | 5 (2.0) |
| Hypertrophic cardiomyopathy | 5 (2.0) | 6 (2.4) |
| Congenital heart disease | 1 (0.4) | 1 (0.4) |
| Previous infective endocarditis | 0 | 0 |
| Setting of infection, No. (%) | | |
| Nosocomial | 85 (33.3) | 82 (32.3) |
| Health care-associated, community-onset | 92 (36.1) | 88 (34.6) |
| Community-acquired | 78 (30.6) | 84 (33.1) |
| Classification by diagnosis, No. (%)[e] | | |
| Simple or uncomplicated bacteremia | 209 (81.9) | 221 (87.0) |
| Simple coagulase-negative staphylococci | 136 (53.3) | 124 (48.8) |
| Uncomplicated coagulase-negative staphylococci | 39 (15.3) | 52 (20.5) |
| Uncomplicated *S aureus* | 34 (13.3) | 45 (17.7) |
| Complicated bacteremia | 42 (16.4) | 29 (11.4) |
| Complicated coagulase-negative staphylococci | 19 (7.5) | 15 (5.9) |
| Complicated *S aureus* | 23 (9.0) | 14 (5.5) |
| Nonstaphylococcal infection | 4 (1.6) | 4 (1.6) |
| Echocardiogram performed, among patients with *S aureus*, No./total (%) | 56/57 (98.2) | 58/59 (98.3) |
| Transesophageal echocardiogram | 25/57 (43.9) | 27/59 (45.8) |
| Diagnosed with endocarditis[f] | 4/57 (7.0) | 1 (1.7) |
| Median vancomycin minimum inhibitory concentration, µg/mL | 1.0 | 1.0 |
| Median daptomycin dose (IQR), mg/kg | 6.0 (5.8-7.6) [n = 42] | 6.0 (5.8-7.0) [n = 43] |
| Median vancomycin trough (IQR), µg/mL, No.[g] | 13.6 (10.1-20.4) [n = 111] | 13.1 (9.5-19.8) [n = 100] |
| *S aureus* | 17.4 (7.2-21.2) [n = 35] | 12.4 (9.0-22.5) [n = 39] |
| Coagulase-negative staphylococci | 13.4 (10.3-19.8) [n = 76] | 13.3 (9.5-18.8) [n = 61] |
| Not simple coagulase-negative staphylococcus and intravenous catheter not removed, No. (%)[h] | 1 (0.4) | 2 (0.8) |
| *S aureus* treatment characteristics, No./total (%) | | |
| Patients with *S aureus* receiving appropriate empirical antibiotic therapy[i] | 57/57 (100) | 58/59 (98.3) |
| MRSA receiving appropriate empirical therapy | 12/12 (100) | 21/21 (100) |
| MSSA receiving appropriate empirical therapy | 45/45 (100) | 37/38 (97.4) |
| MSSA receiving empirical beta-lactam therapy | 39/45 (86.7) | 28/38 (73.7) |
| Infectious diseases consultation for *S aureus* bacteremia | 41/57 (71.9) | 37/59 (62.7) |

# Rezultati

Table 3. Outcomes at Test-of-Cure Visit

| Criteria | No./Total No. (%) | | Difference, % (1-Sided 97.5% CI) |
|---|---|---|---|
| | Algorithm-Based Therapy | Usual Practice | |
| Overall success in the ITT population[a] | 209/255 (82.0) | 207/254 (81.5) | 0.5 (−6.2 to ∞) |
| Success according to assessment of complication[b] | | | |
| Simple or uncomplicated bacteremia | 173/209 (82.8) | 191/221 (86.4) | −3.7 (−10.5 to 3.2) |
| Complicated bacteremia | 36/42 (85.7) | 16/29 (55.2) | 30.5 (9.6 to 51.5) |
| Success according to clinical category | | | |
| All *Staphylococcus aureus* | 43/57 (75.4) | 39/59 (66.1) | 9.3 (−7.1 to ∞) |
| Uncomplicated *S aureus* | 24/34 (70.6) | 34/45 (75.6) | −5.0 (−24.8 to ∞) |
| Complicated *S aureus* | 19/23 (82.6) | 5/14 (35.7) | 46.9 (17.4 to ∞) |
| All coagulase-negative staphylococci | 166/194 (85.6) | 168/191 (88.0) | −2.4 (−9.2 to ∞) |
| Simple coagulase-negative staphylococci | 115/136 (84.6) | 109/124 (87.9) | −3.3 (−11.7 to ∞) |
| Observed without antibiotics | 37/46 (80.4) | 35/38 (92.1) | −11.7 (−26.0 to ∞) |
| Treated with antibiotics | 78/90 (86.7) | 74/86 (86.0) | 0.6 (−9.5 to ∞) |
| Uncomplicated coagulase-negative staphylococci | 34/39 (87.2) | 48/52 (92.3) | −5.1 (−17.9 to ∞) |
| Complicated coagulase-negative staphylococci | 17/19 (89.5) | 11/15 (73.3) | 16.1 (−10.2 to ∞) |
| Overall success in the per-protocol population | 185/207 (89.4) | 178/203 (87.7) | 1.7 (−4.5 to ∞) |
| Success according to pathogen in the ITT population[c] | | | |
| *S aureus* | | | |
| Methicillin-susceptible | 33/45 (73.3) | 23/38 (60.5) | 12.8 (−7.4 to ∞) |
| Methicillin-resistant | 10/12 (83.3) | 16/21 (76.2) | 7.1 (−20.7 to ∞) |
| Coagulase-negative staphylococci | | | |
| Methicillin-susceptible | 81/90 (90.0) | 82/88 (93.2) | −3.2 (−11.3 to ∞) |
| Methicillin-resistant | 84/98 (85.7) | 86/100 (86.0) | −0.3 (−10.0 to ∞) |

# Rezultati

Table 4. Safety Outcomes

| Criteria | Algorithm-Based Therapy | Usual Practice |
|---|---|---|
| Serious adverse events in the ITT population, No./total (%)[a] | 83/255 (32.5) | 72/254 (28.3) |
| Mortality, No./total (%)[b,c] | 16/255 (6.3) | 14/254 (5.5) |
| No. related to infection per blinded adjudication/ total deaths (%) | 2/16 (12.5) | 3/14 (21.4) |
| According to clinical category, No./total | | |
| Simple coagulase-negative staphylococci | 0/6 | 0/4 |
| Uncomplicated coagulase-negative staphylococci | 0/0 | 0/3 |
| Complicated coagulase-negative staphylococci | 0/3 | 0/1 |
| Uncomplicated *Staphylococcus aureus* | 1/5 | 1/3 |
| Complicated *S aureus* | 1/2 | 2/3 |

(32.5% vs 28.3%; difference, 4.2% [95% CI, −3.8% to 12.2%]

# Rezultati

Table 5. Duration of Therapy Among Per-Protocol Patients With Simple or Uncomplicated Staphylococcal Bacteremia[a]

| | Algorithm-Based Therapy | | | Usual Practice | | | Difference of Means, d (95% CI) |
|---|---|---|---|---|---|---|---|
| | Mean | Median (IQR) | No. | Mean | Median (IQR) | No. | |
| Duration of therapy, d | 4.4 | 3.0 (1.0 to 5.0) | 171 | 6.2 | 3.0 (1.0 to 13.0) | 183 | −1.8 (−3.1 to −0.6) |
| Simple coagulase-negative staphylococci | 1.8 | 2.0 (0.0 to 3.0) | 114 | 1.8 | 1.0 (0.0 to 3.0) | 103 | 0.0 (−0.5 to 0.6) |
| Uncomplicated coagulase-negative staphylococci | 5.3 | 5.0 (5.0 to 6.0) | 33 | 8.4 | 7.5 (5.0 to 14.0) | 42 | −3.1 (−4.9 to −1.3) |
| Uncomplicated *Staphylococcus aureus* | 15.3 | 14.0 (14.0 to 15.0) | 24 | 15.9 | 16.0 (14.0 to 17.0) | 38 | −0.6 (−3.4 to 2.2) |

# Zaključek

**CONCLUSIONS AND RELEVANCE** Among patients with staphylococcal bacteremia, the use of an algorithm to guide testing and treatment compared with usual care resulted in a noninferior rate of clinical success. Rates of serious adverse events were not significantly different, but interpretation is limited by wide confidence intervals. Further research is needed to assess the utility of the algorithm.

JAMA | Original Investigation

# Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

## A Randomized Clinical Trial

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# Izhodišče in namen raziskave

**IMPORTANCE** Extended-spectrum β-lactamases mediate resistance to third-generation cephalosporins (eg, ceftriaxone) in *Escherichia coli* and *Klebsiella pneumoniae*. Significant infections caused by these strains are usually treated with carbapenems, potentially selecting for carbapenem resistance. Piperacillin-tazobactam may be an effective "carbapenem-sparing" option to treat extended-spectrum β-lactamase producers.

**OBJECTIVES** To determine whether definitive therapy with piperacillin-tazobactam is noninferior to meropenem (a carbapenem) in patients with bloodstream infection caused by ceftriaxone-nonsusceptible *E coli* or *K pneumoniae*.

# Velikost vzorca

carbapenem. Based on a mortality rate of 14% in the control group (assuming mortality in observational cohorts may be greater than in trials with exclusion criteria) and a noninferiority margin of 5%, 454 patients were needed in total to achieve 80% power with a 1-sided α level of .025, allowing for 10% dropout.[22] A 5% noninferiority margin was chosen as the maximal difference in mortality between treatments that would be clinically acceptable, by consultation with infec-

- 26 bolnic v Avstraliji, JV Aziji, Italiji,Kanada
- Feb 2014-Jul 2017
- Sledenje 30 dni od vključitve

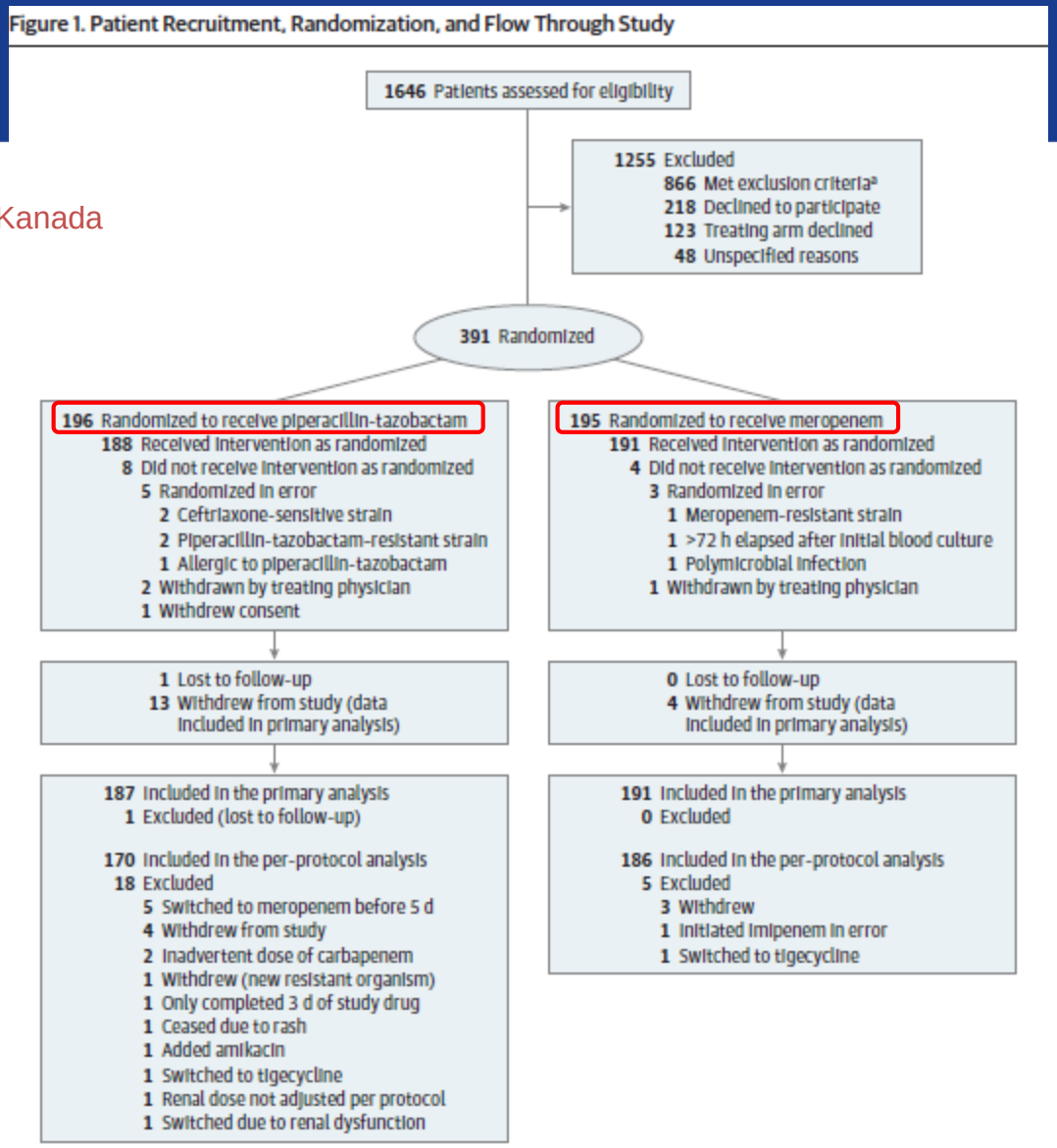


Table 1. Baseline Characteristics of Patients in the Primary Analysis Population[a]

| Characteristic | Pipercillin-Tazobactam (n = 188) | Meropenem (n = 191) |
|---|---|---|
| Organism | | |
| *Escherichia coli* | 162 (86.2) | 166 (86.9) |
| *Klebsiella pneumoniae* | 26 (13.8) | 25 (13.1) |
| Stratification[b] | | |
| E1 (*E coli*, less severe infection) | 159 (84.6) | 162 (84.8) |
| E2 (*E coli*, more severe infection) | 3 (1.6) | 3 (1.6) |
| K1 (*K pneumoniae*, less severe infection) | 23 (12.2) | 25 (13.1) |
| K2 (*K pneumoniae*, more severe infection) | 3 (1.6) | 1 (0.5) |
| Country | | |
| Singapore | 72 (38.3) | 82 (42.9) |
| Australia | 42 (22.3) | 43 (22.5) |
| New Zealand | 10 (5.3) | 9 (4.7) |
| Canada | 1 (0.5) | 1 (0.5) |
| South Africa | 5 (2.7) | 6 (3.1) |
| Italy | 15 (8.0) | 10 (5.2) |
| Turkey | 24 (12.8) | 22 (11.5) |
| Lebanon | 8 (4.3) | 7 (3.7) |
| Saudi Arabia | 11 (5.9) | 11 (5.8) |
| Age, median (IQR), y | 70 (55-78) | 69 (59-78) |
| Male | 101 (53.7) | 97 (50.8) |
| Acquisition | | |
| Hospital-acquired | 52 (27.7) | 46 (24.1) |
| Health care-associated | 55 (29.3) | 61 (31.9) |
| Community-associated | 81 (43.1) | 84 (44.0) |
| Source of bacteremia | | |
| Urinary tract | 103 (54.8) | 128 (67.0) |
| Intra-abdominal infection | 34 (18.1) | 28 (14.7) |
| Vascular catheter-related infection | 3 (1.6) | 3 (1.6) |
| Surgical site infection | 8 (4.3) | 4 (2.1) |
| Pneumonia | 9 (4.8) | 3 (1.6) |
| Mucositis/neutropenia | 12 (6.4) | 7 (3.7) |
| Musculoskeletal | 1 (0.5) | 0 (0) |
| Skin and soft tissue | 4 (2.1) | 1 (0.5) |
| Other | 2 (1.1) | 1 (0.5) |
| Unknown | 12 (6.4) | 16 (8.4) |
| Surgery within past 14 d | 19 (10.1) | 14 (7.3) |
| ICU admission | 13 (7.0) | 14 (7.5) |
| APACHE II Score, mean (SD)[c] | 17.9 (6.1) | 21.0 (6.9) |
| Charlson Comorbidity Index score, median (IQR)[d] | 2.0 (1.0-4.0) | 2.0 (1.0-4.0) |
| Pitt score, median (IQR)[e] | 1.0 (0-2.0) | 1.0 (0-2.0) |
| Immune compromise | 51 (27.1) | 40 (20.9) |
| Neutropenia | 16 (8.5) | 9 (4.7) |
| Central venous catheter | 35 (18.6) | 20 (10.5) |
| Urinary catheter/ nephrostomy | 51 (27.1) | 37 (19.4) |
| Moderate-severe renal dysfunction[f] | 31 (16.5) | 30 (15.7) |
| Diabetes[f] | 59 (31.4) | 79 (41.4) |
| Liver disease[f] | 12 (6.4) | 18 (9.4) |
| qSOFA score ≥2[g] | 86 (45.7) | 77 (40.3) |
| Weight, mean (SD), kg | 67.2 (18.1) | 69.3 (19.3) |
| Empirical antibiotic category | | |
| β-lactam/ β-lactamase inhibitor | 38 (20.2) | 49 (25.7) |
| Carbapenem | 26 (13.8) | 28 (14.7) |
| Other | 124 (66.0) | 114 (59.7) |
| Appropriate empirical antibiotic | 126 (67.0) | 127 (66.5) |
| Time to randomization, median (IQR), h | 53.6 (44.9-65.6) | 52.5 (46.0-63.7) |
| Time to appropriate antibiotics, median (IQR), h | 5.5 (0.4-31.5) | 9.6 (0.5-32.1) |

# Rezultati

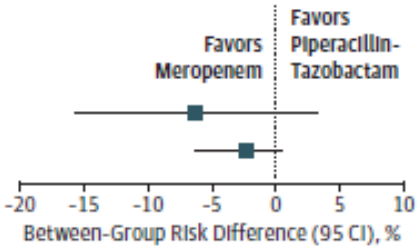
**Table 2. Primary Analysis and Subgroup Analyses**

| | 30-d Mortality, No./Total No. (%) | | Risk Difference, % (1-Sided 97.5% CI)[a] | *P* Value for Noninferiority |
|---|---|---|---|---|
| | Piperacillin-Tazobactam | Meropenem | | |
| Primary analysis | 23/187 (12.3) | 7/191 (3.7) | 8.6 (−∞ to 14.5) | .90 |
| Per-protocol analysis | 18/170 (10.6) | 7/186 (3.8) | 6.8 (−∞ to 12.8) | .76 |
| Subgroup analyses[b] | | | | *P* Value for Interaction |
| OECD country income | | | | |
| Middle income | 8/37 (21.6) | 1/35 (2.9) | 18.8 (−∞ to 35.0) | .31 |
| High income | 15/150 (10.0) | 6/156 (3.9) | 6.2 (−∞ to 12.5) | |
| Pitt score | | | | |
| ≥4 | 5/18 (27.8) | 0/9 | 27.8 (−∞ to 51.3) | .99 |
| <4 | 18/169 (10.7) | 7/182 (3.9) | 6.8 (−∞ to 12.8) | |
| Infecting species | | | | |
| *E coli* | 17/161 (10.6) | 7/166 (4.2) | 6.3 (−∞ to 12.6) | .99 |
| *K pneumoniae* | 6/26 (23.1) | 0/25 | 23.1 (−∞ to 42.3) | |
| Infection | | | | |
| HAI | 18/107 (16.8) | 4/107 (3.7) | 13.1 (−∞ to 21.8) | .26 |
| Non-HAI | 5/80 (6.3) | 3/84 (3.6) | 2.7 (−∞ to 10.7) | |
| Appropriate empirical antibiotic therapy | | | | |
| Appropriate | 18/126 (14.3) | 5/127 (3.9) | 10.3 (−∞ to 18.0) | .70 |
| Inappropriate | 5/61 (8.2) | 2/64 (3.1) | 5.1 (−∞ to 15.2) | |
| UT vs non-UT source | | | | |
| UT | 7/102 (6.9) | 4/128 (3.1) | 3.7 (−∞ to 10.7) | .44 |
| Non-UT | 16/85 (18.8) | 3/63 (4.8) | 14.1 (−∞ to 24.5) | |
| Immune compromise[c] | | | | |
| Present | 10/51 (19.6) | 1/40 (2.5) | 17.1 (−∞ to 30.5) | .27 |
| Absent | 13/136 (9.6) | 6/151 (4.0) | 5.6 (−∞ to 12.2) | |

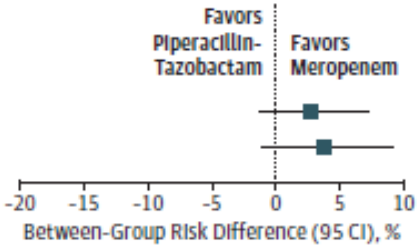
# Rezultati

**Figure 2. Secondary Outcomes**

| Measure of Success | Patients Meeting End Point, No./Total No. (%) | | Between-Group Difference (95% CI) |
|---|---|---|---|
| | Piperacillin-Tazobactam | Meropenem | |
| Clinical and microbiological success at day 4[a] | 121/177 (68.4) | 138/185 (74.6) | -6.2 (-15.5 to 3.1) |
| Microbiological success at day 4 | 169/174 (97.1) | 184/185 (99.5) | -2.3 (-6.1 to 0.4) |




| Measure of Failure | Patients Meeting End Point, No./Total No. (%) | | Between-Group Difference (95% CI) |
|---|---|---|---|
| | Piperacillin-Tazobactam | Meropenem | |
| Microbiological relapse | 9/187 (4.8) | 4/191 (2.1) | 2.7 (-1.1 to 7.1) |
| Secondary infection with multiresistant organism or *Clostridium difficile* | 15/187 (8.0)[b] | 8/191 (4.2)[c] | 3.8 (-1.1 to 9.1) |



# Zaključek

**CONCLUSIONS AND RELEVANCE** Among patients with *E coli* or *K pneumoniae* bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in a noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.

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# Should we consider faecal colonisation with extended-spectrum β-lactamase-producing Enterobacteriaceae in empirical therapy of community-onset sepsis?

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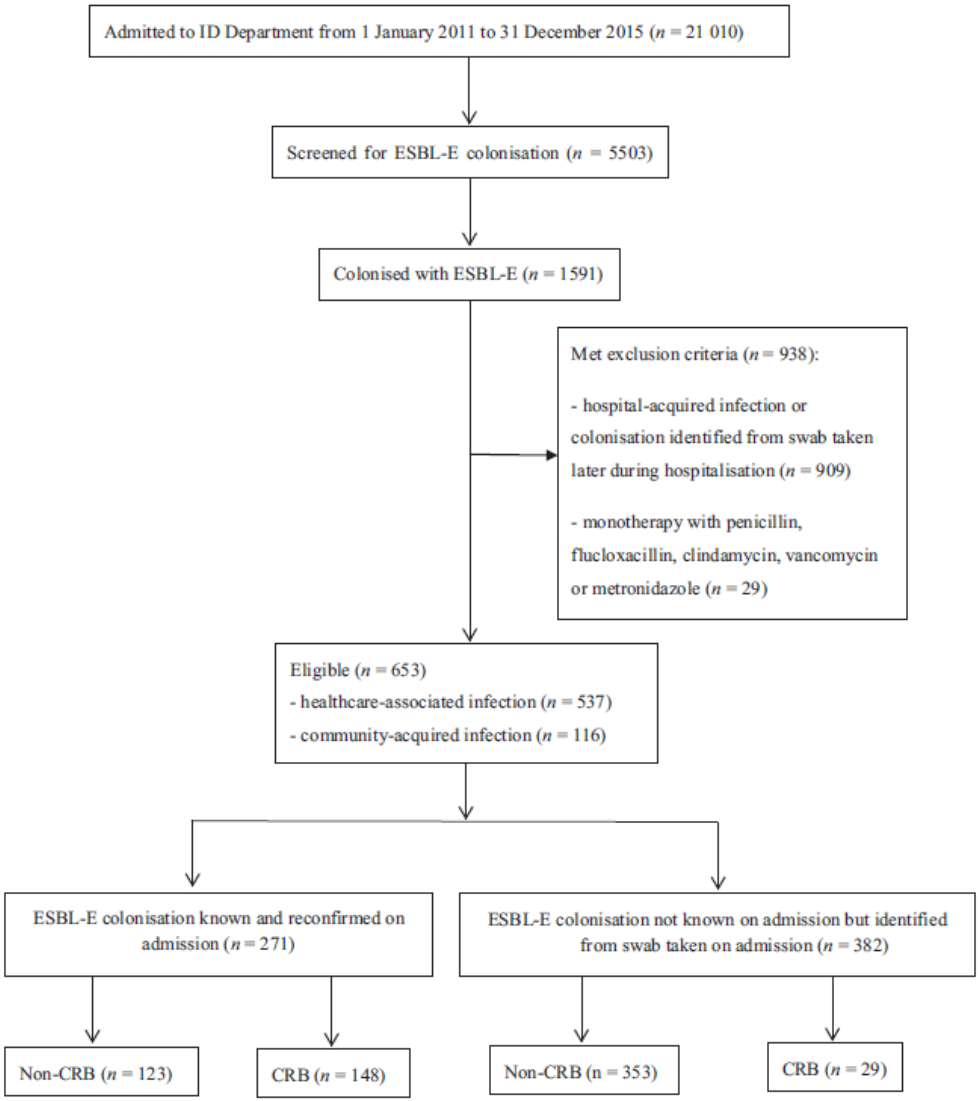


**Fig. 1.** Flow diagram. ID, infectious diseases; ESBL-E, extended-spectrum β-lactamase-producing Enterobacteriaceae; CRB, carbapenem.

**Table 2**
Univariate analysis and multiple regression analysis of associations between selected variables and 30-day mortality.

| Variable | Univariate analysis | | Multiple regression analysis [a] | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Age | 1.06 (1.04–1.08) | <0.001 | 1.05 (1.03–1.08) | <0.001 |
| Male sex | 0.62 (0.43–0.89) | 0.010 | 0.77 (0.49–1.19) | 0.23 |
| Charlson comorbidity index | 1.19 (1.11–1.29) | <0.001 | 1.10 (1.00–1.21) | 0.06 |
| Pitt bacteraemia score | 1.75 (1.55–1.96) | <0.001 | 1.81 (1.59–2.06) | <0.001 |
| Site of sepsis origin | | 0.002 | | 0.03 |
| Other | 1 | 1 | 1 | |
| RTI | 2.37 (1.15–4.85) | 0.02 | 2.33 (1.00–5.43) | |
| UTI | 1.18 (0.56–2.52) | 0.66 | 1.13 (0.47–2.74) | |
| Unknown | 2.37 (0.99–5.68) | 0.05 | 2.29 (0.82–6.39) | |
| Non-CRB vs. CRB | 1.53 (1.0–2.34) | 0.049 | 1.11 (0.66–1.87) | 0.68 |
| Aetiology of sepsis | | 0.69 | | 0.66 |
| Unidentified | 1 | 1 | 1 | |
| Identified, ESBL-E | 0.82 (0.52–1.29) | 0.39 | 1.06 (0.57–1.98) | |
| Identified, not ESBL-E | 0.92 (0.61–1.38) | 0.68 | 1.25 (0.76–2.07) | |

OR, odds ratio; CI, confidence interval; RTI, respiratory tract infection; UTI, urinary tract infection; CRB, carbapenem; ESBL-E, extended-spectrum β-lactamase-producing Enterobacteriaceae.

[a] The value of the intercept in the multivariable model was –7.50.

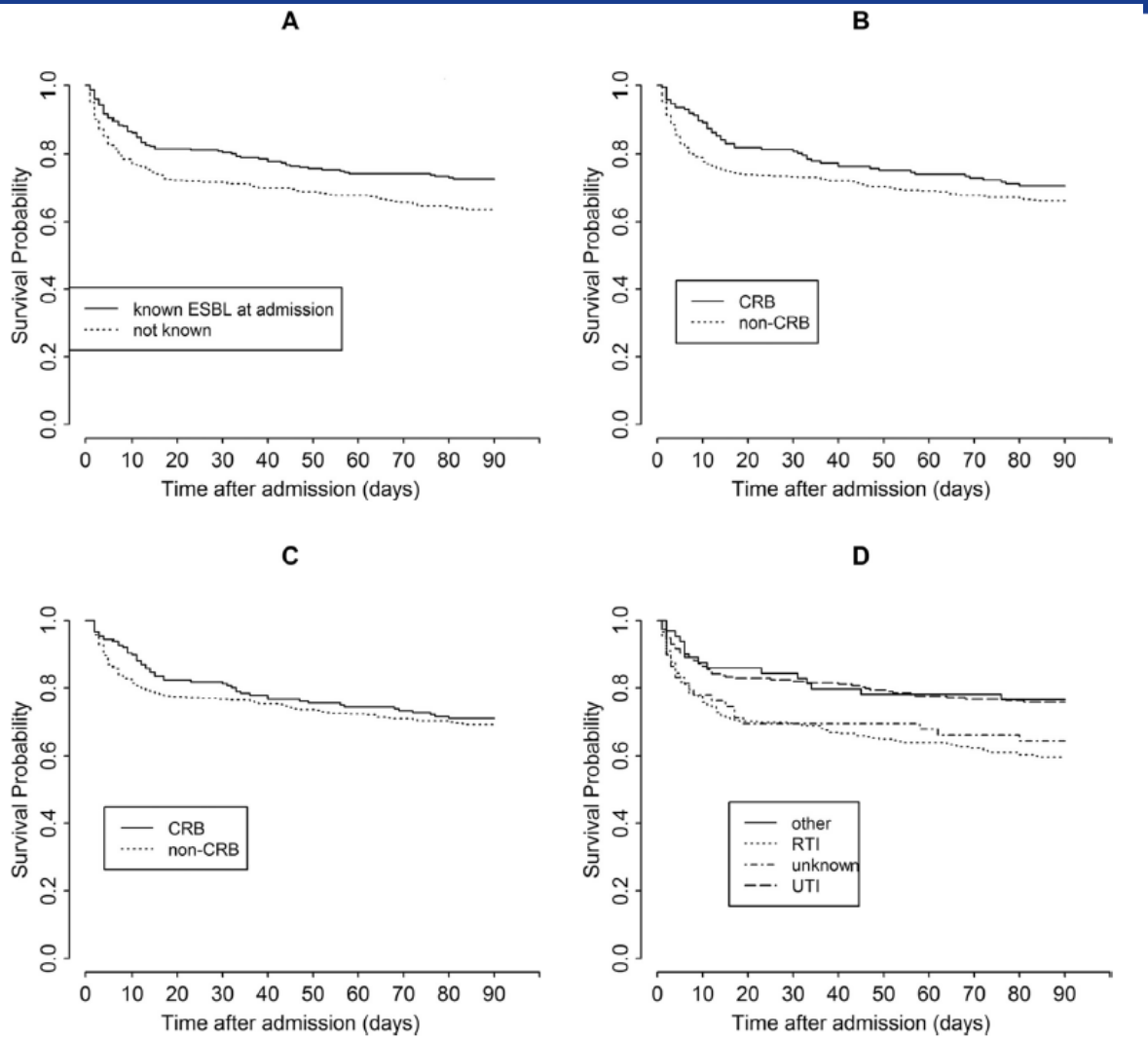


**Fig. 2.** Estimated probability of survival in the first 90 days after admission for (A) patients known versus not known to be already colonised with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) on admission, (B,C) patients empirically treated with a carbapenem (CRB) versus a non-CRB antibiotic for all patients (B) and for those who survived >24 h (C), and (D) patients with different origins of sepsis. RTI, respiratory tract infection; UTI, urinary tract infection.

# Zaključek

In conclusion, with the increasing global antibiotic resistance associated with undue use of broad-spectrum antibiotics and the few new anti-Gram-negative antibacterial drugs on the horizon, the current data suggest that CRB-sparing empirical treatment may be reasonable in patients colonised with ESBL-E who have community-onset sepsis but are not critically ill. This is particularly the case if sepsis originates from a site other than a UTI; the PPV for ESBL-E sepsis is >60% if the site of origin is a UTI, where Enterobacteriaceae are the most prevalent aetiology.

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ORIGINAL ARTICLE

# 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.

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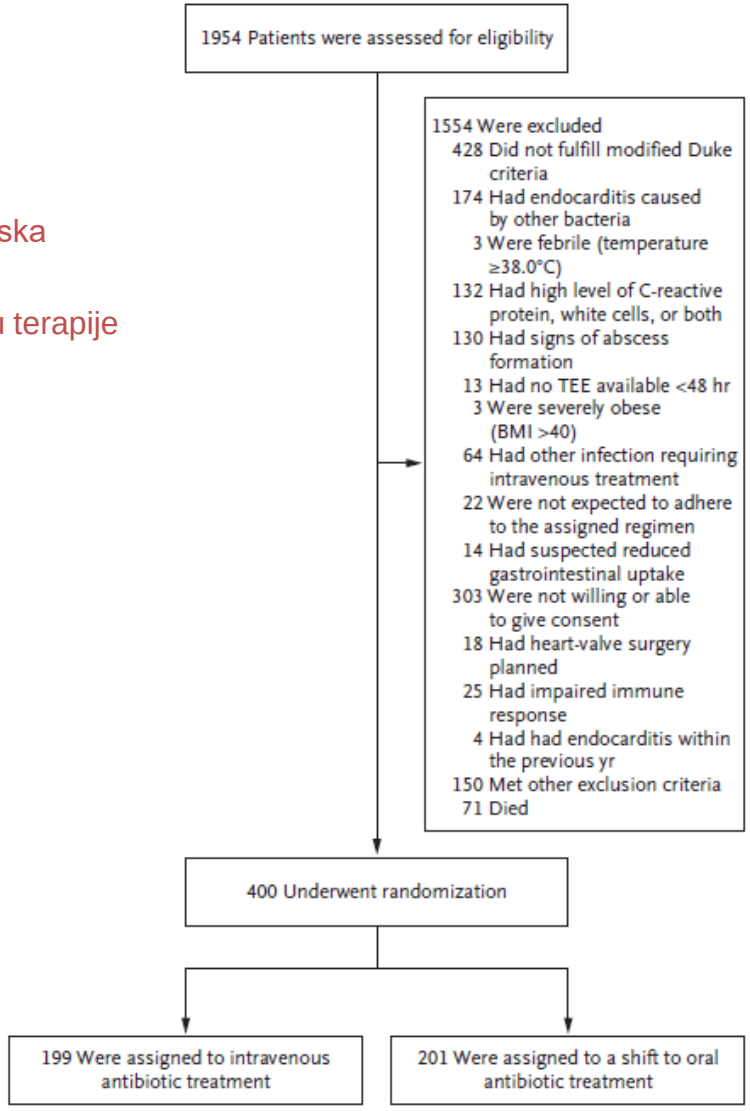


**Table 1. Characteristics of the Patients at Baseline.***

| 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 — $\times 10^{-9}$/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) |

| | IV | Oral |
|---|---|---|
| Čas od dg do randomizacije (dni) | 17 (13-23) | 17 (12-24) |
| Čas zdravljenja po randomizaciji (dni) | 19 (14-25) | 17 (14-25) |
| Čas hospitalizacije po randomizaciji (dni) | 19 (14-25) | 3 (1-10) |

# Rezultati

**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.

| | | | |
|---|---|---|---|
| 24 (12.1) | 18 (9.0) | 3.1 (-3.4-9.6) | 0.72 (0.37-1.36) |

# Rezultati

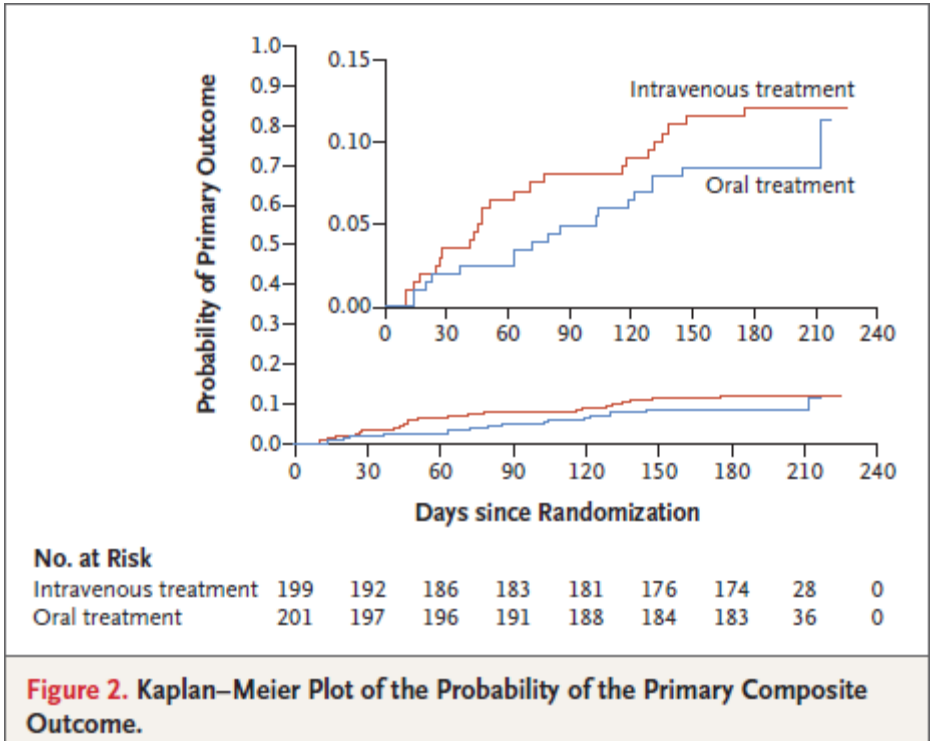
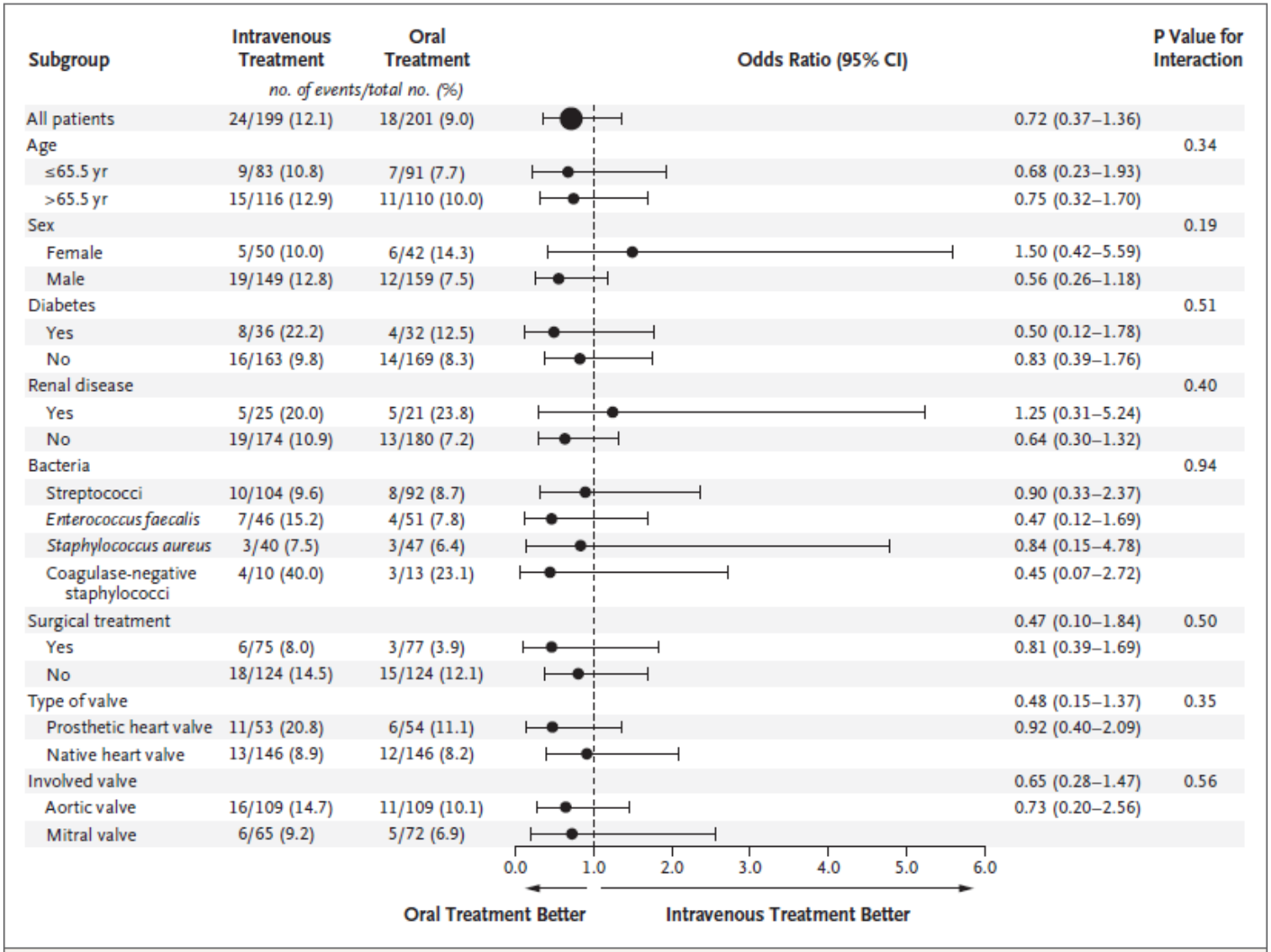



**Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.**

# Rezultati



| 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) | | |



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

# Zaključek

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.