ORIGINAL ARTICLE

# Trial of Vancomycin and Cefazolin as Surgical Prophylaxis in Arthroplasty

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## ABSTRACT

### BACKGROUND

The addition of vancomycin to beta-lactam prophylaxis in arthroplasty may reduce surgical-site infections; however, the efficacy and safety are unclear.

### METHODS

In this multicenter, double-blind, superiority, placebo-controlled trial, we randomly assigned adult patients without known methicillin-resistant *Staphylococcus aureus* (MRSA) colonization who were undergoing arthroplasty to receive 1.5 g of vancomycin or normal saline placebo, in addition to cefazolin prophylaxis. The primary outcome was surgical-site infection within 90 days after surgery.

### RESULTS

A total of 4239 patients underwent randomization. Among 4113 patients in the modified intention-to-treat population (2233 undergoing knee arthroplasty, 1850 undergoing hip arthroplasty, and 30 undergoing shoulder arthroplasty), surgical-site infections occurred in 91 of 2044 patients (4.5%) in the vancomycin group and in 72 of 2069 patients (3.5%) in the placebo group (relative risk, 1.28; 95% confidence interval [CI], 0.94 to 1.73; P=0.11). Among patients undergoing knee arthroplasty, surgical-site infections occurred in 63 of 1109 patients (5.7%) in the vancomyin group and in 42 of 1124 patients (3.7%) in the placebo group (relative risk, 1.52; 95% CI, 1.04 to 2.23). Among patients undergoing hip arthroplasty, surgical-site infections occurred in 28 of 920 patients (3.0%) in the vancomyin group and in 29 of 930 patients (3.1%) in the placebo group (relative risk, 0.98; 95% CI, 0.59 to 1.63). Adverse events occurred in 35 of 2010 patients (1.7%) in the vancomycin group and in 35 of 2030 patients (1.7%) in the placebo group, including hypersensitivity reactions in 24 of 2010 patients (1.2%) and 11 of 2030 patients (0.5%), respectively (relative risk, 2.20; 95% CI, 1.08 to 4.49), and acute kidney injury in 42 of 2010 patients (2.1%) and 74 of 2030 patients (3.6%), respectively (relative risk, 0.57; 95% CI, 0.39 to 0.83).

### CONCLUSIONS

The addition of vancomycin to cefazolin prophylaxis was not superior to placebo for the prevention of surgical-site infections in arthroplasty among patients without known MRSA colonization. (Funded by the Australian National Health and Medical Research Council; Australian New Zealand Clinical Trials Registry number, ACTRN12618000642280.)

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This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

N Engl J Med 2023;389:1488-98.
DOI: 10.1056/NEJMoa2301401

Knee and hip arthroplasty are two high-volume operations performed in the United States[1] and are projected to exceed 2.7 million procedures annually by 2030.[2] Surgical-site infections after arthroplasty result in high patient morbidity and mortality.[3] In addition to the increased health risk to patients, the economic burden is substantial, with inpatient costs exceeding $28,000 per infection in the United States and annual national hospital costs projected to exceed $1.85 billion.[4]

Current guidelines[3,5-7] recommend administering a first- or second-generation cephalosporin antimicrobial agent, such as cefazolin, at the time of arthroplasty to prevent infection.[3,5-7] Cefazolin, however, may not prevent infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermidis*, which are increasingly reported pathogens in arthroplasty infections.[8-10] The addition of a glycopeptide antimicrobial, such as vancomycin, to prophylaxis regimens provides a broader spectrum of activity; however, the benefit remains unclear. We conducted the Australian Surgical Antibiotic Prophylaxis (ASAP) trial to assess the efficacy of adding vancomycin to standard surgical antimicrobial prophylaxis with cefazolin to prevent surgical-site infection in adults undergoing arthroplasty.

## Methods

### Trial Design

In this phase 4, multicenter, double-blind, parallel-group, superiority, randomized, placebo-controlled trial, we assigned patients without known MRSA colonization who were undergoing arthroplasty to receive 1.5 g of vancomycin or normal saline placebo in addition to standard surgical antimicrobial prophylaxis with cefazolin. The protocol was approved by the institutional review board at each participating site, and written informed consent was obtained from the patients. The protocol has been published[11] and is available with the full text of this article at NEJM.org. Members of the project steering committee designed the trial and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### Patient Selection and Randomization

The trial was conducted at 11 hospitals in Australia. Eligible adult patients were randomly assigned in a 1:1 ratio to receive either vancomycin or placebo by means of a central, computer-based randomization program with blocks of four, stratified according to the center and procedure. The randomization sequence was generated by the trial statistician (the sixth author). Patients, treating clinicians, and members of the research team and end-point adjudication committee were unaware of the trial-group assignments. Blinding of data was maintained until finalization of all statistical analyses and completion of the first draft of the manuscript.

*A Quick Take is available at NEJM.org*

### Trial Procedures

Patients received prophylaxis with 2 g of cefazolin, administered intravenously within 60 minutes before skin incision.[5] Active treatment consisted of 1.5 g of intravenous vancomycin (1 g in patients with a body weight of <50 kg). The pharmaceutical company from which the investigational trial product was purchased removed the commercial labels and placed a sheath over the vial. Placebo consisted of matching empty vials with an identical sheath. The vials were reconstituted with normal saline. Vancomycin or placebo was administered within 120 minutes before incision. There was no mandated order of administration for vancomycin or placebo and cefazolin. All other aspects of care, including infection-prevention approaches, followed local protocols (Table S1 in the Supplementary Appendix, available at NEJM.org).

### Substudy of Perioperative Staphylococcal Carriage

In addition to the presurgical screening and decolonization processes, we assessed perioperative carriage of staphylococcus species in a separate substudy. Anterior nares and groin swabs were collected preoperatively, before the administration of prophylaxis.

### Outcomes

Patients were followed 180 days after the index surgery. Data were gathered by the site research personnel. The primary outcome was the occurrence of any surgical-site infection (superficial incisional, deep, or organ-space infection), assessed to 90 days after index surgery and defined according to the Centers for Disease Control and Prevention.[12] Secondary outcomes included superficial, deep, and organ-space infections assessed separately; deep or organ-space infections occurring between 90 to 180 days; surgical-site

infections in patients with methicillin-resistant staphylococcus species detected on the substudy perioperative swabs; and other health care–associated infections.[13-15] Safety outcomes included acute kidney injury,[16] hypersensitivity reactions to antimicrobials, and death from any cause at 180 days.

### STATISTICAL ANALYSIS

The statistical analysis plan is available with the protocol. The estimated sample size required was 2115 in each group, resulting in a total sample of 4230; this number was increased to 4450 to allow for a 5% loss to follow-up. A single interim analysis was planned and performed after 2000 patients had been enrolled. Efficacy stopping was based on O'Brien–Fleming stopping limits.[17,18] A second unplanned interim analysis was requested by the data and safety monitoring committee, which examined safety outcomes after 3000 patients had been enrolled.

The primary analysis of superiority was performed in the modified intention-to-treat population, which included all the patients who had undergone randomization and the assigned surgery. The Mantel–Haenszel test, stratified according to affected joint, was performed in the modified intention-to-treat population. Reported P values for the primary outcome were two-tailed, and a P value significance boundary of 0.0492, adjusted for the interim analysis, was applied.[17] Per-protocol analyses involved patients who completed the trial regimen (vancomycin or placebo) to which they were assigned and patients who completed the assigned regimen (vancomycin or placebo) and cefazolin prophylaxis. The safety population included all the patients who had undergone randomization and received a dose of vancomycin or placebo, including those who did not undergo surgery. The point estimates of effects for primary, secondary, and safety outcomes were reported with 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The trial statistician completed the analysis.

## RESULTS

### RECRUITMENT AND FOLLOW-UP

Recruitment began on January 15, 2019. Owing to disruptions to the supply of vancomycin or placebo and prolonged suspensions of elective surgery at participating centers as part of state and national responses to the coronavirus disease 2019 (Covid-19) pandemic and after discussion with the data and safety and monitoring committee, the trial was closed after 4362 patients (98.0% of planned 4450) had been enrolled. The last patient underwent randomization on October 29, 2021, and final follow-up was completed on May 13, 2022.

Of the 6592 patients who met eligibility criteria, 4362 agreed to participate and 4239 underwent randomization. A total of 4113 patients were included in the modified intention-to-treat population: 2044 who were assigned to receive vancomycin and 2069 who were assigned to receive placebo (Fig. 1). Follow-up data at 90 days were available for 4062 patients (98.8%): 2016 in the vancomycin group and 2046 in the placebo group. Cefazolin prophylaxis was administered in 4076 patients (99.1%): 2025 in the vancomycin group and 2051 in the placebo group.

A total of 3932 patients agreed to take part in the substudy of perioperative staphylococcal carriage, of whom 3748 were included in the modified intention-to-treat population. Perioperative *S. aureus* carriage was detected in 1089 of 3748 patients (29.1%), most of whom had carriage of methicillin-susceptible *S. aureus* (1069 of 3748 [28.5%]). Perioperative carriage of MRSA and methicillin-resistant *S. epidermidis* was detected in 24 of 3748 patients (0.6%) and 981 of 3748 patients (26.2%), respectively.

There were no clinically important between-group differences in the baseline characteristics (Table 1 and Table S2). The baseline characteristics of the patients were consistent with the epidemiologic data reported by the national and international registries and published epidemiologic studies (Table S3).

### PRIMARY OUTCOME

A surgical-site infection occurred in 163 of 4113 patients (4.0%). The majority of infections were superficial (148 of 163 [90.8%]). No patient with

**Figure 1 (facing page). Screening, Randomization, and Follow-up.**

Individual patients could be excluded from the per-protocol analyses for more than one reason. Details regarding the per-protocol analyses 1, 2, and 3 are provided in the Supplementary Appendix. MRSA denotes methicillin-resistant *Staphylococcus aureus*.

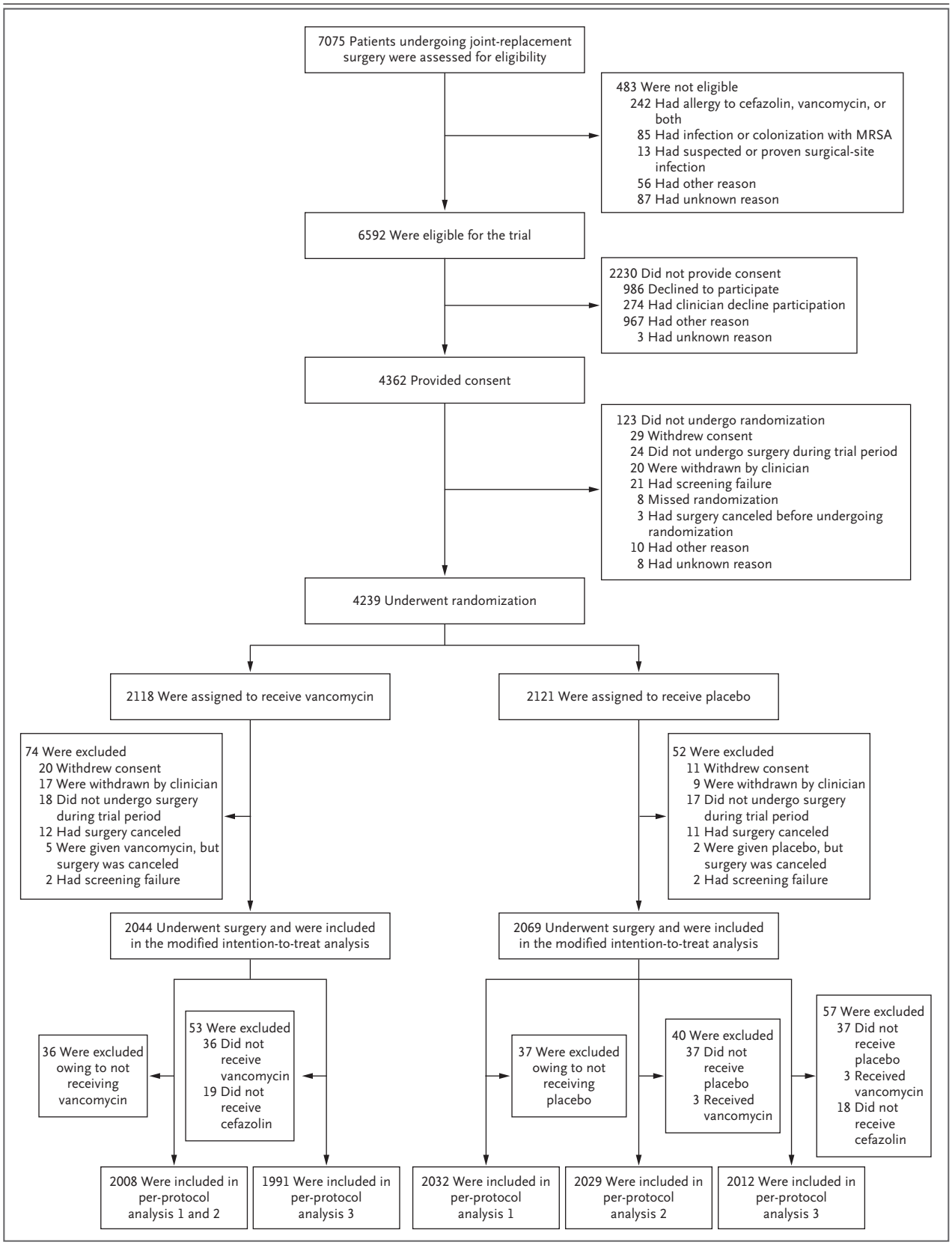

**Table 1. Demographic and Preoperative Characteristics in the Modified Intention-to-Treat Population.***

| Characteristic | Vancomycin (N=2044) | Placebo (N=2069) |
|---|---|---|
| Age — yr | 66.6±10.5 | 67.1±10.3 |
| Male sex — no. (%) | 982 (48.0) | 989 (47.8) |
| Affected joint — no. (%) | | |
| Knee | 1109 (54.3) | 1124 (54.3) |
| Hip | 920 (45.0) | 930 (44.9) |
| Shoulder | 15 (0.7) | 15 (0.7) |
| Operation type — no. (%) | | |
| Primary | 1837 (89.9) | 1868 (90.3) |
| Revision | 32 (1.6) | 29 (1.4) |
| Height — cm | 168.5±10.2 | 168.0±10.0 |
| Weight — kg | 87.4±19.6 | 87.1±19.3 |
| Body-mass index† | 30.7±6.5 | 30.8±6.3 |
| ASA class — no. (%)‡ | | |
| 1 | 188 (9.2) | 189 (9.1) |
| 2 | 1120 (54.8) | 1132 (54.7) |
| 3 | 710 (34.7) | 702 (33.9) |
| 4 | 25 (1.2) | 43 (2.1) |
| Missing data | 1 (<0.1) | 3 (0.1) |
| Diabetes — no. (%) | 259 (12.7) | 241 (11.6) |
| Immunosuppressed state — no. (%) | 122 (6.0) | 115 (5.6) |
| Perioperative carriage of staphylococcus species detected on substudy swabs — no./total no. (%)§ | | |
| *Staphylococcus aureus* | 548/1860 (29.5) | 541/1888 (28.7) |
| Methicillin-susceptible | 543/1860 (29.2) | 526/1888 (27.9) |
| Methicillin-resistant | 7/1860 (0.4) | 17/1888 (0.9) |
| Methicillin-resistant *S. epidermidis* | 498/1860 (26.8) | 483/1888 (25.6) |
| Time from cefazolin administration to first incision — min | 28.8±24.5 | 28.8±24.5 |
| Time from administration of vancomycin or placebo to first incision — min | 35.9±42.1 | 37.3±38.8 |

* Plus–minus values are means ±SD. The modified intention-to-treat population included all the patients who had undergone randomization and the assigned surgery. Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ American Society of Anesthesiologists (ASA) physical-status classes range from 1 to 5, with higher classes indicating more severe systemic disease.
§ A total of 3748 patients in the modified intention-to-treat population consented to take part in the substudy of perioperative staphylococcal carriage. Individual patients could contribute multiple events across multiple categories.

a deep or organ-space infection had a preceding superficial infection.

A surgical-site infection occurred in 91 of 2044 patients (4.5%) in the vancomycin group and in 72 of 2069 patients (3.5%) in the placebo group (relative risk, 1.28; 95% confidence interval [CI], 0.94 to 1.73; P=0.11) (Table 2). Among patients undergoing knee arthroplasty, a surgical-site infection occurred in 63 of 1109 patients (5.7%) in the vancomycin group and in 42 of 1124 patients (3.7%) in the placebo group (relative risk, 1.52; 95% CI, 1.04 to 2.23). In hip arthroplasty, infection occurred in 28 of 920 patients (3.0%) in the vancomycin group and in 29

of 930 patients (3.1%) in the placebo group (relative risk, 0.98; 95% CI, 0.59 to 1.63); in shoulder arthroplasty, infection occurred in 0 of 15 patients in the vancomycin group and in 1 of 15 patients (7%) in the placebo group. There was not a substantial difference in surgical-site infection between knee and hip procedures (relative risk, 1.14; 95% CI, 0.99 to 1.31) or between hip and shoulder procedures (relative risk, 0.97; 95% CI, 0.74 to 1.27); however, there was a greater difference between knee and shoulder procedures (relative risk, 1.21; 95% CI, 1.03 to 1.42).

Results of the per-protocol analysis, post hoc sensitivity analyses, and analyses that were adjusted for confounding factors are provided in Tables S4 through S10. Details of the treatment for and outcomes of surgical-site infections are provided in Tables S15 and S16.

### SECONDARY AND SAFETY OUTCOMES

The results of secondary and safety outcomes are shown in Table 2. The safety population comprised 4040 patients: 2010 in the vancomycin group and 2030 in the placebo group. Death occurred in 5 patients: 2 (0.1%) in the vancomycin group and 3 (0.1%) in the placebo group (relative risk, 0.67; 95% CI, 0.11 to 4.03) (Table S11). An adverse event was reported in 613 patients (303 [15.1%] in the vancomycin group and 310 [15.3%] in the placebo group); 70 patients had events that were deemed by the site primary investigator to be related to vancomycin or placebo (35 of 2010 [1.7%] in the vancomycin group and 35 of 2030 [1.7%] in the placebo group) (Table S12).

Acute kidney injury occurred in 42 of 2010 patients (2.1%) in the vancomycin group and in 74 of 2030 patients (3.6%) in the placebo group (relative risk, 0.57; 95% CI 0.39 to 0.83). Acute kidney injury was classified as stage 1 in 104 patients (2.6%), stage 2 in 5 patients (0.1%), and stage 3 in 7 patients (0.2%) (Table 2). A higher percentage of patients in the placebo group than in the vancomycin group had stage 2 or stage 3 acute kidney injury. Data on kidney injury were collected only during the index admission, and long-term outcomes are unknown. Hypersensitivity reactions occurred in 24 of 2010 patients (1.2%) in the vancomycin group and in 11 of 2030 patients (0.5%) in the placebo group (relative risk, 2.20; 95% CI, 1.08 to 4.49), including two episodes of severe immediate hypersensitivity in patients assigned to vancomycin.

### MICROBIOLOGIC RESULTS

A microbiologic specimen was collected in 64 of 163 confirmed surgical-site infections (39.3%): 37 of 91 (41%) in the vancomycin group and 27 of 72 (38%) in the placebo group. Among these specimens, one or more microorganisms were isolated in 51 patients (32 in the vancomycin group and 19 in the placebo group). *S. aureus* was isolated in 31 infections: 19 of 37 (51%) in the vancomycin group and 12 of 27 (44%) in the placebo group. All *S. aureus* isolates, except 1 in the vancomycin group, were methicillin-susceptible (Tables S13 and S14). Gram-negative bacilli were isolated in 10 of 37 infections (27%) in the vancomycin group and in 5 of 27 infections (19%) in the placebo group. In 19 of the 64 patients (30%) with an infection, the same organism was isolated in both the substudy of perioperative staphylococcal carriage and in the microbiologic culture (on the basis of the antimicrobial susceptibility of the species); all these organisms were methicillin-susceptible *S. aureus*. (Further studies examining the genomic relatedness of these isolates are under way.) No patient with methicillin-resistant staphylococcus species that was detected in the substudy of perioperative staphylococcal carriage went on to have an infection in which the same organism was isolated (Tables S17 and S18). A microorganism was isolated in 12 of 25 health care–associated infections (48%) (Tables S19 and S20).

### SUBGROUP ANALYSIS

The percentage of surgical-site infections at 90 days among male patients appeared higher in the vancomycin group (53 of 982 [5.4%]) than in the placebo group (30 of 989 [3.0%]) (relative risk, 1.78; 95% CI, 1.15 to 2.76); the difference was driven by those undergoing knee arthroplasty (31 of 510 [6.1%] in the vancomycin group and 16 of 524 [3.1%] in the placebo group; relative risk, 1.99; 95% CI, 1.10 to 3.60). There appeared to be a higher percentage of surgical-site infections among patients 65 to less than 70 years of age in the vancomycin group (23 of 387 patients [5.9%]) than in the placebo group (8 of 393 patients [2.0%]) (relative risk, 2.92; 95% CI, 1.32 to 6.45) (Fig. 2 and Table S21).

## DISCUSSION

In this pragmatic trial involving patients undergoing arthroplasty, the addition of vancomycin

**Table 2. Outcomes in the Modified Intention-to-Treat Population.**

| Outcome | Vancomycin (N = 2044) | Placebo (N = 2069) | Relative Risk (95% CI)* |
|---|---|---|---|
| | *no./total no. (%)* | | |
| **Primary** | | | |
| Surgical-site infection at 90 days | 91/2044 (4.5) | 72/2069 (3.5) | 1.28 (0.94–1.73)† |
| Knee | 63/1109 (5.7) | 42/1124 (3.7) | 1.52 (1.04–2.23) |
| Hip | 28/920 (3.0) | 29/930 (3.1) | 0.98 (0.59–1.63) |
| Shoulder | 0/15 | 1/15 (6.7) | — |
| **Secondary** | | | |
| Superficial surgical-site infection at 30 days | | | |
| Knee | 59/1109 (5.3) | 39/1124 (3.5) | 1.53 (1.03–2.28) |
| Hip | 25/920 (2.7) | 24/930 (2.6) | 1.05 (0.61–1.83) |
| Shoulder | 0/15 | 1/15 (6.7) | — |
| Pooled | 84/2044 (4.1) | 64/2069 (3.1) | 1.33 (0.97–1.83) |
| Deep surgical-site infection at 90 days | | | |
| Knee | 2/1109 (0.2) | 0/1124 | — |
| Hip | 2/920 (0.2) | 0/930 | — |
| Shoulder | 0/15 | 0/15 | — |
| Pooled | 4/2044 (0.2) | 0/2069 | — |
| Organ-space surgical-site infection at 90 days | | | |
| Knee | 2/1109 (0.2) | 3/1124 (0.3) | 0.68 (0.11–4.04) |
| Hip | 1/920 (0.1) | 5/930 (0.5) | 0.20 (0.02–1.73) |
| Shoulder | 0/15 | 0/15 | — |
| Pooled | 3/2044 (0.1) | 8/2069 (0.4) | 0.38 (0.10–1.43) |
| Deep or organ-space surgical-site infection at 90 days | | | |
| Knee | 4/1109 (0.4) | 3/1124 (0.3) | 1.35 (0.30–6.03) |
| Hip | 3/920 (0.3) | 5/930 (0.5) | 0.61 (0.15–2.53) |
| Shoulder | 0/15 | 0/15 | — |
| Pooled | 7/2044 (0.3) | 8/2069 (0.4) | 0.89 (0.32–2.44) |
| Surgical-site infection at 90 days according to carriage of methicillin-resistant staphylococcus species | | | |
| Methicillin-resistant staphylococcus carriage | 25/590 (4.2) | 16/577 (2.8) | 1.53 (0.82–2.83) |
| No methicillin-resistant staphylococcus carriage | 59/1270 (4.7) | 51/1311 (3.9) | 1.19 (0.83–1.72) |
| Surgical-site infection at 90–180 days | 2/2044 (0.1) | 1/2069 (<0.1) | 2.02 (0.18–22.32) |
| Other health care–associated infection | 11/2044 (0.5) | 14/2069 (0.7) | 0.80 (0.36–1.75) |
| **Safety** | | | |
| Death from any cause at 180 days | 2/2010 (0.1) | 3/2030 (0.1) | 0.67 (0.11–4.03) |
| Acute kidney injury‡ | 42/2010 (2.1) | 74/2030 (3.6) | 0.57 (0.39–0.83) |
| Stage 1 | 41/2010 (2.0) | 63/2030 (3.1) | 0.66 (0.45–0.97) |
| Stage 2 | 1/2010 (<0.1) | 4/2030 (0.2) | 0.25 (0.03–2.26) |
| Stage 3 | 0/2010 | 7/2030 (0.3)§ | — |
| Hypersensitivity reaction | 24/2010 (1.2) | 11/2030 (0.5) | 2.20 (1.08–4.49) |
| Mild | 19/2010 (0.9) | 11/2030 (0.5) | 1.74 (0.83–3.66) |
| Moderate | 5/2010 (0.2) | 0/2030 | — |

**Table 2. (Continued.)**

* Relative risk (vancomycin group vs. placebo group) was calculated by means of the Mantel–Haenszel test. The 95% confidence intervals have not been adjusted for multiplicity.
† P=0.11. The P value significance boundary was 0.0492, which allowed for multiplicity of interim analyses.
‡ Stage 1 was defined as an increase in the serum creatinine level to 1.5 to 1.9 times the baseline value or an increase in the serum creatinine level by 0.3 mg per deciliter or more. Stage 2 was defined as an increase in the serum creatinine level to 2.0 to 2.9 times the baseline value. Stage 3 was defined as an increase in the serum creatinine level to 3.0 times the baseline value, an increase in the serum creatinine level to 4.0 mg per deciliter or more, or the initiation of renal-replacement therapy.
§ One patient assigned to the placebo group with stage 3 acute kidney injury began receiving renal-replacement therapy after a cardiac arrest in the postoperative period.

was not superior to surgical antimicrobial prophylaxis with cefazolin alone. The results of subgroup analyses suggested a possible increased risk of surgical-site infection in knee arthroplasty with the addition of vancomycin on secondary analysis. Vancomycin prophylaxis was associated with an increased risk of hypersensitivity reactions and a decreased risk of acute kidney injury.

Previous observational studies examining the addition of a glycopeptide antimicrobial to beta-lactam surgical antimicrobial prophylaxis in arthroplasty have shown mixed results, ranging from no change[19-22] to a reduced incidence of surgical-site infection.[10,23-25] In those studies showing a reduction in infection, teicoplanin was the glycopeptide administered,[10,23] which raises the possibility that glycopeptide selection may influence outcomes.

Methicillin-susceptible *S. aureus* was the most common pathogen detected in our trial. A previous randomized, controlled trial[26] and large cohort studies[27,28] comparing single-agent beta-lactam prophylaxis with glycopeptide-based prophylaxis have shown an increased incidence of methicillin-susceptible *S. aureus* among patients receiving glycopeptides. This increased incidence has been attributed to subtherapeutic tissue levels of glycopeptides at the operative site[27]; however, this supposition does not explain the findings of our trial. We postulate that our findings may reflect antimicrobial pressures with selection of more virulent *S. aureus* variants or gram-negative bacteria in patients receiving combination prophylaxis. Further studies to investigate this hypothesis are under way with isolates collected during our trial.

The overall prevalence of MRSA carriage preoperatively in our cohort was low but consistent with that in other cohort studies.[29] This low prevalence of MRSA was partly due to the exclusion of patients with known infection or colonization with MRSA, although such patients represented only a small percentage of the population (85 of 7075 screened patients [1.2%] met this exclusion criteria). Cohort studies have suggested that infections caused by MRSA may be due to hospital acquisition rather than preoperative or community colonization.[29]

Previous observational studies often involved cohorts with a high incidence of MRSA infection.[10,23,25,30] The addition of glycopeptide prophylaxis in these studies was implemented in concert with other infection-prevention approaches, such as screening and decolonization; therefore, the reported reduction in infections may be related to the introduction of the bundle rather than combination prophylaxis in isolation.[24,31,32]

Current guidelines recommend a weight-based dose of 15 mg per kilogram of body weight for vancomycin.[5,7] Cardiothoracic and orthopedic surgery studies have shown an association between vancomycin dose and surgical-site infections, particularly when a fixed 1-g dose of vancomycin was administered.[33,34] For pragmatic reasons, we opted for a dose of 1.5 g of vancomycin, which (on the basis of the mean weight of the patients in our trial) aligned with the recommended weight-based dose for most trial patients. Guidelines recommend that vancomycin be administered within 120 minutes before surgical incision[5-7]; however, a previous observational study involving patients undergoing arthroplasty suggested that vancomycin should be administered 45 minutes before incision.[21] Although dose and timing issues may explain the lack of efficacy that we observed, it does not explain the increased risk of infection observed among patients undergoing knee arthroplasty.

We observed a lower risk of acute kidney injury among patients receiving vancomycin than

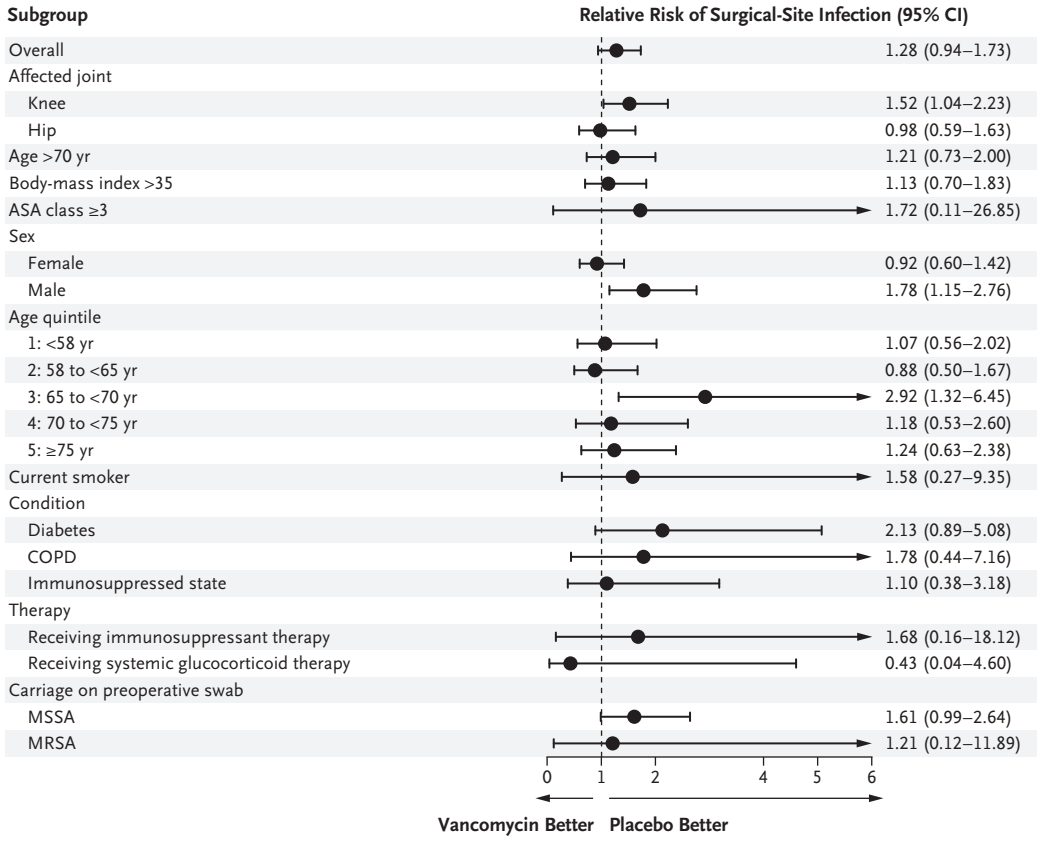


**Figure 2. Subgroup Analyses of the Primary Outcome in the Modified Intention-to-Treat Population.**

The primary outcome was surgical-site infection within 90 days after surgery. The reference group is patients assigned to receive placebo. The widths of the confidence intervals for subgroup analyses were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The body-mass index is the weight in kilograms divided by the square of the height in meters. American Society of Anesthesiologists (ASA) physical-status classes range from 1 to 5, with higher classes indicating more severe systemic disease. Analyses of MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA) carriage involved patients who consented to take part in the substudy of perioperative staphylococcal carriage. All prespecified subgroups are shown; in addition, chronic obstructive pulmonary disease (COPD), immunosuppressed state, and immunosuppressant therapy were included in the subgroup analysis post hoc.

among those receiving placebo. The acute kidney injury was graded as stage 1 in most cases (89.7%),[16] and longer-term outcomes were not collected. Data from observational studies examining the risk of acute kidney injury with combination glycopeptide and beta-lactam antimicrobial prophylaxis in arthroplasty are heterogenous.[20,21,24,35] In those studies showing an increased incidence, vancomycin was frequently continued for up to 24 hours postoperatively.[35] This difference in the duration of postoperative antimicrobial treatment may explain the variation in observational studies; however, it does not explain the increased incidence of acute kidney injury observed in the placebo group in our trial.

Our trial has several limitations. The trial faced disruptions due to the Covid-19 pandemic, which culminated in early closure before the planned enrollment target had been reached. The trial involved patients with a low prevalence of colonization with MRSA. Current Australian guidelines recommend the addition of vancomycin in patients with known infection or coloni-

zation with MRSA; therefore, these patients were not eligible for inclusion.[5] Thus, our results cannot be extrapolated to these patients. In addition, other groups that are considered to be at higher risk for infection from resistant staphylococcus species, such as patients undergoing revision surgery, made up only a small percentage (<2%) of the cohort. Similarly, only a small cohort of patients undergoing shoulder arthroplasty were included. Among eligible patients, the treating clinician declined trial participation in 294 of 6592 (4.5%), which raises the possibility of selection bias (the reasons for declining participation were not documented). Finally, most surgical-site infections observed were superficial. Although the effects and costs of deep and organ-space infections are well recognized, the prevention of superficial infections is of clinical importance because superficial infections are associated with subsequent organ-space infections,[36,37] lead to increased health care costs,[36] and have a detrimental effect on the patient.

A strength of this trial was the pragmatic, placebo-controlled design. Another strength was the inclusion of a variety of surgical centers, including university, metropolitan, and regional hospitals.

In this pragmatic, randomized trial involving adult patients undergoing arthroplasty who had a low prevalence of MRSA colonization, the addition of vancomycin was not superior to surgical antimicrobial prophylaxis with cefazolin.

Supported by a grant (APP1120331) from the Australian National Health and Medical Research Council.

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.

We thank all the orthopedic surgeons, anesthesiologists, clinicians, nursing staff, pharmacy staff, patients, and families at the contributing trial sites for their support of and involvement in the trial.

## APPENDIX

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