Clinical Trials in ID with a Side of Statistics

Radhika S. Polisetty, PharmD, BCIDP, AAHIVP, FIDSA
Associate Professor, Midwestern University College of Pharmacy
Senior Infectious Diseases Specialist, NM Centra DuPage Hospital

Jen Phillips, PharmD, BCPS, FCCP, FASHP
Clinical Professor, Director, Drug Information Group
University of Illinois, Chicago

March 16, 2024

1

Conflicts of Interest

- Jen Phillips has no conflicts of interest to disclose.
- Radhika Polisetty has no conflicts of interest to disclose.

2

Learning Objectives

1. List strategies to keep up-to-date with recent clinical updates in infectious diseases (ID).
2. Describe recently published high-impact trials in ID.
3. Explain research methods and statistical tests utilized in clinical trials.

3

Strategies to keep up-to-date with ID Topics

- Local resources
  - Your hospital, clinic or health-system resources or website
    - For example- www.adsp.nm.org
- State organizations such as Northern Illinois Society of Health-System Pharmacists (NISHP) and Illinois Council of Health System Pharmacists (ICHP)
  - Several CE programs (in-person and virtual) provide updates on vaccines, new therapies and updates.
- National Pharmacy and Medical Organizations
  - Infectious Diseases Society of America (IDSA) Guidelines- https://www.idsociety.org/practice-guideline/practice-guidelines/
  - Society of Infectious Diseases Pharmacists (SIDP)- https://sidp.org
  - Americal College of Clinical Pharmacists- https://www.accp.com/
  - American Society of Health-System Pharmacists- https://www.ashp.org/pharmacy-practice/policy-positions-and-guidelines

4

Strategies to keep up-to-state

- Not but not the least - SOCIAL MEDIA can be a useful tool!!
- Follow your state, local and pharmacy organization on Linked-In, X (formerly Twitter) or Instagram
  - You can also subscribe for email alerts for drug shortages or guidelines
- You can also follow various federal agencies for latest news and alerts
  - Centers for Diseases Control and Prevention (CDC) - https://www.cdc.gov/index.htm
  - National Institute of Health- https://www.nih.gov/
  - Food and Drug Administration- https://www.fda.gov/
  - Illinois Department of Health (IDPH)- https://dph.illinois.gov/

5

Roadmap: Topics to be Discussed

Clinical Topics

- RSV
- Rezafungin
- Allergy Desensitization
- ACORN
- Trial design/analysis elements in each

6

Respiratory Syncytial Virus (RSV) Treatment

ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D., Manuel Baca Cots, M.D., Miroslava Bosheva, M.D., Shabir A. Madhi, Ph.D., William J. Muller, Ph.D., Heather J. Zar, Ph.D., Dennis Brooks, M.D., Amy Greenham, M.Sc., Ulrika Wählby Hamrén, Ph.D., Vaishali S. Mankad, M.D., et al., for the MELODY Study Group*

N Engl J Med 2022; 386:837-846

7

Respiratory Syncytial Virus Treatment

- Nirsevimab is a monoclonal antibody approved in Europe for the treatment of RSV related lower respiratory tract illness.
- MELODY trial is a phase 3 trial designed to assess the efficacy of nirsevimab in infants born at gestational age of at least 35 weeks
- 3019 pts were randomized in a 2:1 ratio as follows
  - 50 mg for babies <5 kg
  - 100 mg for babies > 5 kg

  } Treatment arm with 1988 patients
  - Placebo arm with 996 patients
- Primary endpoint was medically associated RSV related lower respiratory tract infections (LRTI), rate of hospitalizations and severe medically associated RSV related LRTIs

N Engl J Med 2022; 386:837-846

8

Efficacy and Safety endpoints

End Point	Placebo (N=1003)	Nirsevimab (N=2009)	Efficacy (95% CI)
	no. of participants with event (%)		
Medically attended RSV-associated LRTI	54 (5.4)	24 (1.2)	76.4 (62.3–85.2)
Hospitalization for RSV-associated LRTI	20 (2.0)	9 (0.4)	76.8 (49.4–89.4)
Very severe medically attended RSV-associated LRTI	17 (1.7)	7 (0.3)	78.6 (48.8–91.0)

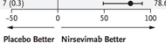


Figure 1. Incidence of Medically Attended Respiratory Syncytial Virus (RSV)–Associated Lower Respiratory Tract Infection (LRTI) through 150 Days after Injection and Efficacy of Nirsevimab as Compared with Placebo.

Very severe medically attended RSV-associated LRTI was defined as infection for which hospitalization and supplemental oxygen or intravenous fluids were warranted. Data are from the intention-to-treat population, which consisted of all infants who had undergone randomization.

Figure 1; N Engl J Med 2022; 386:837-846

- 1.5% of patients in the placebo arm and 1.3% of patients in the treatment arm had adverse effects
- NNT to prevent hospitalization from any cause was 53.1
- 57 days of hospitalization was averted for every 1000 infants who received the drug.

9

Updated recommendations for RSV vaccines

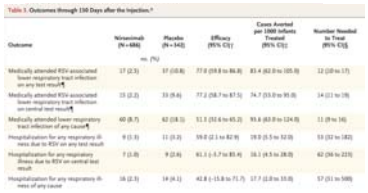
- RSV Vaccines for infants
  - The CDC recommends one dose of nirsevimab for all infants younger than 8 months, born during, or entering, their first RSV season, which is typically fall through spring.
  - For infants who are 8 and 19 months old who are at increased risk of severe RSV disease—such as children who are severely immunocompromised—a dose is recommended in their second season
- RSV vaccine (Arexvy® and ABRYSVO®) for adults
  - Any adult >60 years of age
  - Pregnant people from week 32 through week 36 of pregnancy for the prevention of RSV disease in infants under 6 months of age
  - Arexvy (GSK product) vaccine and contains an adjuvent
  - Abrysvo (Pfizer product) and is a bivalent vaccine that does not contain an adjuvent

Centers for Disease Control and Prevention. RSV Vaccine Information. https://www.cdc.gov/vaccines/vpd/rsv/index.html Accessed Feb 17, 2024

10

Trial Design/Analysis Considerations

- Number Needed to Treat
  - For nominal variables
  - NNT = 1/ARR
    - ARR= absolute risk reduction
    - Control rate – Event rate
    - 1/(0.108-0.025)
      - OR -
    - 100/(10.8-2.5)
- Active learning
  - Calculate NNT for 1-2 more outcomes in the table



N Engl J Med 2022; 386:837-846

11

Trial Design/Analysis Considerations

- Unequal allocation
  - Participants were assigned to treatment in a 2:1 ratio

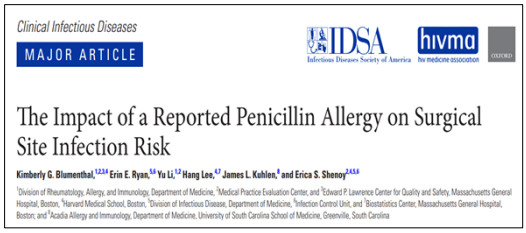
Pros	Cons
Improves recruitment	Requires larger sample sizes to achieve statistical power
Advantageous in early, exploratory trials (e.g., confirm dose)	More expensive to conduct
Enhances ability to detect safety signals	
Cost	

- What are some reasons for using 2:1 allocation in this trial?

Sjzwtqtl~3@7569%Dfs%<@7-6.?<2>

12

Literature review- Penicillin Allergies



Clinical Infectious Diseases

MAJOR ARTICLE

The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk

Kimberly G. Blumenthal,[1,2,3,4] Erin E. Ryan,[5,6] Yu Li,[1,2] Hang Lee,[6,7] James L. Kuhlen,[8] and Erica S. Shenoy[2,4,5,6]

[1]Division of Rheumatology, Allergy, and Immunology, Department of Medicine, [2]Medical Practice Evaluation Center, and [3]Edward P. Lawrence Center for Quality and Safety, Massachusetts General Hospital, Boston, [4]Harvard Medical School, Boston, [5]Division of Infectious Disease, Department of Medicine, [6]Infection Control Unit, and [7]Biostatistics Center, Massachusetts General Hospital, Boston, and [8]Acadia Allergy and Immunology, Department of Medicine, University of South Carolina School of Medicine, Greenville, South Carolina

Clinical Infectious Diseases 2018; 66 (3), 329-326

13

Impact of reported PCN allergies on SSIs

- Retrospective cohort study of surgical patients at Massachusetts General Hospital-
- Included patients undergoing various surgeries (knee arthroplasty, hysterectomy, colon surgery, and coronary artery bypass grafting patients) from 2010 to 2014
- Pts with penicillin (PCN) allergies were compared to those who did not have reported allergies.
- Primary outcome was the presence of a surgical site infection (SSI)

Clinical Infectious Diseases 2018; 66 (3), 329-326

14

Results

- 8385 patients underwent over 9000 procedures
  - 922 (11%) reported a PCN allergy and 241 (2.7 %) had an SSI
  - Pts with a reported PCN allergy have an increased Odds ratio (1.51) of an SSI
  - Increased SSI were attributed to receipt of alternative antibiotics (clindamycin, vancomycin and gentamicin)
- Study concluded that pts with a PCN allergy have a 50% increased odds of having an SSI due to receipt of second line therapy.

15

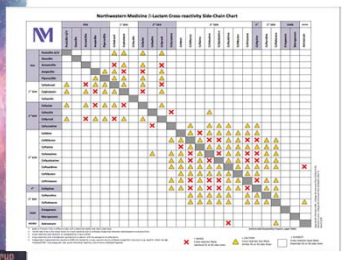
Literature Review- Allergy Assessment

- Around 10% of the US population has reported allergies to penicillin (PCN)
- However, clinically significant IgE-mediated or T lymphocyte–mediated penicillin hypersensitivity is less common and around < 5%
- According to the CDC, less than 1% of the population is truly allergic to PCNs and 80% of pts with IgE-mediated PCN allergy do not have a reaction after 10 years.
- Furthermore, cross-reactivity between PCN and cephalosporin drugs occurs in about 2% of cases
- Several studies have shown the using alternative antibiotics leads to
  - Higher rates of treatment failure
  - Serious adverse effects such *Clostridium difficile*
  - Higher incidence of vancomycin-resistant enterococci (VRE) and MRSA
  - Longer hospital stays and higher healthcare costs

https://www.cdc.gov/antibiotic-use/clinicians/Penicillin-Allergy.html. Accessed October 17, 2023.
https://adsp.nm.org/allergy-resources.html. Accessed October 20, 2023
Jeffres MN, et al. J Allergy Clin Immunol. 2016;137(4):1148–1153.

16

Cross reactivity Chart



Risk of cross- reactivity with similar side chain:
•PCN-CEPH ≈ 20%
•CEPH-CEPH ≈ 40%

Similar side-chains
• Penicillin, ampicillin, amoxicillin, and cephalexin
• Penicillin and cefoxitin
• Cefotaxime, ceftriaxone, cefuroxime, ceftazidime, cefepime
• Ceftazidime and aztreonam

***Cefazolin – no side chain similarities**

https://adsp.nm.org/allergy-resources.html. Accessed Fevb 15, 2024
Romano et al. *Curr Allergy Asthma Rep*. 2016;16:24

17

So, what should you do about those allergies?

Type of allergic reaction	Course of action
Low-risk histories include patients having isolated nonallergic symptoms, such as GI symptoms, childhood reactions, unknown reactions.	Direct amoxicillin challenge
A moderate-risk history includes urticaria (hives) or other pruritic rashes and reactions (IgE-mediated reactions)	Penicillin skin testing, which carries a negative predictive value of 95%-100%, when combined with amoxicillin challenge.
A high-risk history includes patients who have had anaphylaxis, positive PCN skin testing, recurrent PCN reactions, or hypersensitivities to multiple β-lactam antibiotics.	Avoid use and recommend alternative options and/or Allergy consult

Mabilat C. et al. *JAC Antimicrob Resist*. 2022 Nov 19;4(6):dlac116

18

Trial Design Considerations

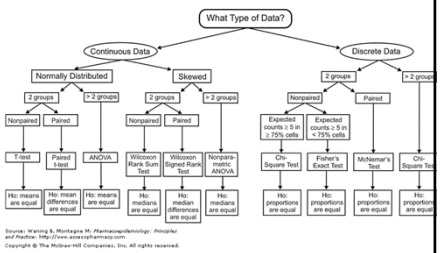
- Cohort Study vs. RCT
  - In RCTs, researcher "controls" allocation and outcome measurements
    - Experimental model
  - Cohort studies are observational
    - "Natural course" of the outcome / disease
  - RCTs are considered more scientifically "robust"
- Guiding rule: Always choose the highest quality of evidence ***available***

- Why did the investigators choose a retrospective cohort design for this study?

19

Trial Design/Considerations

- Common Statistical Tests
  - Type of data
    - Nominal
    - Ordinal
    - Continuous
  - Paired vs. unpaired
  - Normal vs. skewed
- Which test to use?
  - Age (Median, IQR)
  - Sex
  - % having diabetes
  - Procedure duration
  - LOS
  - % trauma patients



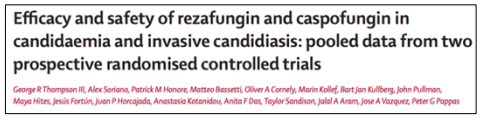
20

Literature review - Rezafungin

Clinical Infectious Diseases
MAJOR ARTICLE

Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial

Clinical Infectious Diseases 2021; 73(11), e3647-55



Efficacy and safety of rezafungin and caspofungin in candidaemia and invasive candidiasis: pooled data from two prospective randomised controlled trials

Lancet 2023 Jan 7;401(10370):49-59

21

Rezafungin - STRIVE and RESTORE trials

- New US Food and Drug Administration (FDA) approved, long-acting echinocandin to treat invasive candiasis (IC) and candidemia
- STRIVE trial (2022) was a multi-center, double-blind, double-dummy, randomized phase 2 trial conducted at 44 centers in 10 countries.
- ReSTORE (2023) was a multi-center, double-blind, double-dummy, randomized phase 3 trial conducted at 66 tertiary care centers in 15 countries.
- Both trials had 2 treatment arms- Rez 400 mg on day 1, 200 mg Day 8 (weekly) OR Caspofungin 70 mg LD, 50 mg for 21 or 28 days

CID 2021; 73(11), e3647-55
Lancet 2023 Jan 7;401(10370):49-59

22

Study Results

- Efficacy Endpoints
  - Primary efficacy endpoint was day 30 all-cause mortality (tested for non-inferiority with a pre-specified margin of 20%).
  - Secondary efficacy endpoint was mycological response. Safety was also evaluated.
- Day 30 all-cause mortality rates were comparable between groups
  - 19% [26/139] for the rezafungin group and 19% [30/155] for the caspofungin group [Diff −1·5% [95% CI −10·7 to 7·7]
  - Mycological eradication occurred by day 5 in 102 (73%) of 139 rezafungin patients and 100 (65%) of 155 caspofungin patients (weighted treatment difference 10% [95% CI −0·3 to 20·4])
- Conclusion- Rezafungin was non-inferior to caspofungin for all-cause mortality, with a potential early treatment benefit

Lancet 2023 Jan 7;401(10370):49-59

23

Study results

	Rezafungin (n=139)	Caspofungin (n=155)	Treatment difference (95% CI)
Primary pooled efficacy endpoint: day 30 all-cause mortality			
Deceased or unknown survival status	26 (19%)	30 (19%)	–
Known deceased	21 (15%)	25 (16%)	–
Unknown survival status	5 (4%)	5 (3%)	–
Alive	113 (81%)	125 (81%)	–
Death rate*	–	–	-1·5% (-10·7 to 7·7)
Secondary efficacy endpoints			
Day 5 mycological response			
Eradication	102 (73%)	100 (65%)	–
Failure or indeterminate	37 (27%)	55 (35%)	–
Eradication rate*	–	–	10·0% (-0·3 to 20·4)
Day 14 mycological response			
Eradication	100 (72%)	106 (68%)	–
Failure or indeterminate	39 (28%)	49 (32%)	–
Eradication rate*	–	–	4·3% (-6·2 to 14·7)

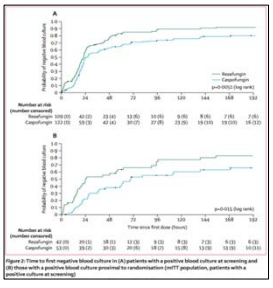
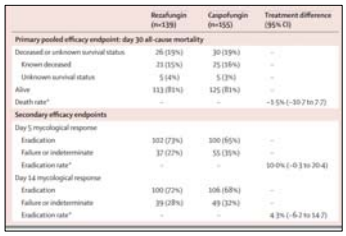


Figure 2: Time to first negative blood culture in (A) patients with a positive blood culture at screening and (B) those with a positive blood culture proximal to randomisation (mITT population, patients with a positive culture at screening)

24

Trial Design/Analysis Considerations

- Confidence intervals
  - Should not contain the number that means "no difference" within the range
    - "1" for ratios
      - If Ra/Rb = 1, then….. Ra = Rb is a possibility!
    - "0" for differences
      - If Xa – Xb = 0, then…. Xa=Xb is a possibility!
  - Strategy:
    - Orient yourself to the endpoint used
    - Ask: "Is it fraction or subtraction?"
    - Interpret accordingly.
  - Let's apply
    - Interpret the following variables:
      - Death rate difference
      - Eradication rate difference



	Rezafungin (n=139)	Caspofungin (n=155)	Treatment difference (95% CI)
Primary pooled efficacy endpoint: day 30 all-cause mortality			
Deceased or unknown survival status	26 (19%)	30 (19%)	–
Known deceased	21 (15%)	25 (16%)	–
Unknown survival status	5 (4%)	5 (3%)	–
Alive	113 (81%)	125 (81%)	–
Death rate*	–	–	-1·5% (-10·7 to 7·7)
Secondary efficacy endpoints			
Day 5 mycological response			
Eradication	102 (73%)	100 (65%)	–
Failure or indeterminate	37 (27%)	55 (35%)	–
Eradication rate*	–	–	10·0% (-0·1 to 20·4)
Day 14 mycological response			
Eradication	100 (72%)	106 (68%)	–
Failure or indeterminate	39 (28%)	49 (32%)	–
Eradication rate*	–	–	4·3% (-6·2 to 14·7)

Lancet Infect Dis. Published online November 23, 2023

25

Trial Design/Analysis Considerations

- Kaplan Meier Plot Tips
  - Orient yourself to the graph
    - Units of measurement for axes
    - Shape of curve
    - When do the curves separate
    - Tick marks indicate censored data
    - The "tail" end is less reliable
  - Understand the statistics behind the data
    - Log-rank test tells if curves are "statistically different"
    - Cox proportional hazards compares the rate of having an event in one curve compared to the other
- Where do these curves separate?

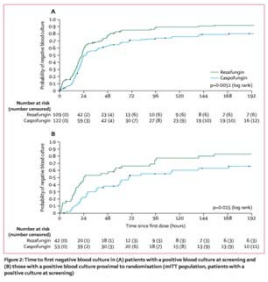


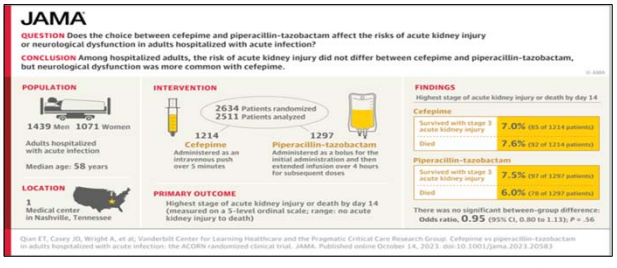
Figure 2: Time to first negative blood culture in (A) patients with a positive blood culture at screening and (B) those with a positive blood culture proximal to randomisation (mITT population, patients with a positive culture at screening)

Mjfi%EjhpQcwL3D565%Qju898-8.2B62:
Lancet Infect Dis. Published online November 23, 2023

26

Literature Update

Clinical Controversy- Risk of AKI with pip/tazo versus cefepime hospitalized patients



JAMA

QUESTION Does the choice between cefepime and piperacillin-tazobactam affect the risks of acute kidney injury or neurological dysfunction in adults hospitalized with acute infection?

CONCLUSION Among hospitalized adults, the risk of acute kidney injury did not differ between cefepime and piperacillin-tazobactam, but neurological dysfunction was more common with cefepime.

POPULATION
1439 Men 1071 Women
Adults hospitalized with acute infection
Median age: 58 years

LOCATION
1 Medical center in Nashville, Tennessee

INTERVENTION
2634 Patients randomized
2511 Patients analyzed
1214 Cefepime — Administered as an intravenous push over 5 minutes
1297 Piperacillin-tazobactam — Administered as a bolus for the initial administration and then extended infusion over 4 hours for subsequent doses

PRIMARY OUTCOME
Highest stage of acute kidney injury or death by day 14 (measured on a 5-level ordinal scale; range: no acute kidney injury to death)

FINDINGS
Highest stage of acute kidney injury or death by day 14

Cefepime	
Survived with stage 3 acute kidney injury	7.0% (85 of 1214 patients)
Died	7.6% (92 of 1214 patients)
Piperacillin-tazobactam	
Survived with stage 3 acute kidney injury	7.5% (97 of 1297 patients)
Died	6.0% (78 of 1297 patients)

There was no significant between-group difference; Odds ratio, 0.95 (95% CI, 0.80 to 1.13); $P = .56$

Qian ET, Casey JD, Wright A, et al; Vanderbilt Center for Learning Healthcare and the Pragmatic Critical Care Research Group. Cefepime vs piperacillin-tazobactam in adults hospitalized with acute infection: the ACORN randomized clinical trial. JAMA. Published online October 14, 2023. doi:10.1001/jama.2023.20583

Qian ET, et al. The ACORN Randomized Clinical Trial. JAMA. 2023 Oct 14:e2320583. doi: 10.1001/jama.2023.20583.

27

ACORN study limitations/ caveats

- Study concluded that there was no association between receipt of cefepime or TZP and the primary outcome of AKI or death by day 14, despite the fact that >75% of the population received concomitant VAN.
- There are concerns about using Serum creatinine (SCr) as a marker for AKI
- There was an imbalance in the baseline characteristics of patients in the two arms- more patients in the cefepime arm were admitted to the ICU than TZP.
- Further studies with longer duration of treatment and use of markers other than Scr are warranted to truly assess the question of nephrotoxicity with these antibiotics.

Open Forum Infectious Diseases, Volume 11, Issue 1, January 2024,

28

Trial Design/Analysis Considerations

- Study group lauded for the following:
  - Recruitment via EMR
    - CDS screen identified eligible patients
  - Clinically relevant outcomes
  - Increased external validity
    - Very broad inclusion/exclusion criteria

Patient Population

Adults (≥18 years of age) in the ED or medical ICU for whom a clinician initiated an order for cefepime or piperacillin-tazobactam within 12 hours of presentation to the hospital were eligible. Patients were excluded if they had an allergy to cephalosporins or penicillins, had received more than 1 dose of an antipseudomonal cephalosporin or penicillin within the previous 7 days (patients who had received other antipseudomonal antibiotics were eligible), were incarcerated, or if the treating clinician determined that 1 of the 2 drugs represented a better treatment option for that patient. An electronic health record tool screened all patients for eligibility and an automated alert within the electronic order entry system confirmed patient eligibility with clinicians.

JAMA. 2023;330(16):1557-1567

29

Trial Design/Analysis Considerations

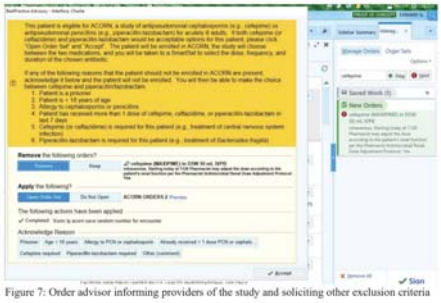


Figure 7: Order advisor informing providers of the study and soliciting other exclusion criteria

BMJ Open. 2023;13(3):e066995

30

Trial Design/Analysis Considerations

- Regression Models
  - Probability of an outcome occurring based on predictor variable(s)
    - Logistic: binary outcome
    - Linear: continuous outcome
  - Odds ratios (OR) used to quantify relationship between predictor and outcome
  - Interpret confidence intervals as noted before!
- Primary outcome: Do cefepime and piperacillin/tazobactam differ?

Table 2. Primary, Secondary, and Exploratory Outcomes

	Cefepime (n = 1214)	Piperacillin-tazobactam (n = 1297)	Between-group difference expressed as RD or OR (95% CI)*
Primary outcome			
Acute kidney injury or death by day 14, No. (%)			OR, 0.95 (0.80 to 1.13)
No stage (survived)	910 (75.0)	952 (73.4)	
Stage 1 (survived)	86 (7.1)	100 (7.7)	
Stage 2 (survived)	41 (3.4)	70 (5.4)	
Stage 3 (survived)	85 (7.0)	97 (7.5)	
Stage 4 (died)	92 (7.6)	78 (6.0)	
Secondary outcomes			
Major adverse kidney events at day 14, No. (%)†	124 (10.2)	114 (8.8)	RD, 1.4 (−1.0 to 3.8)
Death, No. (%)	92 (7.6)	78 (6.0)	RD, 1.6 (−0.5 to 3.6)

JAMA. 2023;330(16):1557-1567

31

Thank you for listening!

Questions?

32