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In Reply: Systematic Antimicrobial Prophylaxis and Antimicrobial-Coated External Ventricular Drain Catheters for Preventing Ventriculostomy-Related Infections: A Meta-Analysis of 5242 Cases

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Cover Letter

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Dear Dr. Oyesiku,

On behalf of the authors, I would like to thank you for the opportunity to submit this response regarding our manuscript, "Systematic Antimicrobial Prophylaxis and Antimicrobial-Coated External Ventricular Drain Catheters for Preventing Ventriculostomy-Related Infections: A Meta-Analysis of 5242 Cases". We have carefully read through and addressed all the points brought to our attention in the letter to the editor.

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I, Isaac Yang, would like to personally thank you in advance allowing us to provide a response to the letter to the editor. We hope that we have addressed all point thoroughly and look forward to hearing back from your editorial office.

Sincerely,

Isaac Yang, MD

In Reply: Systematic Antimicrobial Prophylaxis and Antimicrobial-Coated External Ventricular Drain Catheters for Preventing Ventriculostomy-Related Infections: A Meta-Analysis of 5242 Cases

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To the Editor:

We appreciate the recent letter regarding our recent article. This letter points out an issue in our reporting of ventriculostomy-related infection (VRI) outcomes observed in the prospective study by Murphy *et al*.[1] Namely, Murphy *et al*. found no difference in the incidence of ventriculitis between patients receiving systemic antibiotic prophylaxis relative to peri-procedural systemic prophylaxis alone in the setting of EVD placement with antibiotic-coated EVD catheters (ac-EVD). [1]

The authors responding to our article correctly point out that the data reported in Figure 1A[2] of our original article was mistaken, and we are greatly appreciative that this issue was brought to our attention. Indeed, the VRI incidence data for Murphy *et al*. reported in our original paper were mistaken in that the treatment and control arms were erroneously switched.[1,2] Additionally, the numbers reported in Figure 1A for the study in question correspond to reported cases of nosocomial infections (i.e., ventilator-associated pneumonia or bloodstream infection), and do not reflect incidence of ventriculitis. As such, these data did not meet our criteria for study inclusion and should not have been included in our meta-analysis.

The Murphy *et al*. study reported an incidence density of 0.54 ventriculitis cases per 1000 catheter days for ac-EVD + peri-procedural systemic antibiotics, and 1.35 ventriculitis cases per 1000 catheter days for ac-EVD + extended systemic antibiotics ($P = 0.26$). These results were in contrast to three other studies included in our meta-analysis, which collectively yielded a significant reduction in VRI incidence with ac-EVD + extended systemic prophylaxis versus ac-EVD + peri-procedural prophylaxis alone. However, regarding the ventriculitis incidence data reported by Murphy *et al*., the only reported data we could corroborate was reported in terms of incidence density as above. In terms of the raw number of ventriculitis cases, 8 total cases were reported among the 866 patients spanning both study arms. Murphy *et al*. reported a ventriculitis rate of 1.1% among 410 patients receiving ac-EVD + extended systemic antibiotics, and 0.4% among 135 patients receiving ac-EVD + peri-procedural systemic antibiotics.[1] Our meta-analysis requires binomial data consisting of integer numbers of ventriculitis cases and total patients for each study arm. We were unable to calculate integer numbers of cases from the total number of

patients in either study arm that would yield the reported ventriculitis rates (1.1% and 0.4%), and as such were unable to include ventriculitis outcomes from this study in the revised analysis we provide below.

To assess the impact of the above on our published meta-analysis, we report corrected data showing the core meta-analytic results after exclusion of the ineligible data from the Murphy *et al*. study. **Figure 1** demonstrates that after exclusion of the Murphy *et al.* study, the relative risk remains significantly in favor of extended systemic prophylaxis using either a fixed- or random-effects model for the remaining studies.[1] **Figure 2** displays corrected funnel plots for the corrected set of studies. As before, assessment for study bias using Egger's test was insignificant for studies of extended systemic prophylaxis, or for the pooled set of reviewed studies. **Figure 3** and **Tables 1-2** provide updated results from our mixed effects analysis comparing absolute rates of VRI observed for each intervention strategy after exclusion of the Murphy *et al*. data.

A comparable pattern of results was observed for our cost analysis, which yielded estimated net costs per patient of $6,930 for no prophylaxis, $2,918 for peri-procedural IV prophylaxis, $2,536 for extended IV prophylaxis, $1,818 for ac-EVD + peri-procedural IV prophylaxis, and $1,136 for ac-EVD + extended IV prophylaxis. Relative to no prophylaxis, this translated to estimated cost savings per patient of $4,012 for peri-procedural IV prophylaxis, $4,394 for extended IV prophylaxis, $5,112 for ac-EVD + peri-procedural IV prophylaxis, and $5,794 for ac-EVD + extended IV prophylaxis. The underlying assumptions for this cost analysis are described in our original paper.

To the authors' point, the one consequential difference in our corrected results, as compared to our original published study, concerns the absolute pooled VRI rates obtained for each intervention category. In the corrected analysis, we no longer observe a significant reduction in VRI rates with extended systemic antibiotics alone as monotherapy versus peri-procedural antibiotics alone as monotherapy (Figure 3, Table 2). However, even after exclusion of the data in question, the lowest VRI rates estimated in our meta-analysis were still observed with dual therapy of ac-EVD + extended systemic antibiotics, and VRI rates observed with dual therapy

continued to be significantly lower than all other intervention categories, including ac-EVD ± peri-procedural systemic antibiotics.

In summary, the core findings of our meta-analysis were unaffected by the numbers we originally reported for the Murphy *et al*. study.[1] On the whole, evidence from the literature does support efficacy of using systemic antibiotics or ac-EVDs to lower risk of ventriculitis in the setting of EVD placement. Again, to the authors' point, the question of whether extended systemic antibiotics confer a clinically significant advantage over peri-procedural prophylaxis remains unclear, and more research is needed. Our corrected data demonstrate no additional benefit in pooled outcomes for extended systemic antibiotic monotherapy compared to peri-procedural systemic antibiotic monotherapy, while dual therapy with ac-EVD + extended systemic antibiotics remained significantly favorable compared to ac-EVD use without extended systemic antibiotics. An important caveat to this finding is that the ventriculitis outcomes from the Murphy *et al*. study argue against additional benefit of extended IV antibiotics in the setting of ac-EVD use, but these data were not amenable to our analysis because we were unable to derive the number of ventriculitis cases in each study arm.[1] Moreover, our study does not consider important disadvantages of IV antibiotic administration, including adverse drug events, increased risk of nosocomial infections (e.g., *C diff* colitis), and risk of selection for antimicrobial-resistant organisms, among other risks.

The reporting of ventriculitis outcomes as incidence density by Murphy *et al*. also emphasizes the fact that risk of ventriculitis increases with duration of EVD placement.[1] Although several studies only report on overall incidence of ventriculitis cases, considering the duration of catheter insertion will be important in future research to compare literature outcomes under different intervention studies. VRI prophylactic strategies may have different cost-benefit tradeoffs depending upon the anticipated duration of EVD placement. Aside from these issues, many other aspects of EVD management affect ventriculitis risk and were not considered in our study, including antibiotic regimens, indication and setting of EVD placement, study design, sterile and CSF surveillance protocols, protocols regarding EVD catheter exchange (or not), and other factors. We view our study as a first attempt at a general picture of ventriculitis incidence under different broad intervention strategies. More fully delineating best practices to minimize the risk

of VRI will require extensive future effort. We deeply appreciate the authors' interest in our study and thank them for pointing out this mistake in our results as originally published.

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2. Sheppard JP, Ong V, Lagman C, et al. Systemic Antimicrobial Prophylaxis and Antimicrobial-Coated External Ventricular Drain Catheters for Preventing Ventriculostomy-Related Infections: A Meta-Analysis of 5242 Cases. *Neurosurgery*. November 2018. doi:10.1093/neuros/nyy522

FIGURE LEGEND

Figure 1. Corrected forest plot summarizing VRI incidence and risk ratios in reviewed studies of extended systemic antimicrobial prophylaxis.

Figure 2. Corrected funnel plots assessing bias in reviewed studies of **A**, extended IV therapy, and **B**, all reviewed studies combined. Dotted oblique lines denote 95% confidence boundaries of study variation expected by chance assuming random sampling of patients from a population with a fixed population-level treatment effect. Systematic deviation of points either above or below the expected aggregate risk ratio suggests the presence of systematic bias. T-statistics and P-values indicate results of Egger's tests for funnel plot asymmetry.

Figure 3. Corrected comparison of VRI incidence rates in pooled cohorts grouped by type of prophylactic strategy. Expected incidence rates and confidence intervals were determined via random effects analysis using a general linear mixed model and logistic regression. Error bars indicate 95% confidence intervals. n.s., not significant; * $P < .05$; *** $P < .001$. P-values reflect FDR-corrected significance levels for post-hoc contrasts computed using Tukey's Honestly Significant Difference test.

TABLE LEGEND

Table 1. Corrected Ventriculostomy Related Infection (VRI) Incidence by Intervention Strategy Observed in Mixed Effects Analysis Using General Linear Mixed Models and Logistic Regression

Table 2. Corrected Pair-Wise Treatment Effect Contrasts of Intervention Strategies Between Pooled Cohorts Using Mixed Effects General Linear Mixed Models

Figure 1

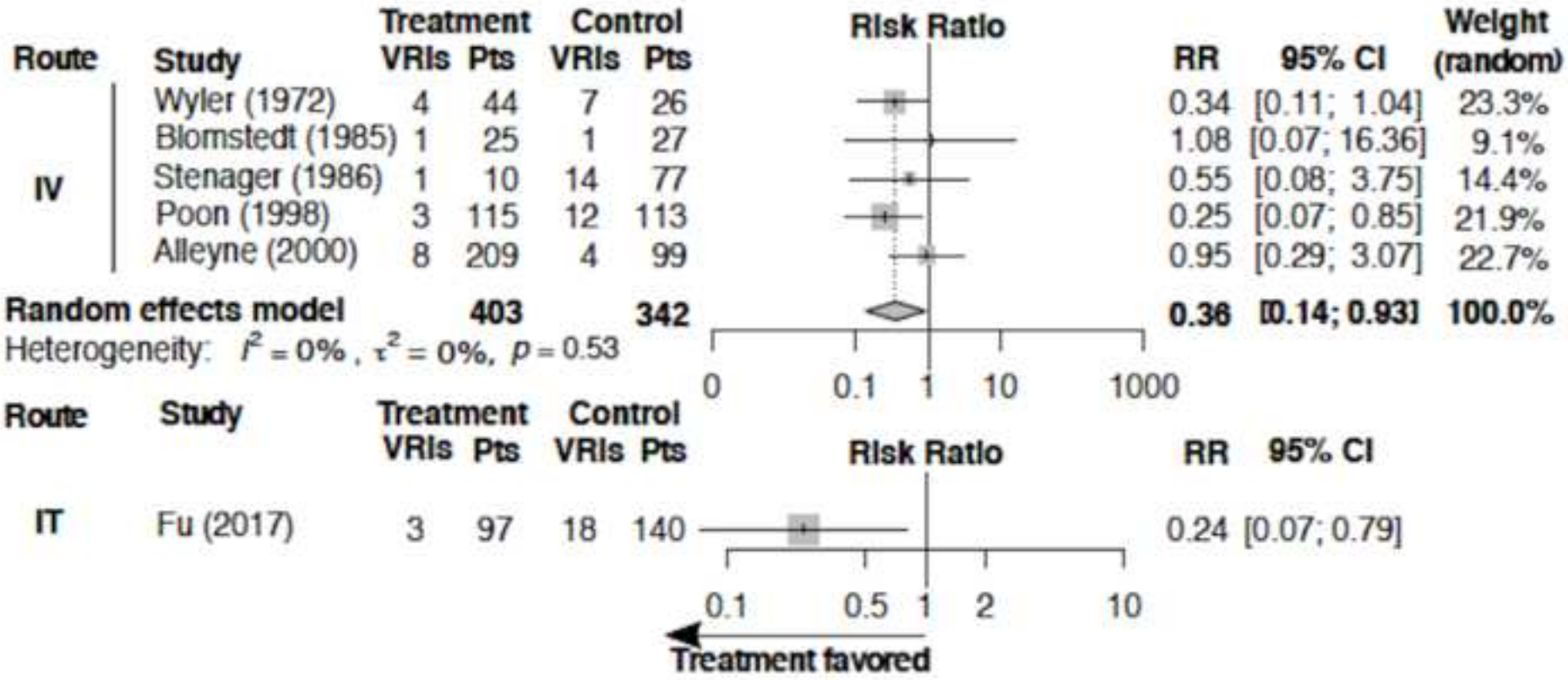

Figure 2A

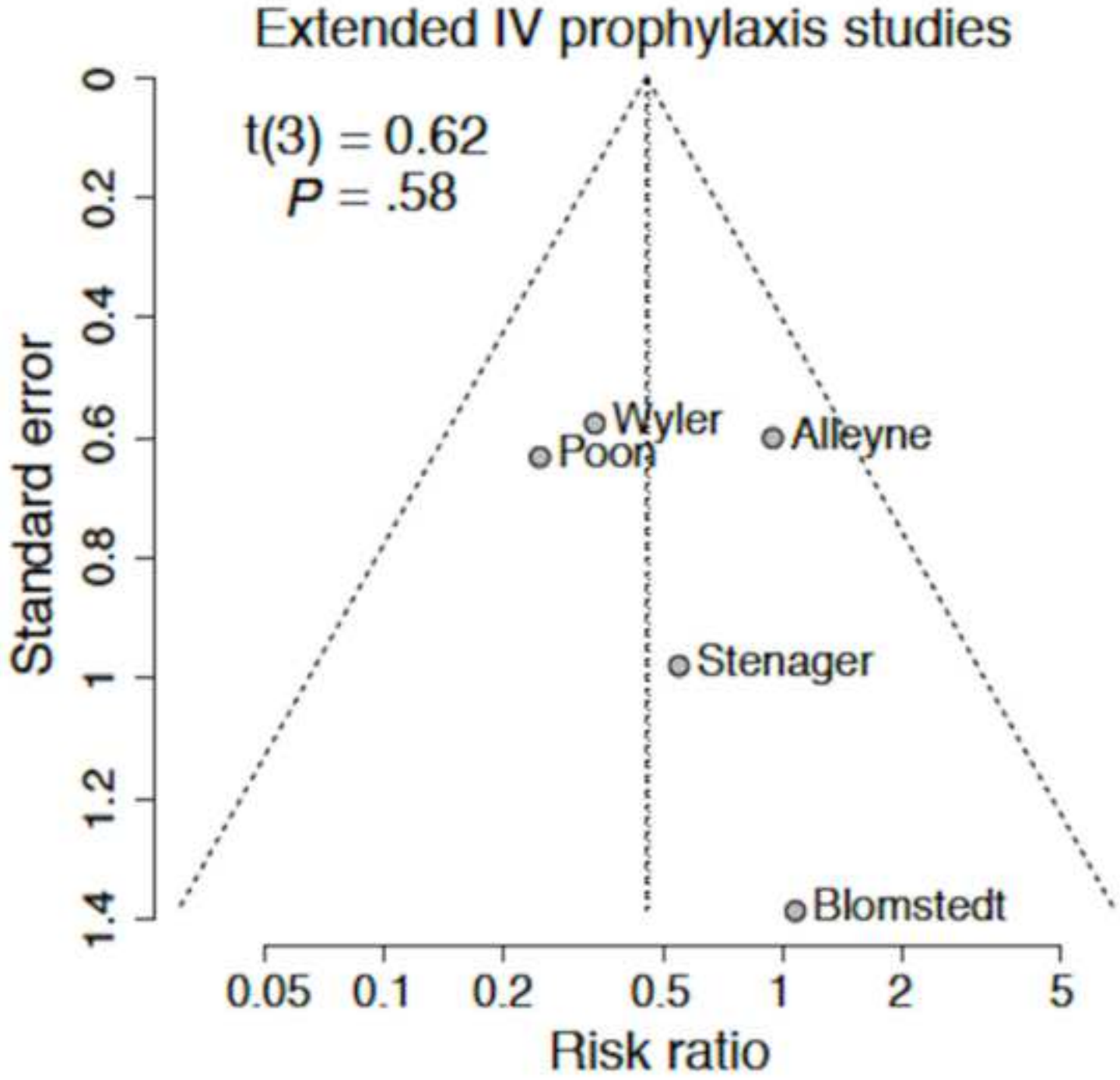

Figure 2B

Click here to access/download;Figure;Fig 2B.tiff

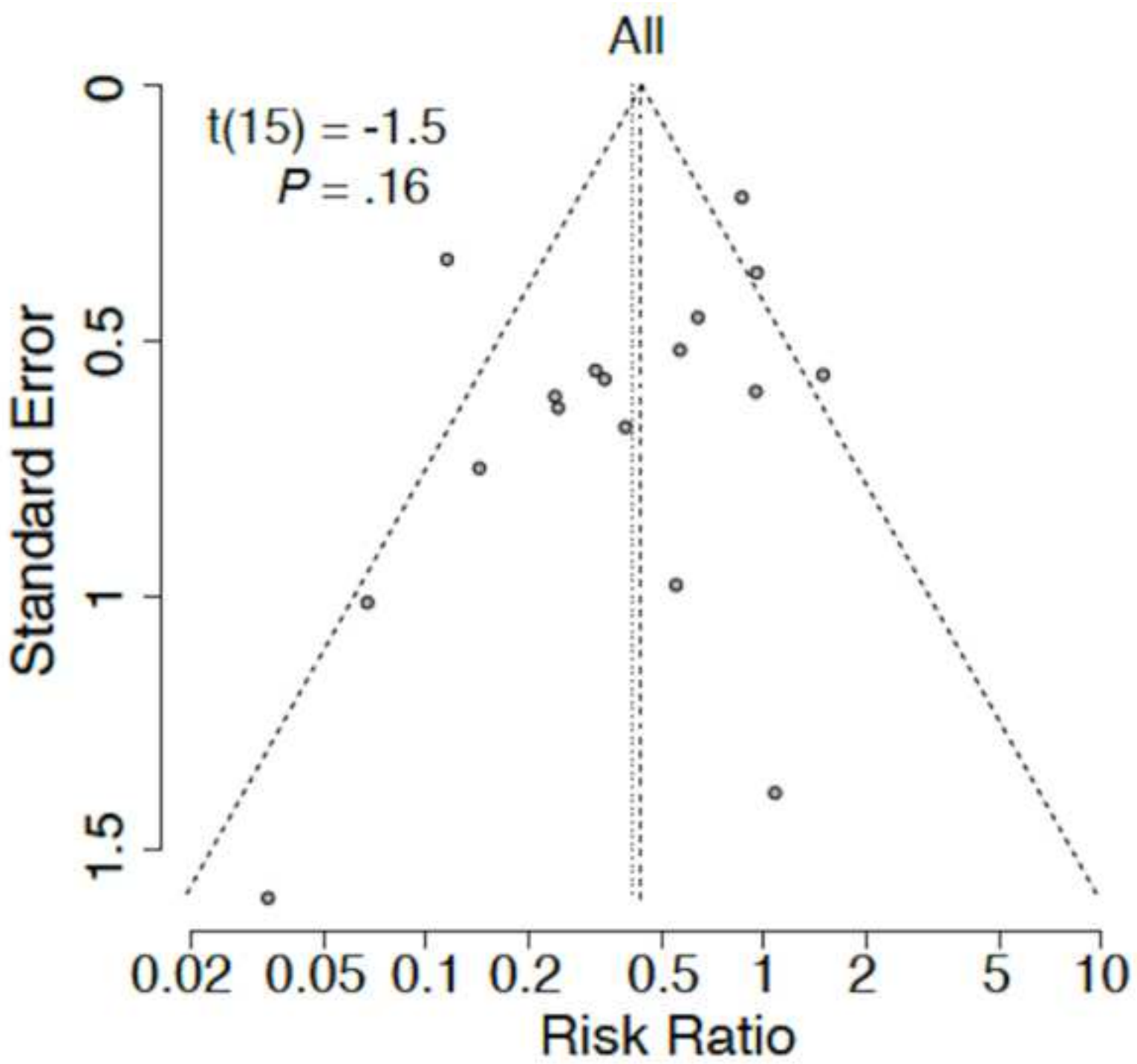

Figure 3

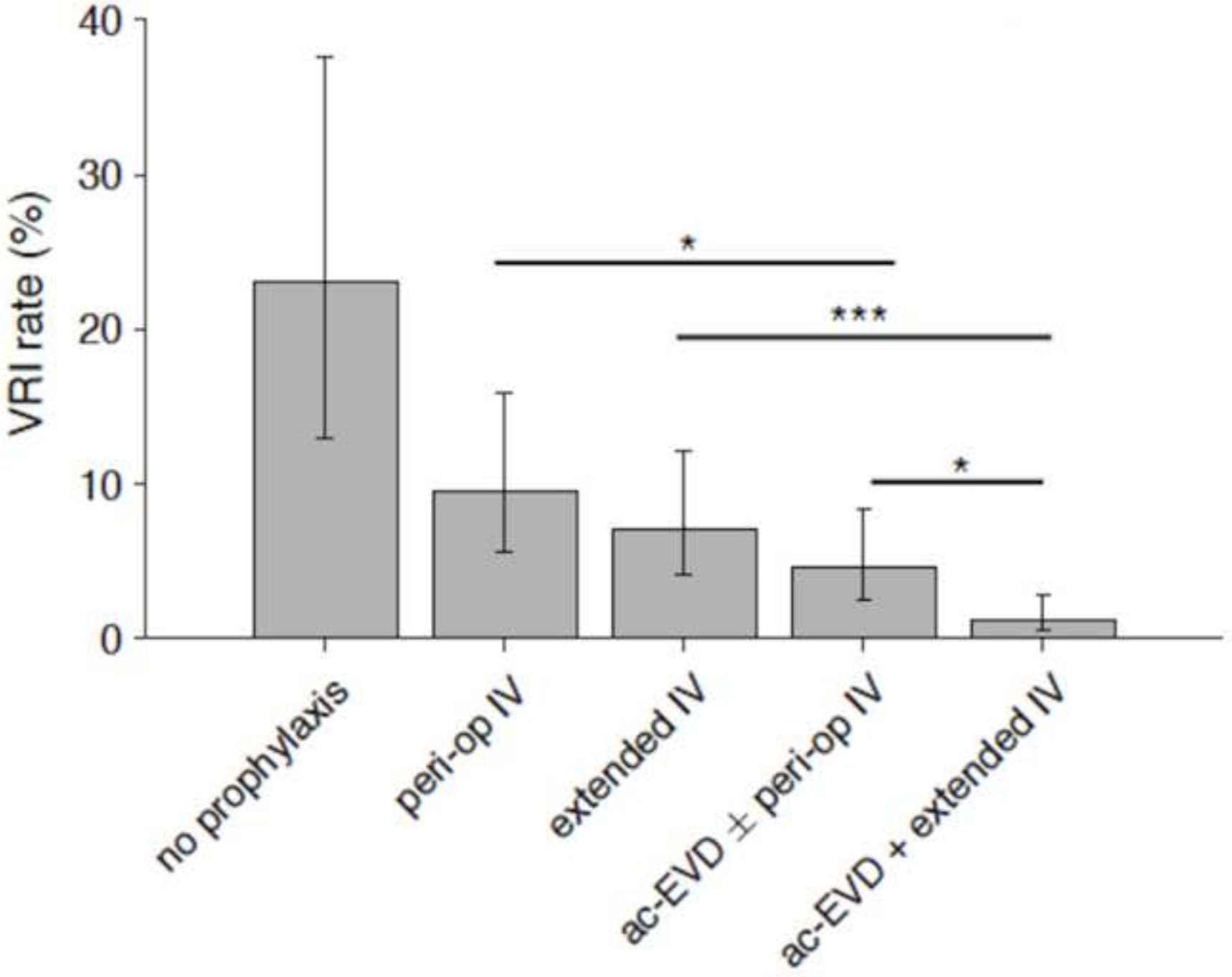

Table 1. Corrected Ventriculostomy Related Infection (VRI) Incidence

Prophylactic intervention	Total Pts	VRI cases	VRI incidence (%)	β
no prophylaxis	568	57	23.1 [13.0, 37.6]	-1.20 [-1.90, -0.51]
peri-op IV	662	62	9.6 [5.6, 15.9]	-2.25 [-2.83, -1.66]
extended IV	749	54	7.2 [4.1, 12.1]	-2.56 [-3.14, -1.98]
ac-EVD ± peri-op IV	1739	45	4.6 [2.5, 8.3]	-3.03 [-3.66, -2.40]
ac-EVD + extended IV	272	6	1.2 [0.5, 2.8]	-4.43 [-5.32, -3.55]

β, model coefficients for fixed treatment effects of each prophylactic intervention category. Brackets indicate 95% confidence intervals.

Table 2. Corrected Pair-Wise Treatment Effect Contrasts of Intervention Strategies

Contrast	Estimate	Z-value	Adjusted p-value
(no prophylaxis) - (peri-op IV)	1.04	3.07	.003**
(no prophylaxis) - (extended IV)	1.36	3.82	.0003***
(no prophylaxis) - (ac-EVD ± peri-op IV)	1.83	6.61	3.7e-10***
(no prophylaxis) - (ac-EVD + extended IV)	3.23	5.68	6.9e-08***
(peri-op IV) - (extended IV)	0.31	1.06	0.29
(peri-op IV) - (ac-EVD ± peri-op IV)	0.78	3.05	0.003**
(ac-EVD ± peri-op IV) - (extended IV)	0.47	1.45	.16
(peri-op IV) - (ac-EVD + extended IV)	2.18	4.12	9.6e-05***
(extended IV) – (ac-EVD + extended IV)	1.87	4.14	9.6e-05***
(ac-EVD ± peri-op IV) - (ac-EVD + extended IV)	1.40	2.57	.013*

*p<.05, **p<.01, ***p<.001. peri-op IV, IV prophylaxis for <24 post-operative hours. extended IV, IV prophylaxis for >24 hrs post-operative hours. ac-EVD, antibiotic-coated external ventricular drain. Estimates indicate estimated difference in model coefficients for fixed effects of each prophylactic intervention category.