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MAJOR ARTICLE

Participant- and Disease-Related Factors as Independent Predictors of Treatment Outcomes in the RESTORE-IMI 2 Clinical Trial: A Multivariable Regression Analysis

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Background. In the RESTORE-IMI 2 trial, imipenem/cilastatin/relebactam (IMI/REL) was noninferior to piperacillin/tazobactam in treating hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia. This post hoc analysis was conducted to determine independent predictors of efficacy outcomes in the RESTORE-IMI 2 trial, to assist in treatment decision making.

Methods. A stepwise multivariable regression analysis was conducted to identify variables that were independently associated with day 28 all-cause mortality (ACM), favorable clinical response at early follow-up (EFU), and favorable microbiologic response at end of treatment (EOT). The analysis accounted for the number of baseline infecting pathogens and in vitro susceptibility to randomized treatment.

Results. Vasopressor use, renal impairment, bacteremia at baseline, and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores ≥15 were associated with a greater risk of day 28 ACM. A favorable clinical response at EFU was associated with normal renal function, an APACHE II score <15, no vasopressor use, and no bacteremia at baseline. At EOT, a favorable microbiologic response was associated with IMI/REL treatment, normal renal function, no vasopressor use, nonventilated pneumonia at baseline, intensive care unit admission at randomization, monomicrobial infections at baseline, and absence of *Acinetobacter calcoaceticus-baumannii* complex at baseline. These factors remained significant after accounting for polymicrobial infection and in vitro susceptibility to assigned treatment.

Conclusions. This analysis, which accounted for baseline pathogen susceptibility, validated well-recognized patient- and disease-related factors as independent predictors of clinical outcomes. These results lend further support to the noninferiority of IMI/REL to piperacillin/tazobactam and suggests that pathogen eradication may be more likely with IMI/REL.

Clinical Trials Registration. NCT02493764.

Keywords. antibiotic; HABP; imipenem; relebactam; VABP.

Nosocomial pneumonia, including hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), is one of the most common healthcare-associated infections, occurring in about 34% of patients in the intensive care unit (ICU) and accounting for 22% of all healthcare infections [1, 2]. Due to broad antibacterial spectrum and good tolerability, carbapenem-class antibacterial agents have become a mainstay of HABP/VABP treatment, in particular for seriously ill, high-risk patients [3]. This critical role of carbapenems is increasingly being threatened by the worldwide emergence of carbapenem resistance among key causative pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter* spp, and Enterobacterales [4, 5]; carbapenem resistance is associated with poor clinical outcomes, including higher mortality [6–12].

Imipenem is a well-established carbapenem that is co-formulated with cilastatin, a dehydropeptidase inhibitor that prevents degradation of imipenem by renal dehydropeptidase [13]. The addition of relebactam, a novel β-lactamase inhibitor, can restore imipenem susceptibility to imipenem-nonsusceptible isolates that produce class A (eg, *Klebsiella pneumoniae* carbapenem) or class C β-lactamases and has been shown to enhance imipenem activity in already susceptible isolates (ie, relebactam acts to lower the minimum inhibitory concentration [MIC]) [14–18]. The combination of imipenem/cilastatin/relebactam

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(IMI/REL) demonstrated efficacy for the treatment of serious infections, including HABP/VABP, caused by carbapenem-nonsusceptible pathogens (mainly *P aeruginosa*) in the randomized, controlled RESTORE-IMI 1 phase 3 trial [19].

IMI/REL is approved for the treatment of HABP/VABP in adults [20], based predominantly on the results of RESTORE-IMI 2, a randomized, double-blind, noninferiority phase 3 trial of IMI/REL versus piperacillin/tazobactam (PIP/TAZ) [21]. In RESTORE-IMI 2, IMI/REL was noninferior to PIP/TAZ for both the primary end point of day 28 all-cause mortality (ACM) and the key secondary end point of favorable clinical response at early follow-up (EFU) in the modified intent-to-treat (MITT) population. Overall favorable microbiologic response at EFU was also similar between treatment arms. In addition, there was a lower incidence of serious adverse events with IMI/REL than PIP/TAZ. Of note, IMI/REL was also associated with greater survival than PIP/TAZ in important prespecified subgroups (ie, mechanically ventilated participants with HABP/VABP and critically ill participants with Acute Physiologic Assessment and Chronic Health Evaluation [APACHE] II scores of ≥15). Although primary and secondary end points for a number of clinically relevant subgroups in RESTORE-IMI 2 were prospectively assessed, factors other than treatment that may have contributed to the observed subgroup differences were not evaluated and the analyses were not adjusted for multiplicity [21]. We therefore conducted a post hoc analysis to identify clinically relevant independent predictors of treatment outcomes in this trial population, with a focus on key causative pathogens, baseline in vitro susceptibility to the study drug, and clinical factors of importance in patients with HABP/VABP.

METHODS

Study Design and Participants

The methodology of the RESTORE-IMI 2 trial has been previously reported [21]. In brief, participants were randomized to IMI/REL (imipenem 500 mg, cilastatin 500 mg, relebactam 250 mg) or PIP/TAZ (piperacillin 4 g, tazobactam 500 mg); dose adjustments were made based on renal function. Treatment was administered as 30-minute intravenous infusions every 6 hours for 7–14 days, with 14 days required for participants with HABP/VABP due to *P aeruginosa* or with concurrent bacteremia.

The primary efficacy end point was day 28 ACM in the MITT population, which comprised all randomized patients who had received ≥1 dose of study treatment and whose baseline Gram stain did not show only gram-positive cocci. The key secondary end point of favorable clinical response at EFU (7–14 days after end of treatment [EOT]) was also evaluated in the MITT population. Favorable clinical response was defined as resolution of baseline HABP/VABP signs/symptoms and no administration of nonstudy antibacterial therapy for HABP/VABP. Other secondary end points included day 28 ACM, favorable clinical response at EFU, and favorable microbiologic response at EOT, all assessed in the microbiologic MITT (mMITT) population. The mMITT population was defined as MITT patients with ≥1 baseline lower respiratory tract pathogen species against which IMI/REL is known to have antibacterial activity, thereby excluding participants with infections caused solely by methicillin-resistant *Staphylococcus aureus* or by *Stenotrophomonas maltophilia*. Favorable per-participant microbiologic response was defined as the absence of the baseline pathogen in the lower respiratory tract culture at the posttreatment time point (eradication) or clinical cure in the absence of a lower respiratory tract culture (presumed eradication).

Ethics and Patient Consent

The RESTORE-IMI 2 trial was conducted in accordance with the principles of Good Clinical Practice; the appropriate institutional review boards and regulatory agencies approved the protocol and the study was conducted in conformance with the ethical principles of the Helsinki Declaration. Written informed consent was obtained from all participants before enrollment into the study.

Multivariable Analysis

Using participant-level data from the RESTORE-IMI 2 trial, we developed a stepwise-selection multivariable regression model to conduct a post hoc analysis of independent predictors of day 28 ACM, favorable clinical response at EFU, and favorable microbiologic response at EOT. Prospectively collected participant clinical and microbiologic baseline characteristics that were historically associated with treatment outcomes were identified as candidate variables for inclusion in the model (Table 1). These factors were prospectively chosen by clinical experts based on disease and patient characteristics identified in the literature as important predictors of outcomes in patients with HABP/VABP and treated with antimicrobial agents [22–24]. The model included main effects for the characteristics, and variables were added to the model if they were significant ($P < .05$) and removed if their significance was reduced ($P > .05$) by the addition of other variables. Odds ratios (ORs) and 95% confidence intervals (CIs) representing the increase in the odds of outcome were estimated from the final model. Mortality modeled the risk of death such that ORs >1 showed increased odds of dying (negative outcome). Clinical and microbiologic response modeled the risk of clinical cure and microbiologic eradication/presumed eradication, respectively, such that ORs >1 showed increased odds of having a favorable response (positive outcome).

Multivariable analyses were performed to assess day 28 ACM and favorable clinical response at EFU in the MITT and

Table 1. Candidate Baseline Variables Included in the Multivariable Regression Models

Variable Description	Subgroup
APACHE II score	≥15 or <15
Renal status	• Moderate to severe (≥15 to <60 mL/min) • Mild (≥60 to <90 mL/min) • Normal (≥90 to <150 mL/min)[a] •Augmented (≥150 mL/min)
Pneumonia type at baseline	Ventilated or nonventilated
Clinical pulmonary infection score	≤5 or ≥6
Region in which patient was enrolled	Asia-Pacific, Americas[b], or Europe
Vasopressor use within 72 h before the first study dose or during the study	Yes or no
Concurrent bacteremia	Yes or no[c]
Age group	<65 or ≥65 y
Admitted in ICU at randomization	Yes or no[c]
Treatment arm	IMI/REL or PIP/TAZ
Klebsiella pneumoniae	Present or not detected[c]
Pseudomonas aeruginosa	Present or not detected[d]
Escherichia coli	Present or not detected[c]
Acinetobacter calcoaceticus-baumannii complex	Present or not detected[c]
Number of baseline pathogens	Polymicrobial or monomicrobial
All baseline pathogens susceptible to assigned treatment	Yes or no

Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; PIP/TAZ, piperacillin/tazobactam.

[a]Normal renal function was the reference for the subgroup comparison.

[b]The Americas was the reference for the subgroup comparison.

[c]Not available in the exploratory *Pseudomonas aeruginosa* subset analysis; the sample size and numbers of events were limited and did not allow for adequate assessment.

[d]*Pseudomonas aeruginosa* was only a candidate variable for the modified intent-to-treat (MITT) and microbiologic MITT (mMITT) multivariable analyses. In the subgroup analysis of mMITT participants with infections due to *P aeruginosa*, this was not a candidate variable.

mMITT populations, as well as favorable per-participant microbiologic response at EOT in the mMITT population. All analyses conducted in the MITT population included 14 clinical and microbiologic variables known or presumed to affect outcomes in HABP/VABP. Analyses in the mMITT population included 2 additional microbiologic variables (ie, polymicrobial infection and susceptibility to assigned treatment). Susceptibility of baseline pathogens was assigned on the participant level as a dichotomous variable of "yes" if all of the baseline lower respiratory tract pathogens were susceptible to assigned treatment and "no" otherwise. Susceptibility of baseline pathogens was assessed based on Clinical and Laboratory Standards Institute MIC breakpoints. All instances of methicillin-resistant *S aureus* and *Stenotrophomonas* spp were considered resistant to both treatments.

Considering the clinical significance of *P aeruginosa*, an additional exploratory multivariable analysis was performed in the subgroup of 82 mMITT participants presenting with this pathogen. In this subgroup at baseline, 10 of the 16 covariates were available for use in the modeling, as indicated in Table 1.

As collinearity is a concern when performing multivariable logistic regression, the Cramer V statistic was used to assess relationships among covariates prior to multivariable modeling. Additionally, 2-factor interactions were assessed among all significant predictors of outcome and between treatment assignment and significant predictors of outcome. All analyses were performed using SAS Proc Logistic (SAS Institute, Cary, North Carolina).

RESULTS

Participants

Participants with HABP/VABP from 27 countries were randomized between January 2016 and April 2019. Baseline demographic and clinical characteristics were comparable between the IMI/REL and PIP/TAZ treatment arms and suggested enrollment of an overall severely ill trial population, which included the following: 66.1% of all participants were in the ICU, 47.5% had an APACHE II score ≥15, 48.6% had mechanically ventilated HABP/VABP, 42.9% were ≥65 years of age, 24.7% had moderate to severe renal impairment (creatinine clearance ≥15 to <60 mL/minute), 23.4% had mild renal impairment (creatinine clearance ≥60 to <90 mL/minute), and 16.6% had augmented renal clearance (ARC; creatinine clearance ≥150 mL/minute) (Table 2). Median treatment duration was 6.8 days in both treatment arms. A detailed description of the study population has been previously published [21].

Day 28 ACM

Results from the multivariable regression analysis found that day 28 ACM was significantly associated with vasopressor use, renal impairment, bacteremia at baseline, and APACHE II scores ≥15 in the MITT population. Significant findings are shown in Figure 1*A*. Results for the mMITT population, which included the 2 additional variables of polymicrobial infection and susceptibility to assigned treatment into the respective model, were consistent with those for the MITT population, with the exception that bacteremia no longer remained significant (Figure 1*B*).

Clinical Response at EFU

Results in the MITT population from the multivariable regression of clinical response at EFU found that no vasopressor use, normal renal function, no bacteremia at baseline, and APACHE II scores <15 remained significant in the model, indicating these were all independent predictors for favorable clinical response. Significant findings are shown in Figure 2*A*. Results for the mMITT population, which included the 2 additional microbiologic variables and accounted for polymicrobial infection and susceptibility to assigned treatment into the respective model, were consistent with those for the MITT population (Figure 2*B*).

Table 2. Baseline Demographic, Clinical, and Microbiologic Characteristics Included in the Multivariable Regression Models

Characteristic	IMI/REL (n = 264)	PIP/TAZ (n = 267)	Total (N = 531)
APACHE II score			
<15	139 (52.7)	140 (52.4)	279 (52.5)
≥15	125 (47.3)	127 (47.6)	252 (47.5)
Renal function[a]			
Moderate to severe impairment	71 (26.9)	60 (22.5)	131 (24.7)
Mild impairment	52 (19.7)	72 (27.0)	124 (23.4)
Normal	103 (39.0)	85 (31.8)	188 (35.4)
Augmented	38 (14.4)	50 (18.7)	88 (16.6)
Pneumonia type			
Ventilated	122 (46.2)	136 (50.9)	258 (48.6)
Nonventilated	142 (53.8)	131 (49.1)	273 (51.4)
CPIS			
<6	114 (43.2)	95 (35.6)	209 (39.4)
≥6	150 (56.8)	172 (64.4)	322 (60.6)
Region of enrollment			
Asia-Pacific	39 (14.8)	36 (13.5)	75 (14.1)
Americas	59 (22.3)	71 (26.6)	130 (24.5)
Europe	166 (62.9)	160 (59.9)	326 (61.4)
Vasopressor use			
Yes	54 (20.5)	57 (21.3)	111 (20.9)
Concurrent bacteremia			
Yes	15 (5.7)	16 (6.0)	31 (5.8)
Age group			
≥65 y	113 (42.8)	115 (43.1)	228 (42.9)
<65 y	151 (57.2)	152 (56.9)	303 (57.1)
ICU admission			
Yes	175 (66.3)	176 (65.9)	351 (66.1)
Baseline pathogens present[b]			
Klebsiella pneumoniae	58 (27.0)	53 (24.3)	111 (25.6)
Pseudomonas aeruginosa	34 (15.8)	48 (22.0)	82 (18.9)
Escherichia coli	30 (14.0)	37 (17.0)	67 (15.5)
Acinetobacter calcoaceticus-baumannii complex	32 (14.9)	36 (16.5)	68 (15.7)
MICs to baseline pathogens present[b] ($MIC_{50/90}$ range), μg/mL			
K pneumoniae	0.12/1 (0.06–16)	4/>64 (≤2 to >64)	…
P aeruginosa	0.5/8 (≤0.03 to >32)	8/64 (≤2 to >64)	…
E coli	0.12/0.12 (0.06–0.25)	≤2/>64 (≤2 to >64)	…
A calcoaceticus-baumannii complex	>32/>32 (0.12 to >32)	>64/>64 (≤2 to >64)	…
Baseline pathogens[b]			
Polymicrobial	62 (28.8)	66 (30.3)	128 (29.6)
Monomicrobial	153 (71.2)	152 (69.7)	305 (70.4)
All baseline pathogens susceptible to assigned treatment[b,c]			
No	51 (23.7)	73 (33.5)	124 (28.6)
Yes	164 (76.3)[b]	145 (66.5)	309 (71.4)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; CPIS, Clinical Pulmonary Infection Score; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; MIC, minimum inhibitory concentration; PIP/TAZ, piperacillin/tazobactam.

[a]Moderate to severe renal impairment, creatinine clearance (CrCl) ≥15 to <60 mL/min; mild renal impairment, CrCl ≥60 to <90 mL/min; normal renal function, CrCl ≥90 to <150 mL/min; augmented renal clearance, CrCl ≥150 mL/min.

[b]Parameters assessed in the microbiologic modified intent-to-treat population (n = 215 IMI/REL, n = 218 PIP/TAZ [N = 433 total]).

[c]The majority of IMI/REL-nonsusceptible pathogens were *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, or *Stenotrophomonas maltophilia*.

Microbiologic Response at EOT

Results from the multivariable regression of microbiologic response at EOT in the mMITT population showed that treatment with IMI/REL, no vasopressor use, nonventilated pneumonia type at baseline, normal renal function, ICU admission at randomization, monomicrobial infections at baseline, and absence of *Acinetobacter calcoaceticus-baumannii* complex at baseline remained significant in the model, indicating these were independent predictors of favorable microbiologic response. Significant findings are shown in Figure 3*A*.

A sensitivity multivariable regression analysis was performed to assess whether treatment with IMI/REL would remain

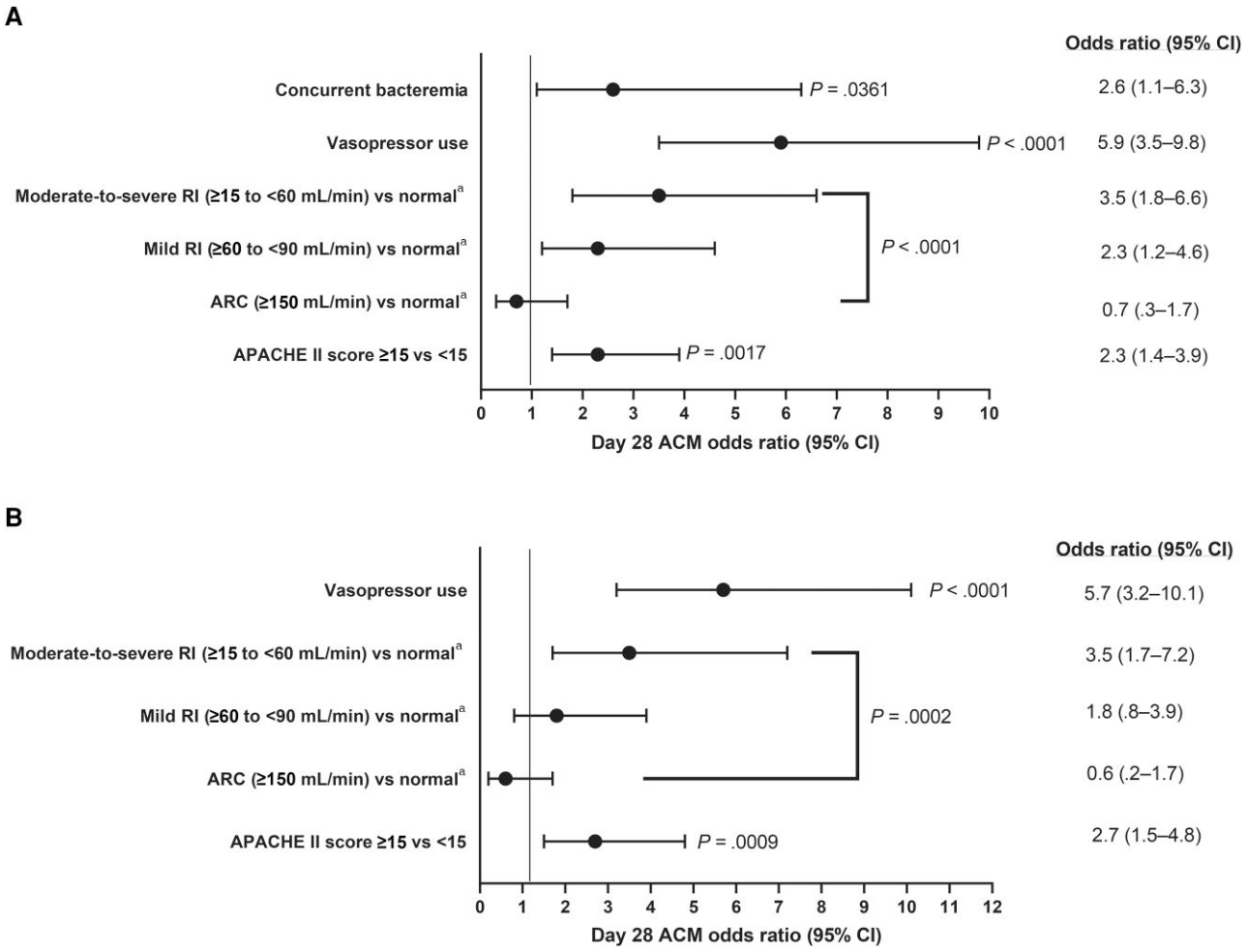

Figure 1. Odds ratio estimates for day 28 all-cause mortality in the modified intent-to-treat (MITT) population (*A*) and the microbiologic MITT (mMITT) population (*B*). The mMITT population includes polymicrobial infection and susceptibility to assigned treatment. [a]Normal renal function is creatinine clearance ≥90 to <150 mL/min. Abbreviations: ACM, all-cause mortality; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; ARC, augmented renal clearance; CI, confidence interval; RI, renal impairment.

significantly related to favorable microbiologic response when the model accounted for baseline pathogen susceptibility to assigned treatment. It is important to evaluate microbiologic response in the presence of baseline pathogen susceptibility, so that the significance of the resulting ORs could be adjusted for any impact of susceptibility on the aforementioned variables. Treatment with IMI/REL remained significantly associated with favorable microbiologic response, along with no vasopressor use, nonventilated pneumonia type at baseline, normal renal function, ICU admission at randomization, and monomicrobial infections at baseline. Significant findings are shown in Figure 3*B*.

Patients With *P aeruginosa*

Among patients with *P aeruginosa* at baseline (n = 82), assigned treatment was not significantly related to day 28 ACM, clinical response at EFU, or microbiologic response at EOT in this exploratory multivariable regression analysis adjusting for baseline pathogen susceptibility.

Collinearity and 2-Factor Interaction

Collinearity between all candidate variables was explored using the Cramer's V statistic for categorical data before the multivariable modeling; results are presented in the Supplementary Material. All results were consistent with the original analyses (data not shown).

Interactions among significant predictors of outcome and between treatment and significant predictors of outcome were assessed using logistic regression models and are discussed in the Supplementary Material. As a result of these investigations, no interaction terms were included in the models (Supplementary Table 1).

DISCUSSION

This multivariable analysis, which accounted for in vitro susceptibility to randomized study drug, was performed to identify clinically relevant factors independently predicting clinical or

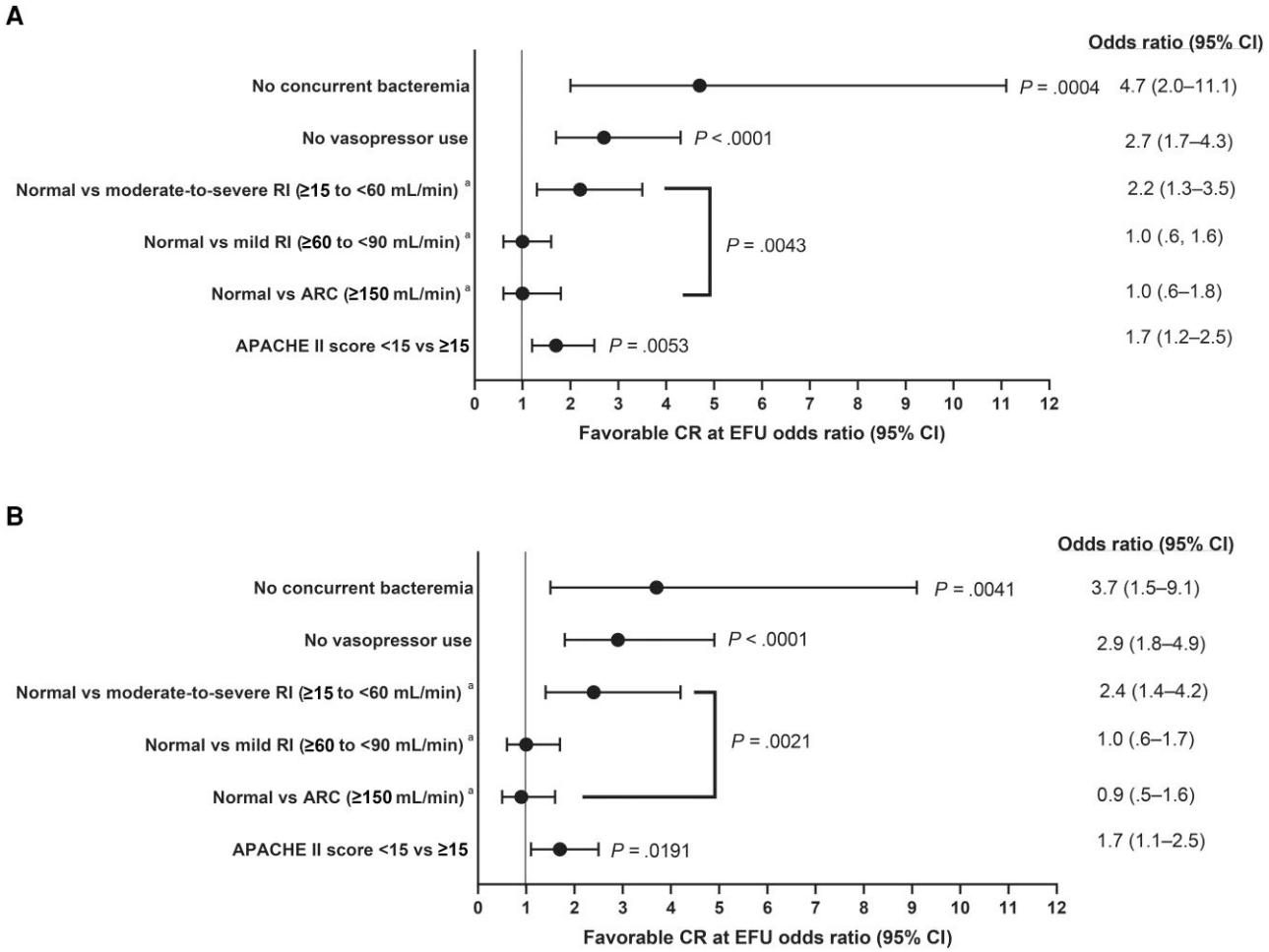

Figure 2. Odds ratio estimates for favorable clinical response at end of follow-up in the modified intent-to-treat (MITT) population (*A*) and the microbiologic MITT population (mMITT) (*B*). The mMITT population includes polymicrobial infection and susceptibility to assigned treatment. [a]Normal renal function is creatinine clearance ≥90 to <150 mL/min. Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; ARC, augmented renal clearance; CI, confidence interval; CR, clinical response; EFU, end of follow-up; RI, renal impairment.

microbiologic outcomes in the study population of the RESTORE-IMI 2 clinical trial. The population enrolled in this trial (which compared IMI/REL with PIP/TAZ for the treatment of HABP/VABP in adults) was considered critically ill, given that substantial proportions of participants were in the ICU, had APACHE II scores ≥15, and/or had either ARC or moderate to severe renal impairment [21]. The study population was representative of real-world patients with HABP/VABP in terms of comorbidities and severity of illness [25, 26]. Participant- and disease-related factors that emerged as independent predictors of greater day 28 ACM in both the MITT and mMITT populations were APACHE II scores ≥15, renal impairment, and vasopressor use (indicative of septic shock). In the primary analysis MITT population only, the presence of concurrent bacteremia was found to be an additional independent predictor of greater likelihood of death by day 28. These factors are commonly associated with poor outcomes in patients with HABP/VABP [27–31], although not all studies have confirmed the total set of these factors to be prognostic [32]. Similar factors were observed as independent predictors for the clinical response outcome as well.

Notably, treatment with IMI/REL (instead of PIP/TAZ) was independently associated with favorable microbiologic response at EOT even when adjusting for characteristics assumed to impact pathogen eradication, such as the susceptibility of baseline causative pathogens to the respective study drug that participants were treated with and presence of polymicrobial infections. A potential explanation for this finding may be the potentiating effect of relebactam when added to imipenem, resulting in lower imipenem MIC values compared with imipenem alone even in imipenem-susceptible isolates (including *P aeruginosa* and Enterobacterales). This effect translates into a greater percentage of time that the free imipenem concentration exceeds the (reduced) imipenem MIC values, which may be particularly important in critically ill

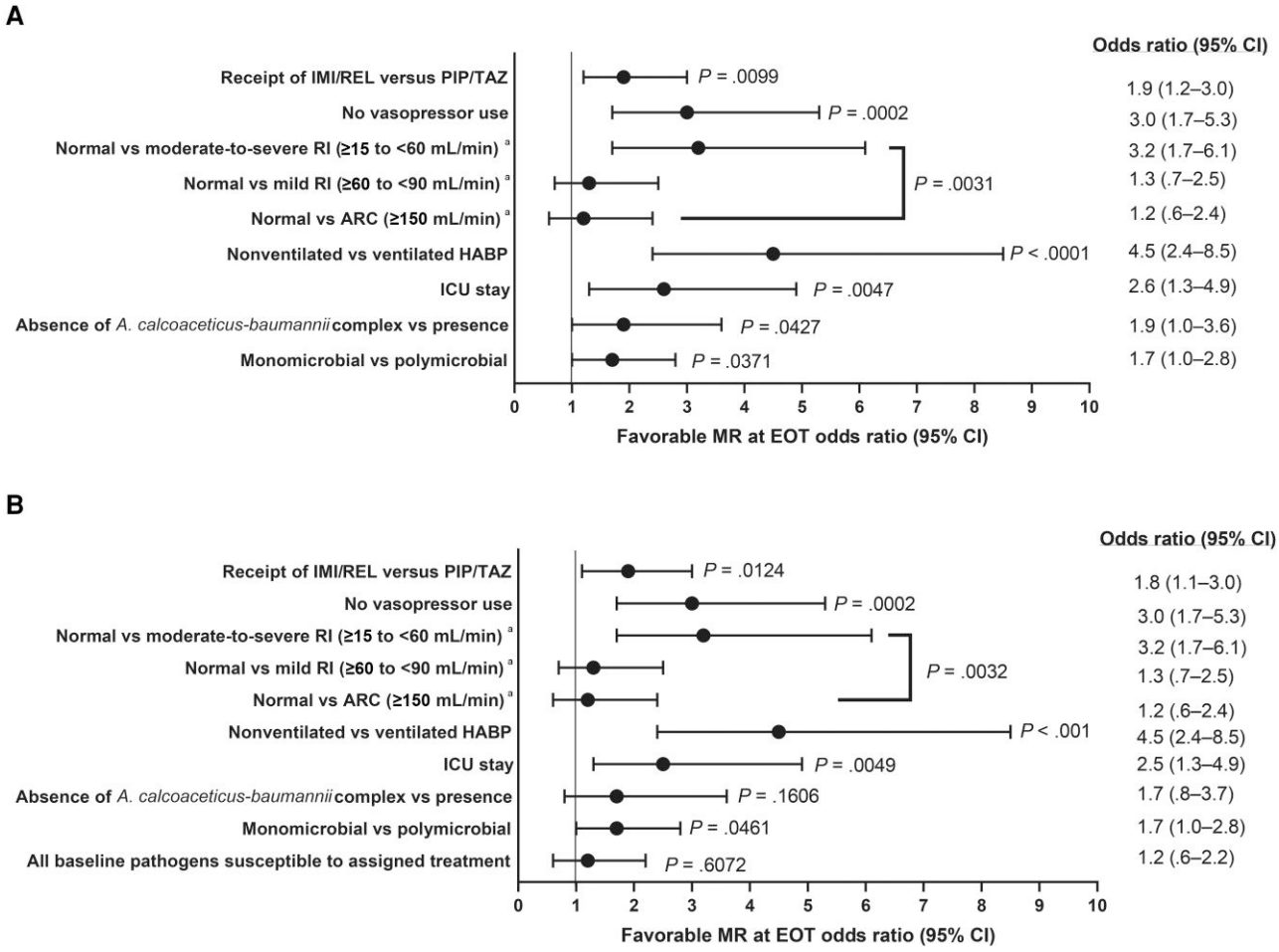

Figure 3. Odds ratio estimates for overall favorable MR at end of treatment in the microbiologic modified intent-to-treat population (*A*) and the susceptibility-sensitivity analysis (*B*). The susceptibility-sensitivity analysis accounts for susceptibility to assigned treatment for causative pathogens. [a]Normal renal function is creatinine clearance ≥90 to <150 mL/min. Abbreviations: ARC, augmented renal clearance; CI, confidence interval; EOT, end of treatment; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; MR, microbiologic response; PIP/TAZ, piperacillin/tazobactam; RI, renal impairment.

patients with ARC for whom there is a risk of underdosing with antibacterial agents in general [17, 18, 33, 34]. In critically ill patients with ARC, IMI/REL was previously shown to achieve adequate exposure to treat most susceptible pathogens [35, 36]. In our multivariable analysis, other factors that independently predicted favorable microbiologic response at EOT were ICU stay, normal renal function, not requiring mechanical ventilation, no vasopressor use, monomicrobial infection, and absence of *A calcoaceticus-baumannii* complex. These findings are largely as expected, since most of these factors are associated with less severe disease and *A calcoaceticus-baumannii* generally has reduced susceptibility to carbapenems, including imipenem [37–43]. Overall, results were comparable between the MITT and mMITT populations for all 3 end points assessed in our analyses, and all independent predictors identified appear valid from a clinical perspective and based on prior experience [27, 29, 31].

Of particular interest for our analyses were participants with *P aeruginosa* isolated at baseline, given the globally increasing prevalence of multidrug and carbapenem resistance in this pathogen and the potential role of IMI/REL in treating HABP/VABP caused by resistant *P aeruginosa* [4, 5, 19, 21]. In vitro susceptibility of *P aeruginosa* to IMI/REL is reported to be high, with 90% overall to 82% in multidrug-resistant strains [44, 45]. In another phase 3 study evaluating IMI/REL (RESTORE-IMI 1), IMI/REL was deemed an efficacious treatment for carbapenem-nonsusceptible infections [19]. In that relatively small trial, all participants with HABP/VABP in the IMI/REL arm had imipenem-nonsusceptible *P aeruginosa* at baseline, and 7 of 8 (88%) of those participants survived through day 28 [19]. Similarly, in a real-world, multicenter case series comprising 21 critically ill and/or otherwise medically complex patients in which multidrug-resistant *P aeruginosa* was the predominant causative pathogen and

52% of patients had lower respiratory tract infections, IMI/REL was also associated with favorable clinical outcomes [46]. In RESTORE-IMI 2, PIP/TAZ was associated with numerically higher survival and clinical cure rates than IMI/REL in participants with *P aeruginosa*, despite comparable microbiologic response rates [21]. Taken together, preclinical, phase 1, and modeling data provide support that adequate pharmacokinetic/pharmacodynamic target attainment in HABP/VABP against *P aeruginosa* up to an IMI/REL MIC value of 2 μg/mL is achieved with the currently approved dosing regimen of imipenem/cilastatin/relebactam 500 mg/500 mg/250 mg every 6 hours [45, 47–50]. As previously reported, differences between treatment arms (ie, higher rate of serious/fatal adverse events unrelated to pneumonia [and study drug]) in the small subgroup of RESTORE-IMI 2 participants with *P aeruginosa* observed in the IMI/REL arm may have contributed to these results [21]. Although the subpopulation was small in our multivariable analysis, this conclusion is supported, since we found that (1) *P aeruginosa* at baseline was not independently associated with worse outcomes and (2) that treatment with IMI/REL was not an independent predictor of worse outcomes, specifically in the *P aeruginosa* subgroup, when adjusting for susceptibility and other baseline predictors of outcomes. Our results are thus supportive of current treatment guidelines recommending either IMI/REL or PIP/TAZ as empiric and definitive treatment options for HABP/VABP, including infections suspected or confirmed to be caused by susceptible *P aeruginosa* [3, 51, 52]. Multivariable analyses of other pathogens was not feasible given the small number of participants presenting with each individual pathogen.

A strength of our multivariable analysis is that the independent predictors we identified for mortality and clinical failure had all been frequently reported in previous work, and that all of these predictors are plausible from a clinical and/or physiological perspective [27–31]. This result confirms the validity of our model, and thus strengthens the overall conclusions. A limitation of our multivariable analysis is that we could not evaluate all factors previously shown to have prognostic significance in patients with HABP/VABP, such as Sequential Organ Failure Assessment (SOFA) score and change in partial pressure arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio [22, 23, 53]. These data were not consistently collected in RESTORE-IMI 2. However, neither SOFA score nor PaO_2/FiO_2 ratio were found to predict outcomes in a multivariable analysis of another recent phase 3 clinical trial in HABP/VABP with a comparable study design [24]. Another limitation is the post hoc nature of our analyses, thus requiring caution when interpreting the results and an appreciation that these findings are hypothesis generating instead of confirmatory. Some variables (eg, bacteremia) had ORs with wider CIs, likely due to the limited number of patients available who exhibited the characteristics in question. This indicates a lack of precision in the quantification of the corresponding effects. Therefore, conclusions should be focused on whether or not any particular characteristic impacted a particular outcome rather than on the calculated magnitude of that influence.

In conclusion, this analysis based on prospectively collected data from a severely ill study population supports the main noninferiority finding of RESTORE-IMI 2 in that IMI/REL treatment yielded favorable efficacy outcomes when compared with PIP/TAZ. The results also validate patient- and disease-related predictors of clinical outcomes, namely vasopressor use, bacteremia, APACHE II scores ≥15, and renal impairment, as well as other factors, and demonstrate that treatment with IMI/REL (vs PIP/TAZ) was significantly associated with favorable microbiologic outcomes. The factors we identified remained significant even after accounting for polymicrobial infection and susceptibility to assigned treatment. *Pseudomonas aeruginosa* was not an independent predictor of worse clinical outcomes overall, nor was IMI/REL treatment an independent predictor in participants with *P aeruginosa*, lending further support to the clinical value of IMI/REL in treating HABP/VABP caused by multidrug-resistant *P aeruginosa* [21]. These results support IMI/REL as an effective treatment option for HABP/VABP.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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