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Rates of Major Cardiovascular Events in Severe Asthma: U.S. Real-World and Clinical Trial–Eligible Populations

To the Editor:

Clinical trials typically exclude patients having serious comorbidities with the goal of recruiting only those patients who are likely to successfully complete the trial (1–5). As a consequence, trial subjects are expected to have a lower incidence of certain adverse events, including cardiovascular events (CVEs), compared with patients who will be using those medications after approval. This discrepancy between trial-eligible (TE) and real-world populations can complicate the CV safety assessment of new drugs. This is particularly concerning for patients with severe asthma who have a higher risk of CV disease than patients without asthma or those with milder asthma (6–9). Trials for severe asthma treatments also exclude patients with comorbid chronic obstructive pulmonary disease (COPD); therefore, CV safety data are not available for this subpopulation even though they will be using the same asthma medications. Although differences in CVE incidence between TE and real-world populations are not unexpected, the magnitude of these differences is less clear. This study aimed to understand the differences in CVE incidence between TE and broader populations of patients with severe, suboptimally controlled asthma with and without concomitant COPD.

Supported by Genentech, Inc.

Author Contributions: P.D. and C.V.S. were responsible for the study concept, design, and statistical analysis. All authors were responsible for the interpretation of the results. P.D. and C.V.S. drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content.

Methods

This retrospective cohort study used insurance claims data in the IBM MarketScan database from 2009 to 2018. We selected patients

Table 1. Baseline characteristics of cohorts of patients with severe asthma

Characteristic	TE	GSA	ACO
Overall, *n*	20,768	32,439	13,028
Follow-up duration, yr			
Mean (SD)	2.2 (1.2)	2.3 (1.3)	2.6 (1.6)
Median (IQR)	1.8 (1.4–2.6)	1.9 (1.4–2.7)	2.0 (1.5–3.2)
Male, *n* (%)	7,335 (35.3)	10,175 (31.4)	4,469 (34.3)
Age at first high-dose fill,* yr			
Median (IQR)	46 (37–55)	47 (37–56)	61 (55–69)
18–34, *n* (%)	4,155 (20.0)	6,466 (19.9)	—
35–44, *n* (%)	5,190 (25.0)	8,279 (25.5)	—
45–54, *n* (%)	5,760 (27.7)	8,674 (26.7)	2,729 (20.9)
55–64, *n* (%)	5,005 (24.1)	7,662 (23.6)	5,788 (44.4)
65 and older,† *n* (%)	658 (3.2)	1,358 (4.2)	4,511 (34.6)
Number of OCS bursts in 1 yr from first high-dose fill,* *n* (%)			
1	9,249 (44.5)	14,207 (43.8)	5,776 (44.3)
2	5,329 (25.7)	8,245 (25.4)	2,650 (20.3)
3 or more	6,010 (28.9)	9,987 (30.8)	4,602 (35.3)

Definition of abbreviations: ACO = asthma–COPD overlap; COPD = chronic obstructive pulmonary disease; GSA = general severe asthma; IQR = interquartile range; OCS = oral corticosteroid; SD = standard deviation; TE = trial-eligible.
*Date of the patient's first high-dose inhaled corticosteroid and long-acting β_2-agonist fill during the study period.
†65–75 yr for the TE cohort.

with severe, suboptimally controlled asthma, defined as adults who had *1*) an asthma diagnosis recorded at two or more medical encounters, *2*) two or more prescription fills ⩾13 days apart for a high-dose inhaled corticosteroid and long-acting β_2-agonist combination, *3*) one or more oral corticosteroid bursts (i.e., prescription for <30 d) during each full year of follow-up, and *4*) no evidence of chronic oral corticosteroid treatment within 1 year of the first high-dose inhaled corticosteroid and long-acting β_2-agonist fill. We considered patients with asthma as having COPD if they had one or more encounters for emphysema or chronic bronchitis at or after the age of 45 years. The following cohorts were created:

1. General severe asthma (GSA): patients with severe suboptimally controlled asthma but not COPD
2. Asthma–COPD overlap (ACO): patients with severe suboptimally controlled asthma and COPD
3. Trial-eligible (TE): patients with GSA excluding those with the following conditions (common clinical trial exclusion criteria):

- Cardiovascular disease that was not well managed (i.e., patients who had a CVE within the first year of follow-up)
- Neoplasm, obesity, uncontrolled diabetes, Hepatitis C, HIV/AIDS, helminthiases, tuberculosis, compromised immune system, smoking history, or pregnancy

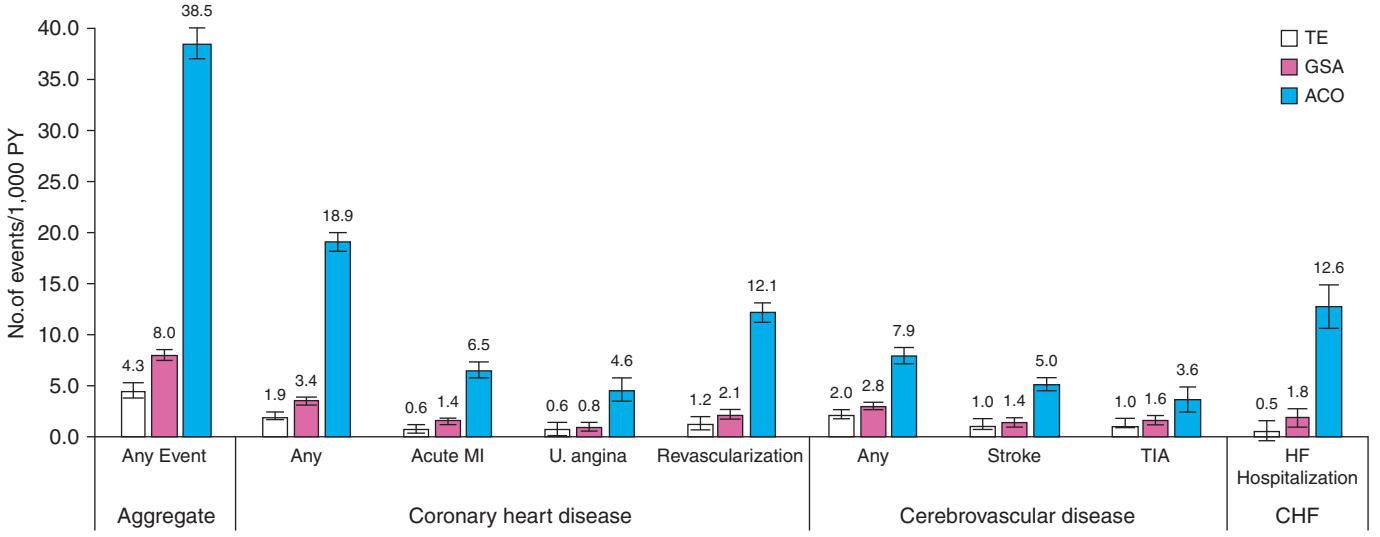

Figure 1. Age- and sex-standardized rates of cardiovascular events in cohorts of severe asthma patients. ACO = asthma–COPD overlap; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; GSA = general severe asthma; HF = heart failure; MI = myocardial infarction; PY = patient-years; TE = trial-eligible; TIA = transient ischemic attack; U. angina = unstable angina.

Table 2. Rates of cardiovascular events per 1,000 person-years with 95% CIs by age group and sex

CV Event	TE				GSA				ACO		
All patients	All Ages*	18–44 Yr	45–64 Yr	65–75 Yr	All Ages*	18–44 Yr	45–64 Yr	⩾65 Yr	All Ages*	45–64 Yr	⩾65 Yr
All patients											
Any event (aggregate)	4.3 (3.4–5.4)	2.3 (1.5–3.4)	5.9 (4.7–7.5)	11.9 (5.7–24.8)	8.0 (7.2–8.9)	3.3 (2.7–4.1)	9.2 (8.1–10.4)	27.2 (20.3–36.5)	38.5 (36.4–40.6)	35.8 (32.7–39.2)	41.8 (37.3–46.8)
Any coronary heart disease	1.9 (1.3–2.7)	0.7 (0.3–1.4)	3.0 (2.1–4.2)	6.3 (2.3–17.4)	3.4 (2.9–3.9)	0.8 (0.5–1.1)	4.7 (4–5.5)	11.9 (8.1–17.4)	18.9 (17.5–20.5)	17.1 (15.2–19.2)	21.2 (18.3–24.5)
Acute MI	0.6 (0.4–1.1)	0.2 (0–0.8)	1.4 (0.9–2.3)	0.0 (0.0–4.0‡)	1.4 (1.1–1.8)	0.5 (0.3–0.8)	1.8 (1.4–2.3)	5.0 (2.9–8.9)	6.5 (5.6–7.4)	6.0 (5.1–7.1)	6.9 (5.6–8.5)
Unstable angina	0.6 (0.3–1.2)	0.5 (0.2–1.2)	0.7 (0.4–1.6)	1.4 (0.1–13.4)	0.8 (0.6–1.1)	0.2 (0.1–0.5)	1.1 (0.8–1.5)	2.7 (1.3–5.8)	4.6 (3.9–5.3)	4.5 (3.6–5.7)	4.4 (3.3–6)
Coronary revascularization	1.2 (0.7–1.9)	0.1 (0–0.7)	2.1 (1.4–3.1)	5.0 (1.7–14.9)	2.1 (1.7–2.6)	0.2 (0.1–0.5)	3.2 (2.7–3.9)	7.6 (4.8–12)	12.1 (11.0–13.4)	11 (9.5–12.7)	13.3 (11.2–15.9)
Any cerebrovascular disease	2.0 (1.4–2.7)	1.3 (0.8–2.3)	2.7 (1.9–3.8)	2.6 (0.6–10.8)	2.8 (2.4–3.4)	1.7 (1.3–2.2)	3.1 (2.6–3.8)	7.0 (4.3–11.5)	7.9 (6.9–8.8)	7.6 (6.4–9)	8.3 (6.7–10.3)
TIA	1.0 (0.6–1.7)	0.8 (0.4–1.5)	1.2 (0.7–1.9)	2.6 (0.7–10.6)	1.6 (1.3–2.0)	1 (0.7–1.4)	1.5 (1.2–2)	4.9 (2.7–8.6)	3.6 (3.0–4.3)	3.5 (2.8–4.3)	4.0 (3.0–5.3)
Stroke	1.0 (0.6–1.6)	0.6 (0.3–1.3)	1.7 (1.1–2.6)	0.0 (0.0–4.0‡)	1.4 (1.1–1.8)	0.8 (0.6–1.2)	1.9 (1.5–2.4)	2.4 (1.1–5.2)	5.0 (4.3–5.8)	4.8 (4–5.8)	5.3 (4.1–6.7)
HF hospitalization	0.5 (0.1–1.1)	0.2 (0.1–0.9)	0.2 (0.1–0.7)	3.6 (0.6–23.8)	1.8 (1.4–2.3)	0.8 (0.5–1.3)	1.4 (1–1.9)	8.3 (3.7–18.5)	12.6 (11.5–13.9)	11.8 (9.9–14)	13.7 (11–17)
Females†											
Any event (aggregate)	3.5 (2.6–4.8)	2.0 (1.2–3.5)	4.9 (3.6–6.6)	5.9 (1.8–19.1)	6.9 (6.0–8.0)	3.0 (2.4–3.9)	7.3 (6.3–8.6)	22.1 (15.2–32.1)	30.2 (28.9–31.5)	29.6 (26.4–33.2)	33.6 (28.8–39.3)
Any coronary heart disease	1.3 (0.7–2.3)	0.5 (0.1–1.5)	1.7 (1–3)	3.8 (0.7–20)	2.3 (1.8–3.0)	0.5 (0.3–0.9)	3.1 (2.4–3.9)	7.7 (4.5–13.4)	13.1 (12.3–14.0)	12.2 (10.3–14.3)	15.7 (12.8–19.3)
Acute MI	0.4 (0.2–1.1)	0.2 (0–1.2)	0.8 (0.3–1.8)	0.0 (0.0–5.8‡)	0.9 (0.6–1.3)	0.4 (0.2–0.7)	1.0 (0.7–1.5)	2.9 (1.2–6.7)	4.6 (4.1–5.2)	4.5 (3.5–5.7)	5.3 (3.8–7.2)
Unstable angina	0.4 (0.1–1.2)	0.3 (0.1–1.3)	0.2 (0.1–0.9)	1.9 (0.3–13.7)	0.6 (0.3–1.0)	0.1 (0–0.4)	0.7 (0.5–1.1)	2 (0.7–5.3)	3.5 (3.1–4.0)	3.6 (2.7–4.8)	3.6 (2.4–5.4)
Coronary revascularization	0.6 (0.2–1.4)	0.0 (0.0–5.0‡)	1.0 (0.5–2.0)	1.8 (0.2–16.6)	1.4 (1.0–1.9)	0.0 (0–0.3)	1.9 (1.4–2.5)	5.8 (3–10.9)	7.2 (6.6–7.9)	6.7 (5.4–8.4)	8.6 (6.5–11.3)
Any cerebrovascular disease	1.9 (1.3–2.9)	1.4 (0.7–2.7)	3.0 (2.1–4.4)	0.0 (0.0–5.8‡)	3.0 (2.4–3.7)	1.9 (1.4–2.5)	3.2 (2.5–4)	7.2 (4–12.8)	7.6 (7.0–8.3)	8.1 (6.6–9.8)	7.4 (5.6–9.9)
TIA	0.9 (0.5–1.7)	0.8 (0.3–1.9)	1.4 (0.8–2.4)	0.0 (0.0–5.8‡)	1.6 (1.2–2.1)	1.0 (0.7–1.5)	1.4 (1.0–2.0)	4.6 (2.2–9.3)	3.7 (3.3–4.2)	4.1 (3.2–5.2)	3.4 (2.3–5)
Stroke	1.1 (0.7–1.9)	0.6 (0.2–1.7)	1.9 (1.2–3.1)	0.0 (0.0–5.8‡)	1.6 (1.2–2.1)	0.8 (0.5–1.3)	2.1 (1.6–2.7)	3.0 (1.3–6.8)	4.5 (4.1–5.1)	4.7 (3.7–6)	4.6 (3.2–6.5)
HF hospitalization	0.3 (0.03–1.1)	0.2 (0–1.1)	0.1 (0–0.8)	1.9 (0.3–13.7)	1.6 (1.2–2.2)	0.7 (0.4–1.3)	1.1 (0.7–1.8)	7.3 (2.7–19.7)	10.1 (9.4–10.9)	9.9 (7.9–12.4)	11.4 (8.4–15.3)
Males†											
Any event (aggregate)	6.2 (4.3–8.5)	2.7 (1.4–4.9)	8.2 (5.6–12)	23.8 (8.7–65.2)	10.5 (9.0–12.2)	4.0 (2.9–5.5)	13.6 (11.2–16.4)	38.4 (24.1–61.4)	51.6 (49.6–53.7)	49.4 (42.9–56.9)	54.9 (46.6–64.8)
Any coronary heart disease	3.4 (2.1–5.3)	1 (0.4–2.6)	5.6 (3.6–8.7)	11.6 (3.3–41.6)	5.8 (4.7–7.0)	1.4 (0.8–2.4)	8.7 (7–10.8)	20.8 (12.2–35.4)	28.6 (27.1–30.2)	27.8 (23.5–32.9)	29.9 (24.5–36.4)
Acute MI	1.1 (0.6–2.3)	0.2 (0–1.8)	2.7 (1.5–4.8)	0.0 (0.0–12.5‡)	2.7 (1.9–3.6)	0.8 (0.4–1.5)	3.8 (2.7–5.2)	9.9 (4.6–21.2)	9.5 (8.7–10.5)	9.6 (7.5–12.2)	9.5 (7.1–12.7)
Unstable angina	1.1 (0.5–2.3)	0.7 (0.2–2.5)	1.9 (0.8–4.5)	0.0 (0.0–12.5‡)	1.4 (0.9–2.1)	0.5 (0.2–1.2)	1.9 (1.2–3.1)	4.5 (1.4–13.9)	6.2 (5.5–7.0)	6.5 (4.5–9.4)	5.8 (3.7–9.3)
Coronary revascularization	2.6 (1.4–4.3)	0.2 (0–1.8)	4.4 (2.7–7)	11.9 (3.5–40.3)	3.7 (2.9–4.8)	0.7 (0.3–1.4)	6.5 (5.1–8.4)	11.5 (5.9–22.2)	20.5 (19.3–21.9)	20.3 (16.8–24.5)	20.9 (16.8–26.2)
Any cerebrovascular disease	2.0 (1.0–3.7)	1.3 (0.5–3.3)	2.1 (1–4.6)	7.6 (1.2–47.7)	2.5 (1.8–3.3)	1.4 (0.8–2.4)	3 (2–4.3)	6.8 (2.7–17.3)	7.9 (7.1–8.8)	6.7 (4.7–9.4)	9.7 (6.8–13.9)
TIA	1.3 (0.4–2.8)	0.7 (0.2–2.3)	0.7 (0.2–2.2)	8.3 (2.1–33.3)	1.6 (1.1–2.4)	0.8 (0.4–1.7)	1.8 (1.2–2.9)	5.5 (2.1–14.4)	3.2 (2.7–3.8)	2.3 (1.3–4)	4.6 (2.8–7.8)
Stroke	0.8 (0.2–2.2)	0.5 (0.1–2)	1.2 (0.5–2.9)	0.0 (0.0–12.5‡)	1.0 (0.6–1.6)	0.8 (0.4–1.6)	1.4 (0.8–2.4)	1.1 (0.1–8.8)	5.7 (5.0–6.5)	5.1 (3.5–7.5)	6.5 (4.3–9.9)
HF hospitalization	0.8 (0.2–2.2)	0.4 (0.1–1.9)	0.5 (0.1–2.2)	5.9 (0.3–102.6)	2.2 (1.5–3.1)	1.1 (0.6–2.2)	1.9 (1.1–3.3)	10.5 (2.8–38.7)	16.5 (15.4–17.7)	15.9 (12.1–20.9)	17.4 (12.6–24)

Definition of abbreviations: ACO = asthma–COPD overlap; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; GSA = general severe asthma; HF = heart failure; MI = myocardial infarction; TE = trial-eligible; TIA = transient ischemic attack.

*Age- and sex-standardized rates.

†Age-standardized rates.

‡Estimated upper bound using the "rule of three." The rule of three states that the 95% upper confidence bound when 0 events are observed in *N* trials can be estimated as 3/*N* (11, 12).

The following CVEs were evaluated: *1*) coronary heart disease, defined as acute myocardial infarction (any diagnosis), unstable angina (primary diagnosis) during an inpatient or emergency department encounter, or coronary revascularization procedure; *2*) cerebrovascular disease, defined as any diagnosis of stroke or transient ischemic attack; and *3*) congestive heart failure (CHF), defined as hospital admission with a primary diagnosis of CHF or secondary diagnosis of CHF with a primary diagnosis of pulmonary edema or hypostatic pneumonia. Events were considered distinct if they were >30 days apart. We calculated aggregate CVE rates (number of events per 1,000 patient-years [PY]) and rates for individual CV conditions using negative binomial regression. We generated age group– (18–44 yr, 45–64 yr, and ≥65 yr) and sex-stratified rates to allow comparisons between cohorts among subgroups with similar CV risk. To improve generalizability, our estimates were standardized to the U.S. severe asthma and ACO populations using age and sex distributions obtained from the National Health Interview Survey (10). To further account for differences by age and improve the comparability of CVE rates between the cohorts, we performed the following sensitivity analyses: *1*) calculated CVE rates for age groups at 5-year intervals from 45 to 75 years (no ACO patients aged <45 yr and no TE patients aged >75 yr) and *2*) calculated age-adjusted CVE rate ratios (RRs) and 95% confidence intervals (CIs) for the ACO versus GSA cohorts and ACO versus TE cohorts.

Results

Baseline characteristics of the TE ($N = 20{,}768$), GSA ($N = 32{,}439$), and ACO ($N = 13{,}028$) cohorts are shown in Table 1. The median age of the ACO cohort (61 yr) was higher than that of the other cohorts (GSA, 47 yr; TE, 46 yr). Compared with the mean aggregate CVE rate in the TE cohort (4.3; 95% CI, 3.4–5.4 per 1,000 PY), the rate in the GSA cohort was almost twofold higher (8.0; 95% CI, 7.2–8.9 per 1,000 PY), whereas that in the ACO cohort was almost ninefold higher (38.5; 95% CI, 36.4–40.6 per 1,000 PY) (Figure 1). Patients in the ACO cohort had several-fold higher CVE rates than those in the TE and GSA cohorts across broad age and sex subgroups (Table 2), with a similar trend across 5-year age subgroups (data not shown) and age-adjusted RRs (vs. TE: RR, 5.7; 95% CI, 4.4–7.3 and vs. GSA: RR, 3.2; 95% CI, 2.8–3.6; data not shown). Men had 1.5- to 1.7-fold higher aggregate CVE rates than women in all three cohorts (Table 2).

Discussion

This study showed that CVE rates in the GSA and ACO cohorts were higher than in the TE cohort. Such population-level differences in background CV risk should be considered when interpreting clinical trial safety data. Patients in the ACO cohort had the highest CVE rates. This trend was consistent across broad and narrow age groups and age-adjusted RRs, indicating that the higher rates in patients with ACO cannot be explained by differences in age alone. Overall, our results show that clinicians should expect to see several-fold higher CVE rates among patients with severe, suboptimally controlled asthma, particularly patients with ACO, than those that have been reported in clinical trials. The higher CVE rates among patients with ACO may be attributed to a higher prevalence of risk factors such as smoking history, greater lung function impairment, and the presence of comorbidities such as diabetes and hypertension. A comprehensive evaluation of these risk factors and their distributions among the patient cohorts was outside the scope of this study.

In our study, the aggregate CVE rate in the TE cohort was 4.3 per 1,000 PY (approximately two events, on average, if 500 patients are followed for 1 year); thus, trialists should expect to see a small number of CVEs independent of the investigational drug even among low-risk (i.e., those without or with well-managed CV disease) patients with severe, suboptimally controlled asthma.

This study has a few limitations inherent to the use of retrospectively collected insurance claims data. First, we could not use the standard definition of major adverse CV events because death is not reliably captured in claims data. Second, the diagnosis of severe asthma was based on diagnosis codes and prescription fills recorded in medical and pharmacy claims. Third, we could not apply certain trial inclusion criteria, such as lung function measures, to the TE cohort because these were not available in the data. Lastly, smoking status, a major determinant of COPD, was not included in the case definition. Furthermore, we relied on COPD diagnoses to identify patients with ACO; however, the diagnosis of COPD in the context of asthma is often ambiguous in the clinical setting. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank Yingjie Ding, M.S., and Anup Abraham, M.P.H. (Genesis Research) for their assistance with data analysis and Deborah Solymar, Ph.D. (Genentech Inc.) for providing editing assistance.

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Secondary Bacterial Pneumonias and Bloodstream Infections in Patients Hospitalized with COVID-19

To the Editor:

Hospitalized patients, particularly those who are critically ill, are at risk for "secondary" infections (1, 2). Initial reports of patients hospitalized with coronavirus disease (COVID-19) indicate that 10–33% develop bacterial pneumonia (3, 4) and 2–6% develop bloodstream infection (BSI) (5, 6). Few studies have reported patient characteristics or the impact of intensive care unit (ICU) admission on secondary infections (3, 6–8). We conducted a descriptive study to identify the prevalence, microbiology, and outcomes of secondary pneumonias and BSIs in patients hospitalized with COVID-19.

Methods

The Emory University Institutional Review Board approved this study. Patients :18 years old with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time polymerase chain reaction assay admitted to four academic hospitals in Atlanta, Georgia, from February 15 to May 16, 2020, were included. Data were extracted from the electronic medical record (Cerner Millennium) through June 16, 2020, including comorbidities (identified by International Classification of Diseases, 10th revision codes).

Blood cultures were incubated in BACT/ALERT 3D (bioMérieux, Inc.), and respiratory cultures were inoculated on 5% sheep blood, chocolate, and MacConkey agars. Organisms were identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (bioMérieux, Inc.). Susceptibility testing was performed by Vitek 2 (bioMérieux, Inc.).

We used the U.S. Centers for Disease Control and Prevention (CDC) criteria to determine ventilator-associated events (VAEs), including infection-related ventilator-associated complications (IVACs) and possible ventilator-associated pneumonia (PVAP) (9).

Blood cultures were considered contaminated if one of two sets grew a typically nonpathogenic organism (e.g., coagulase-negative staphylococci) or if the clinical team determined the organism a contaminant. Two of three infectious diseases physicians (M.W.A., D.R.B., and A.B.) reviewed BSIs to determine clinical source and a third (J.T.J.) arbitrated disagreements. Infections were attributed to skin if there was a clinically infected wound or peripheral intravenous line but no central line.

We assessed in-hospital mortality, comparing patients with and without infections using the χ^2 test. SAS University Edition (SAS Institute) was used for data analysis.

Results

Patients. Among 774 patients hospitalized with COVID-19, the median age was 62 years (interquartile range, 50–73), 49.7% were female, and 66.6% were Black (Table 1). Hypertension (75.5%) and diabetes mellitus (45.7%) were the most common comorbidities. Three hundred thirty-five (43.3%) required ICU admission, 238 (30.7%) required mechanical ventilation, and 120 (15.5%) died.

Respiratory infections. Among 238 intubated patients, 201 (84.5%) had at least one respiratory culture sent, and 65 (27.3%) had a positive respiratory culture, with a total of 84 potential pathogens (Table 2). The most common bacteria were *Staphylococcus aureus* (29/84; 34.5%), *Pseudomonas aeruginosa* (16/84; 19.0%), and *Klebsiella* spp. (14/84; 16.7%), with only one *Aspergillus* spp. Mortality did not differ between intubated patients with an identified bacterial respiratory pathogen and those without (41.5% vs. 35.3%, $P = 0.37$).
Forty-six patients (19.3%) had a CDC-defined VAE (15.3 VAEs per 1,000 ventilator-days), 16 (6.7%) had an IVAC (5.3 IVACs per 1,000 ventilator-days), and 5 (2.1%) had a PVAP (1.7 PVAPs per 1,000 ventilator-days). Eleven (23.9%) patients with a VAE required a tracheostomy and 25 (54.3%) died. None of the five patients with PVAP died.

Among 536 (69.3%) nonintubated patients, 186 (34.7%) had *Legionella* urine antigens sent, and two (0.4%) were positive. Sixty-nine (12.9%) had at least one respiratory culture sent, and one was positive

Supported by the National Institute of Allergy and Infectious Diseases grants K23AI144036 (M.H.W.) and K23AI134182 (S.C.A.) and the National Center for Advancing Translational Sciences grant UL1TR002378, both at the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author Contributions: M.W.A., D.R.B., A.C.H.-R., A.B., M.H.W., C.R., and J.T.J. developed the study design. M.W.A., D.R.B., A.C.H.-R., A.B., D.J.M., S.C.A., C.S.K., and J.T.J. performed data analysis and/or interpretation. M.W.A., D.R.B., A.B., S.C.A., and J.T.J. wrote the manuscript.