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### Authors

Bajema, Kristina L
Berry, Kristin
Streja, Elani
et al.



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# Effectiveness of COVID-19 Treatment With Nirmatrelvir–Ritonavir or Molnupiravir Among U.S. Veterans: Target Trial Emulation Studies With One-Month and Six-Month Outcomes

**Kristina L. Bajema, MD, MSc; Kristin Berry, PhD; Elani Streja, PhD; Nallakkandi Rajeevan, PhD; Yuli Li, MS; Pradeep Mutalik, MD; Lei Yan, PhD; Francesca Cunningham, PharmD; Denise M. Hynes, MPH, PhD, RN; Mazhgan Rowneki, MPH; Amy Bohnert, PhD, MHS; Edward J. Boyko, MD, MPH; Theodore J. Iwashyna, MD, PhD; Matthew L. Maciejewski, PhD; Thomas F. Osborne, MD; Elizabeth M. Viglianti, MD, MPH, MSc; Mihaela Aslan, PhD; Grant D. Huang, MPH, PhD; and George N. Ioannou, BMBCh, MS**

**Background:** Information about the effectiveness of oral antivirals in preventing short- and long-term COVID-19–related outcomes in the setting of Omicron variant transmission and COVID-19 vaccination is limited.

**Objective:** To measure the effectiveness of nirmatrelvir–ritonavir and molnupiravir for outpatient treatment of COVID-19.

**Design:** Three retrospective target trial emulation studies comparing matched cohorts of nirmatrelvir–ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir–ritonavir versus molnupiravir.

**Setting:** Veterans Health Administration (VHA).

**Participants:** Nonhospitalized veterans in VHA care who were at risk for severe COVID-19 and tested positive for SARS-CoV-2 during January through July 2022.

**Intervention:** Nirmatrelvir–ritonavir or molnupiravir pharmacotherapy.

**Measurements:** Incidence of any hospitalization or all-cause mortality at 30 days and from 31 to 180 days.

**Results:** Eighty-seven percent of participants were male; the median age was 66 years, and 18% were unvaccinated. Compared with matched untreated control participants, those treated with nirmatrelvir–ritonavir ($n$ = 9607) had lower 30-day risk for hospitalization (22.07 vs. 30.32 per 1000 participants; risk difference [RD], −8.25 [95% CI, −12.27 to −4.23] per 1000 participants) and death (1.25 vs. 5.47 per 1000 participants; RD, −4.22 [CI, −5.45 to −3.00] per 1000 participants). Among persons alive at day 31, reductions were seen in 31- to 180-day incidence of death (hazard ratio, 0.66 [CI, 0.49 to 0.89]) but not hospitalization (subhazard ratio, 0.90 [CI, 0.79 to 1.02]). Molnupiravir-treated participants ($n$ = 3504) had lower 30-day and 31- to 180-day risks for death (3.14 vs. 13.56 per 1000 participants at 30 days; RD, −10.42 [CI, −13.49 to −7.35] per 1000 participants; hazard ratio at 31 to 180 days, 0.67 [CI, 0.48 to 0.95]) but not hospitalization. A difference in 30-day or 31- to 180-day risk for hospitalization or death was not observed between matched nirmatrelvir- or molnupiravir-treated participants.

**Limitation:** The date of COVID-19 symptom onset for most veterans was unknown.

**Conclusion:** Nirmatrelvir–ritonavir was effective in reducing 30-day hospitalization and death. Molnupiravir was associated with a benefit for 30-day mortality but not hospitalization. Further reductions in mortality from 31 to 180 days were observed with both antivirals.

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Two pharmacotherapies—nirmatrelvir packaged with the boosting agent ritonavir (nirmatrelvir–ritonavir), and molnupiravir—received emergency use authorization from the U.S. Food and Drug Administration (FDA) in December 2021 for treatment of nonhospitalized persons with symptomatic COVID-19 who are at high risk for progression to severe COVID-19 (1, 2). The EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) randomized controlled trial showed a reduction in COVID-19–related hospitalization or death with nirmatrelvir–ritonavir, but there is less evidence of benefit for molnupiravir (3–5).

Effectiveness studies of nirmatrelvir–ritonavir and molnupiravir are needed because early clinical trials were conducted among unvaccinated participants before the emergence of the Omicron variant (B.1.1.529) and subsequent sublineages (3, 4). Randomized controlled trials did not directly compare efficacy of antiviral agents, nor did they evaluate outcomes beyond 29 days after symptomatic infection. Early observational studies of nirmatrelvir–ritonavir (6–9) and molnupiravir (10–12) have shown varying degrees of reduced risk for short-term hospitalization and death. Noninterventional studies that adhere to target trial emulation principles (13) are needed to carefully evaluate whether these antivirals are effective against the now-predominant Omicron variants, especially in older populations that are racially and ethnically diverse and have a high prevalence of underlying conditions.

The Veterans Health Administration (VHA), operated by the U.S. Department of Veterans Affairs (VA), is the

**See also:**

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Supplement

largest integrated health care system in the United States, providing care to more than 9 million veterans, the majority of whom are older and have a high burden of underlying medical conditions. The VHA has provided an opportunity for multiple target trial emulation studies of the comparative effectiveness of COVID-19 pharmacotherapies and vaccines (14–17). We used target trial emulation principles (13) to emulate 3 trials of nirmatrelvir–ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir–ritonavir versus molnupiravir during the Omicron era. We evaluated 30-day and 6-month incidence of hospitalization and death among nonhospitalized adult veterans who were infected with SARS-CoV-2 and were at high risk for progression to severe COVID-19.

## METHODS

### Specification and Emulation of Target Trials: Overall Study Design

We designed this retrospective cohort study to emulate 3 target randomized controlled trials of COVID-19 antivirals among symptomatic, nonhospitalized adult veterans enrolled in the VHA who had a first positive SARS-CoV-2 test result from 1 January through 31 July 2022 and were at high risk for progression to severe COVID-19. The target trials involved nirmatrelvir–ritonavir versus no SARS-CoV-2 antiviral or monoclonal antibody treatment (trial 1), molnupiravir versus no treatment (trial 2), and nirmatrelvir–ritonavir versus molnupiravir (trial 3). Follow-up extended through 31 January 2023 to allow ascertainment of 30-day and 6-month posttreatment outcomes. Target trial emulation applies design principles from randomized trials to the analysis of observational data, thereby explicitly tying the design and analysis to the hypothetical trial it is emulating (18). **Supplement Table 1** (available at Annals.org) compares the critical study design features of the specified and emulated target trials (13). We used a matched cohort design to emulate the balance achieved through randomization. Untreated persons were assigned an index date that was the same number of days after the date they first tested positive for SARS-CoV-2 (test-positive date) as the treatment date of the matched treated patients (**Supplement Figure 1**, available at Annals.org). Eligibility criteria were ascertained as of this index date, and follow-up for each matched set began at the start of the following day and continued until occurrence of an outcome event or the end of the 6-month follow-up. The study was approved by the VA Central Institutional Review Board and followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline.

### Data Sources

We used the VHA's COVID-19 Shared Data Resource (CSDR), supported by the VA Informatics and Computing Infrastructure (VINCI), which integrates multiple data sources to provide patient-level COVID-19–related information on VHA enrollees. The CSDR includes information on laboratory-confirmed SARS-CoV-2 tests (either nucleic acid amplification or antigen tests) with positive results within the VHA as well as SARS-CoV-2 tests performed outside the VHA and documented in VHA clinical records. Positive test results are identified by the VA National Surveillance Tool and provisioned to the CSDR to support national VA research and operational needs. These data were supplemented with detailed claims data from the VA Community Care program, which coordinates and reimburses VA purchased care provided in the community, and from the Centers for Medicare & Medicaid Services (CMS), which are provisioned by the VA Information Resource Center (VIReC). Data from the VA Community Care program and CMS–Medicare data were used to capture additional COVID-19 antiviral or monoclonal antibody treatments (nirmatrelvir–ritonavir, molnupiravir, bebtelovimab, sotrovimab, remdesivir), COVID-19 vaccinations, and hospitalizations. For veterans prescribed nirmatrelvir–ritonavir or molnupiravir, rule-based natural-language processing was used to ascertain the date of symptom onset recorded in clinical notes and curated through chart review.

### Eligibility Criteria and Study Population

We identified all VHA enrollees aged 18 years or older with a first positive SARS-CoV-2 test result in the CSDR from 1 January to 31 July 2022 (**Figure 1**). We limited the study population to VHA enrollees with a VHA primary care encounter in the 18 months preceding the test-positive date who were alive and not hospitalized within 7 days before through the day following the test-positive date. Treated participants who died or were hospitalized on or before their antiviral treatment date were also excluded; identical exclusions for untreated participants relative to their assigned index date were later applied during the matching process. We excluded persons who received any COVID-19 treatment before the test-positive date as well as persons who did not have at least 1 risk factor for progression to severe COVID-19 (**Supplement Tables 2** and **3**, available at Annals.org) (19). For each trial, we identified participants' test-positive location to restrict the eligible population to VA facilities that had prescribed the oral antivirals being compared. For comparisons involving nirmatrelvir–ritonavir, we excluded persons with advanced renal or hepatic disease and those with absolute drug contraindications (**Supplement Methods** and **Supplement Table 4**, available at Annals.org) (20). For comparisons involving molnupiravir, we excluded pregnant persons. Persons were eligible as untreated comparators if they did not receive any outpatient COVID-19 pharmacotherapies on or before their assigned index date.

### Cohort Matching

Two matching steps were used to achieve balance of covariates between comparator groups and reduce confounding.

#### *Exact Matching*

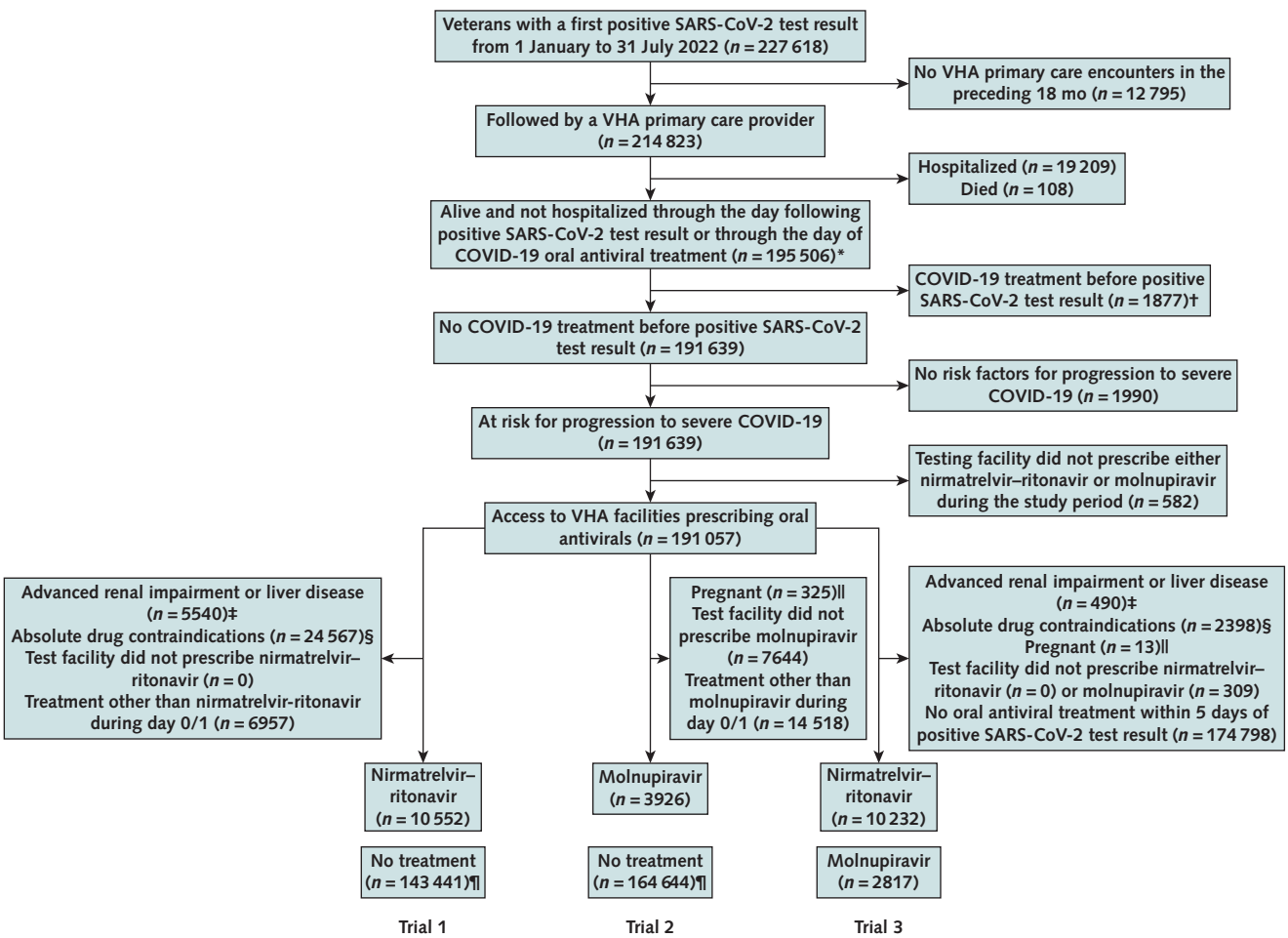
We first performed exact matching of each eligible participant who received nirmatrelvir–ritonavir or molnupiravir to all eligible participants who were untreated as of their assigned index date by using 4 factors: National Institutes of Health tier of prioritization for anti–SARS-CoV-2 therapies (**Supplement Table 5**, available at Annals.

org); Veterans Integrated Services Network (the 18 geographic administrative regions of the VA); VA facility complexity (1a vs. 1b to 3) (21); and calendar time, centered within ±7 days of the test-positive date of the matched comparator. For the comparison of nirmatrelvir–ritonavir versus molnupiravir, additional exact matching based on the interval between the test date and the treatment date (0/1 day [both days considered as a single unit] vs. 2 to 5 days) was done.

### *Propensity Score Matching*

Within each exact-matching stratum, we performed an additional propensity score matching step with replacement in a 1:*k* variable ratio, where *k* varied on the basis of the number of propensity score ties. All ties were included to avoid imbalance due to random pruning. In the propensity score logistic regression model that predicted treatment, we included demographic, geographic, health care utilization, and clinical factors selected a priori on the basis of their association with both the treatment exposure and outcomes (Supplement Tables 6 and 7, available at Annals.org). Missing or unknown values for Care Assessment Need score and race or ethnicity were uncommon and were treated as separate "unknown" categories (22–24). Up to 4 untreated participants with the closest propensity scores within 0.2 standard deviations of the mean (SDM) were matched to each treated participant. Untreated participants could be matched to more than 1 treated participant. In accordance with an intention-to-treat approach to analysis, assigned untreated participants who later received treatment after

***Figure 1.*** Identification of eligible veterans in the emulation of 3 target trials comparing the effectiveness of nirmatrelvir–ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir–ritonavir versus molnupiravir.




VHA = Veterans Health Administration.

* Includes all persons not hospitalized within 7 days before through the day following the date they tested positive for SARS-CoV-2 and treated persons not hospitalized on or before receipt of nirmatrelvir–ritonavir or molnupiravir.

† Nirmatrelvir–ritonavir, molnupiravir, any anti–SARS-CoV-2 monoclonal antibodies, or remdesivir.

‡ See the Supplement Methods (available at Annals.org).

§ See Supplement Table 4 (available at Annals.org).

‖ Documented within 1 week before the date of a SARS-CoV-2 test with a positive result.

¶ Numbers eligible for matching include persons who received nirmatrelvir–ritonavir, molnupiravir, bebtelovimab, sotrovimab, or remdesivir between January and July 2022.

the index date were not censored and were analyzed in the no-treatment group. This approach was also used for participants assigned to nirmatrelvir–ritonavir or molnupiravir groups who later received a different pharmacotherapy. Each molnupiravir-treated participant was matched with replacement to a single participant treated with nirmatrelvir–ritonavir with the closest propensity score within 0.4 SDM. Participants treated with nirmatrelvir–ritonavir could serve as matched comparators for more than 1 molnupiravir-treated participant.

### Primary End Points

#### *Short-Term Outcomes*

Primary short-term outcomes were any hospitalization or all-cause mortality through day 30 after the index date. We also evaluated intensive care unit (ICU) admission and mechanical ventilation occurring during hospitalizations through day 30 as secondary outcomes.

#### *Long-Term Outcomes*

We determined the 6-month incidence of any hospitalization or all-cause mortality, measured from 31 to 180 days among matched groups of participants who were alive at day 31.

### Statistical Analysis

Patient characteristics were compared between groups in each of the 3 trial emulations. For 30-day outcomes of hospitalization or death, we calculated unadjusted risks, risk differences (RDs), and risk ratios (RRs) (and 95% CIs) and plotted Kaplan–Meier curves. For incidence of long-term outcomes extending from 31 to 180 days, we used unadjusted time-to-event analyses that treated death as a competing risk. Prespecified subgroup analyses were considered by age (18 to 64 vs. ≥65 years), vaccination status (unvaccinated vs. any primary or booster vaccination), immunocompromised status, early versus late treatment (0/1 day vs. 2 to 5 days after the test-positive date), presence or absence of COVID-19–related symptoms within 30 days before the test-positive date, and presence of COVID-19–related symptoms within 5 days before the test-positive date. To address the potential effect of illness severity at the time the patient tested positive for SARS-CoV-2 as an unmeasured confounder, we conducted sensitivity analysis by calculating an E-value (25, 26).

All analyses were importance-weighted to account for variable-ratio matching (27). A robust sandwich-type variance estimator was used to account for clustering within the matched group due to ties in the propensity score, clustering within participants due to matching with replacement, and clustering in the cross-classification of the matched and within-participant clusters (28). Analyses were conducted using Stata (StataCorp).

### Role of the Funding Source

The VA Central Office had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. Authors who are employees of the VA participated in each of these activities.

## RESULTS

### Patient Population

A total of 191 057 veterans who first tested positive for SARS-CoV-2 during January through July 2022 were identified for inclusion in our study, of whom 10 552 of 153 993 (6.9%) who were eligible for matching received nirmatrelvir–ritonavir in trial 1 and 3926 of 168 570 (2.3%) who were eligible for matching received molnupiravir in trial 2 (**Figure 1**). In trial 3, 10 232 nirmatrelvir–ritonavir recipients and 2817 molnupiravir recipients who were eligible for matching were identified. Oral antiviral prescriptions and positive SARS-CoV-2 test results during the study period are shown in **Supplement Figure 2** (available at Annals.org). Baseline characteristics were well balanced between the matched comparator groups of each of the 3 emulated trials, with all SDMs below 0.10 (**Appendix Table**, available at Annals.org; **Supplement Figures 3** to **5**, available at Annals.org). Matching with replacement allowed matching of 9607 (91.0%) of the eligible participants treated with nirmatrelvir–ritonavir in trial 1, 3504 (89.3%) of the eligible molnupiravir-treated participants in trial 2, and 1750 (62.1%) of the molnupiravir-treated participants in trial 3, who were matched to 1441 unique participants treated with nirmatrelvir–ritonavir (**Supplement Table 8**, available at Annals.org). Crossovers after initial matched assignment occurred in 372 (3.9%) persons assigned to no treatment in trial 1 and 141 (4.0%) persons assigned to no treatment in trial 2 (**Supplement Table 9**, available at Annals.org).

Across all matched groups in the 3 trials, most participants were male (range, 85.8% to 91.2%) and of advanced age (range of median ages, 66 to 70 years); 6.5% to 9.3% were Hispanic, 62.6% to 68.8% were White, and 14.5% to 19.3% were Black. Participants had a median of 4 to 5 medical conditions associated with risk for severe COVID-19 (19), led by obesity (range, 81.6% to 82.9%), mental health conditions (range, 40.7% to 45.7%), and cardiovascular disease (range, 32.6% to 49.1%) (**Appendix Table**). Overall, 10.7% to 17.9% of participants were not vaccinated against COVID-19. Most participants were treated within 0/1 day of the SARS-CoV-2 test, including 8952 (93.2%) who received nirmatrelvir–ritonavir in trial 1 and 3178 (90.7%) who received molnupiravir in trial 2.

### Short-Term Outcomes

#### *Nirmatrelvir–Ritonavir Versus No Treatment*

The 30-day rate of hospitalization or death was lower in the nirmatrelvir–ritonavir group than the no-treatment group (23.0 vs. 34.17 events per 1000 persons; RD, −11.16 [95% CI, −15.30 to −7.03] events per 1000 persons; RR, 0.67 [CI, 0.58 to 0.79]) (**Figure 2** and **Table 1**). There were reductions in death (RD, −4.22 [CI, −5.45 to −3.00] events per 1000 persons; RR, 0.23 [CI, 0.13 to 0.41]), hospitalization (RD, −8.25 [CI, −12.27 to −4.23] events per 1000 persons; RR, 0.73 [CI, 0.62 to 0.85]), ICU admission (RD, −2.40 [CI, −3.95 to −0.85] events per 1000 persons; RR, 0.51 [CI, 0.32 to 0.81]), and mechanical ventilation (RD, −2.19 [CI, −3.23 to −1.14] events per 1000

persons; RR, 0.28 [CI, 0.13 to 0.58]). Reduction in risk for hospitalization or death was similar across groups based on age, immunocompromised status, and presence or absence of symptoms, whereas nirmatrelvir–ritonavir was associated with benefit only among persons who had received primary or booster vaccination and treatment at day 0/1 (Appendix Figure [*top*], available at Annals.org).

### *Molnupiravir Versus No Treatment*

The 30-day risk for hospitalization or death was similar between the molnupiravir and no-treatment groups overall (43.66 vs. 53.37 events per 1000 persons; RD, −9.70 [CI, −18.04 to −1.37] events per 1000 persons; RR, 0.82 [CI, 0.68 to 0.98]). There was a reduction in death (RD, −10.42 [CI, −13.49 to −7.35] events per 1000 persons; RR, 0.23 [CI, 0.13 to 0.43]) but not hospitalization (RD, −1.00 [CI, −9.05 to −7.05] events per 1000 persons; RR, 0.98 [CI, 0.81 to 1.18]), ICU admission, or mechanical ventilation. Molnupiravir was associated with reduced risk for hospitalization or death only among persons who were aged 65 years or older, were unvaccinated, were immunocompromised, were treated at day 0/1, or had no documented symptoms (Appendix Figure [*bottom*]).

### *Nirmatrelvir–Ritonavir Versus Molnupiravir*

The 30-day risk for hospitalization or death was similar between the nirmatrelvir–ritonavir and molnupiravir groups (28.00 vs. 5.14 events per 1000 persons; RD, 2.86 [CI, −8.17 to 13.89] events per 1000 persons; RR, 1.11 [CI, 0.74 to 1.68]).

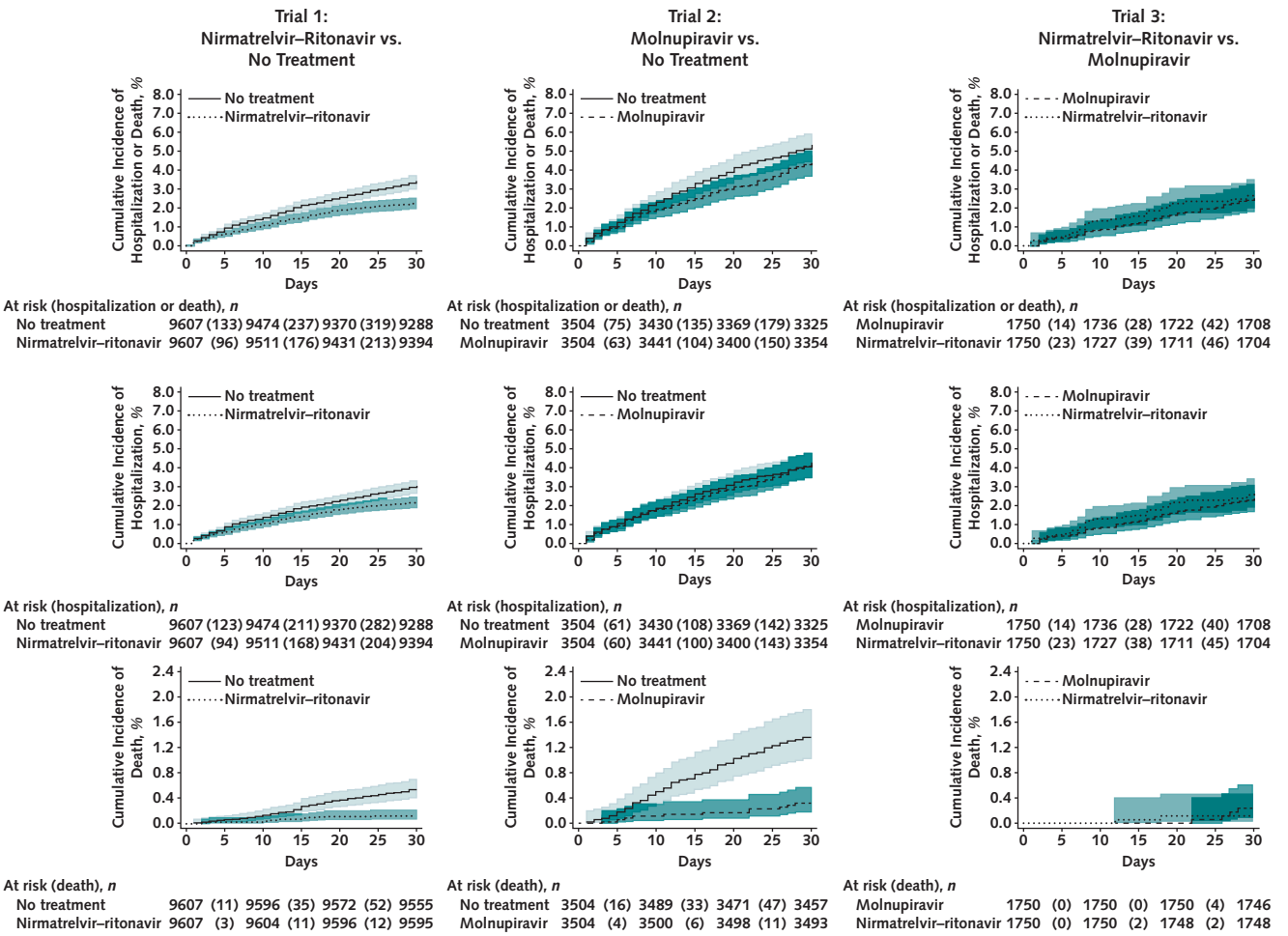
### *Sensitivity Analysis*

The calculated E-value for illness severity using estimates of RR for death within 30 days in trials 1 and 2 was 8.16 (Supplement Figure 6, available at Annals.org).

## Long-Term Outcomes

Compared with the no-treatment group, the 31- to 180-day incidence of death was lower in both the

***Figure 2.*** Cumulative 30-day incidence of hospitalization or death among outpatient veterans testing positive for SARS-CoV-2, by study group.




The figure shows comparisons of nirmatrelvir–ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir–ritonavir versus molnupiravir. Shaded areas indicate 95% CIs.

***Table 1.*** Incidence of Hospitalization, Death, ICU Admission, and Mechanical Ventilation at Day 30 Among Veterans Who Tested Positive for SARS-CoV-2 From 1 January to 31 July 2022

| Outcome | Trial 1: Nirmatrelvir–Ritonavir vs. No Treatment | | | | | |
|---|---|---|---|---|---|---|
| | Events, *n* | | Incidence (95% CI), *events per 1000 persons* | | Risk Difference (95% CI) | Risk Ratio (95% CI) |
| | Nirmatrelvir–Ritonavir (*n* = 9607) | No Treatment (*n* = 9607) | Nirmatrelvir–Ritonavir | No Treatment | | |
| Hospitalization or death* | 221 | 328.3 | 23.00 (20.19 to 26.20) | 34.17 (31.42 to 37.15) | −11.16 (−15.30 to −7.03) | 0.67 (0.58 to 0.79) |
| Hospitalization | 212 | 291.3 | 22.07 (19.31 to 25.20) | 30.32 (27.68 to 33.20) | −8.25 (−12.27 to −4.23) | 0.73 (0.62 to 0.85) |
| Death | 12 | 52.6 | 1.25 (0.71 to 2.20) | 5.47 (4.55 to 6.58) | −4.22 (−5.45 to −3.00) | 0.23 (0.13 to 0.41) |
| ICU admission | 24 | 47.1 | 2.50 (1.67 to 3.72) | 4.90 (3.85 to 6.24) | −2.40 (−3.95 to −0.85) | 0.51 (0.32 to 0.81) |
| Mechanical ventilation | –† | 29 | 0.83 (0.42 to 1.66) | 3.02 (2.26 to 4.03) | −2.19 (−3.23 to −1.14) | 0.28 (0.13 to 0.58) |
| | **Trial 2: Molnupiravir vs. No Treatment** | | | | | |
| | Events, *n* | | Incidence (95% CI), *events per 1000 persons* | | Risk Difference (95% CI) | Risk Ratio (95% CI) |
| | Molnupiravir (*n* = 3504) | No Treatment (*n* = 3504) | Molnupiravir | No Treatment | | |
| Hospitalization or death* | 153 | 187 | 43.66 (37.37 to 50.96) | 53.37 (48.40 to 58.81) | −9.70 (−18.04 to −1.37) | 0.82 (0.68 to 0.98) |
| Hospitalization | 146 | 149.5 | 41.67 (35.53 to 48.81) | 42.67 (38.13 to 47.71) | −1.00 (−9.05 to 7.05) | 0.98 (0.81 to 1.18) |
| Death | 11 | 47.5 | 3.14 (1.74 to 5.66) | 13.56 (11.31 to 16.24) | −10.42 (−13.49 to −7.35) | 0.23 (0.13 to 0.43) |
| ICU admission | 27 | 25.6 | 7.71 (5.29 to 11.21) | 7.30 (5.52 to 9.66) | 0.40 (−3.10 to 3.91) | 1.06 (0.66 to 1.68) |
| Mechanical ventilation | 11 | 11.8 | 3.14 (1.74 to 5.66) | 3.38 (2.43 to 4.70) | −0.24 (−2.40 to 1.93) | 0.93 (0.47 to 1.83) |
| | **Trial 3: Nirmatrelvir–Ritonavir vs. Molnupiravir** | | | | | |
| | Events, *n* | | Incidence (95% CI), *events per 1000 persons* | | Risk Difference (95% CI) | Risk Ratio (95% CI) |
| | Nirmatrelvir–Ritonavir (*n* = 1750) | Molnupiravir (*n* = 1750) | Nirmatrelvir–Ritonavir | Molnupiravir | | |
| Hospitalization or death* | 49 | 44 | 28.00 (20.53 to 38.08) | 25.14 (18.76 to 33.63) | 2.86 (−8.17 to 13.89) | 1.11 (0.74 to 1.68) |
| Hospitalization | 48 | 42 | 27.43 (20.03 to 37.45) | 24.00 (17.78 to 32.33) | 3.43 (−7.43 to 14.29) | 1.14 (0.75 to 1.74) |
| Death | –† | –† | 1.14 (0.29 to 4.57) | 2.29 (0.86 to 6.08) | −1.14 (−3.89 to 1.60) | 0.50 (0.09 to 2.73) |
| ICU admission | –† | –† | 2.86 (1.01 to 8.04) | 3.43 (1.54 to 7.62) | −0.57 (−4.61 to 3.47) | 0.83 (0.22 to 3.09) |
| Mechanical ventilation | –† | –† | 2.29 (0.69 to 7.57) | 1.71 (0.55 to 5.31) | 0.57 (−2.79 to 3.93) | 1.33 (0.26 to 6.94) |

ICU = intensive care unit.

* Any hospitalization or death due to any cause.

† Data from the Centers for Medicare & Medicaid Services (CMS) were combined with data from other sources and masked in accordance with CMS cell size suppression policy (https://resdac.org/articles/cms-cell-size-suppression-policy).

nirmatrelvir–ritonavir group (5.40 vs. 8.22 deaths per 1000 persons; hazard ratio, 0.66 [CI, 0.49 to 0.89]) and the molnupiravir group (11.05 vs. 16.39 deaths per 1000 persons; hazard ratio, 0.67 [CI, 0.48 to 0.95]) (Table 2 and Figure 3). The data did not support a clear difference in incidence of hospitalization in comparisons of nirmatrelvir–ritonavir (subhazard ratio, 0.90 [CI, 0.79 to 1.02]) or molnupiravir (subhazard ratio, 1.10 [CI, 0.95 to 1.29]) versus no treatment.

## Discussion

In 3 target trial emulation studies performed among outpatient U.S. veterans testing positive for SARS-CoV-2 during January through July 2022, nirmatrelvir–ritonavir was effective at preventing 30-day all-cause mortality, hospitalization, ICU admission, and mechanical ventilation, whereas risk reduction associated with molnupiravir was limited to all-cause mortality. Nirmatrelvir–ritonavir and molnupiravir were each associated with a 77% lower risk for death, and nirmatrelvir–ritonavir was also associated with a 27% lower risk for hospitalization. With both antivirals, additional mortality benefit was observed from days 31 to 180, although absolute reductions were small relative to the first 30 days.

Although the combined hospitalization and mortality benefit associated with nirmatrelvir–ritonavir was also observed in EPIC-HR (3), our estimated risk reduction was smaller despite similar event rates among untreated groups in EPIC-HR and our study. EPIC-HR showed an 89% relative reduction and a 6-percentage point absolute reduction in 28-day COVID-19–related hospitalization or death, whereas we observed a 33% lower risk for 30-day hospitalization or death, corresponding to a reduction of 1 percentage point (11 per 1000 persons). Several

factors may have accounted for differences in our findings, including differences in predominant circulating variants, COVID-19 vaccination, age of participants, and burden of underlying conditions. EPIC-HR was conducted during circulation of the Delta (B.1.617.2) variant in 2021, which was associated with more severe clinical outcomes (29), but by January 2022, Omicron (B.1.1.529) had become the main circulating variant. All participants in EPIC-HR were unvaccinated, whereas only 18% in our study were unvaccinated, although we did observe benefit among vaccinated veterans in our study. Older age is associated with increased risk for severe COVID-19–related outcomes (30, 31), and the median age of participants in our study (66 years) was nearly 20 years above the median age of participants in EPIC-HR. Consistent with EPIC-HR, we observed benefit in veterans aged 65 years or older as well as those aged 18 to 64 years; however, we did not find a lower risk for hospitalization or death in the older group compared with the younger group. Finally, veterans in our study had notably higher prevalence of many underlying conditions associated with adverse outcomes (30), including diabetes, chronic kidney disease, and immunosuppression. Several observational studies from Israel, Hong Kong, and the United States have also shown benefit associated with nirmatrelvir–ritonavir with regard to short-term outcomes in severe COVID-19 (6–11, 32).

In our study, short-term benefit from molnupiravir was limited to an absolute risk reduction of 1 percentage point for 30-day mortality. Evidence from clinical trials and observational studies of molnupiravir has been mixed (4, 5, 10–12). The MOVe-OUT randomized trial, which was conducted among unvaccinated participants before emergence of the Omicron variants, showed an absolute risk reduction of 3 percentage points for 29-day hospitalization or death (4). In contrast, the PANORAMIC (Platform Adaptive Trial of Novel Antivirals for Early Treatment of Covid-19 in the Community) study, which was conducted more recently among vaccinated participants, did not find evidence of reduced 28-day hospitalization or death (5). The veteran population included in our comparison of molnupiravir with no treatment was significantly older and had a higher comorbidity burden than either MOVe-OUT or PANORAMIC; among the outcomes we examined, mortality may have been the most sensitive to a weak protective effect of molnupiravir.

This study has several unique strengths. To minimize common biases encountered in observational studies (13), we carefully defined the index date with regard to baseline eligibility, matching, and follow-up. Few studies of COVID-19 pharmacotherapies have minimized immortal time bias in accordance with randomized trial design principles by assigning an index date to untreated participants that was the same number of days after the date they first tested positive for SARS-CoV-2 as the treatment date of the matched treated participants (8). Furthermore, very little is known about the longer-term effect of oral antivirals after SARS-CoV-2 infection. Our study provides important longitudinal information on 6-month outcomes and incorporates VA Community Care and CMS–Medicare data as well as comprehensive VA electronic health record data to increase the completeness of ascertained exposures and outcomes. Finally, there have been no head-to-head clinical trials of nirmatrelvir–ritonavir and molnupiravir. Although clinical guidelines recommend nirmatrelvir–ritonavir over molnupiravir when feasible (1, 2, 33), sufficient use of molnupiravir in the VHA provided an opportunity to conduct an observational comparative effectiveness study.

This study also has several limitations. Eligibility for antiviral treatment of mild to moderate COVID-19 under FDA emergency use authorization requires symptom onset within 5 days, and we were not able to fully ascertain COVID-19–related symptom onset in most patients (1, 2). Although national surveillance is conducted by VA Pharmacy Benefits Management Services to ensure eligibility among veterans receiving treatment in the VHA, untreated comparators in this study may have included asymptomatic persons or symptomatic persons whose diagnosis was delayed beyond the eligible treatment window, representing either more advanced disease or recovery from illness. Although the overall direction of potential bias may have favored oral antivirals compared with no treatment, we attempted to minimize this bias by

***Table 2.*** Incidence of Hospitalization or Death From 31 to 180 Days Among Veterans Who Tested Positive for SARS-CoV-2 From 1 January to 31 July 2022

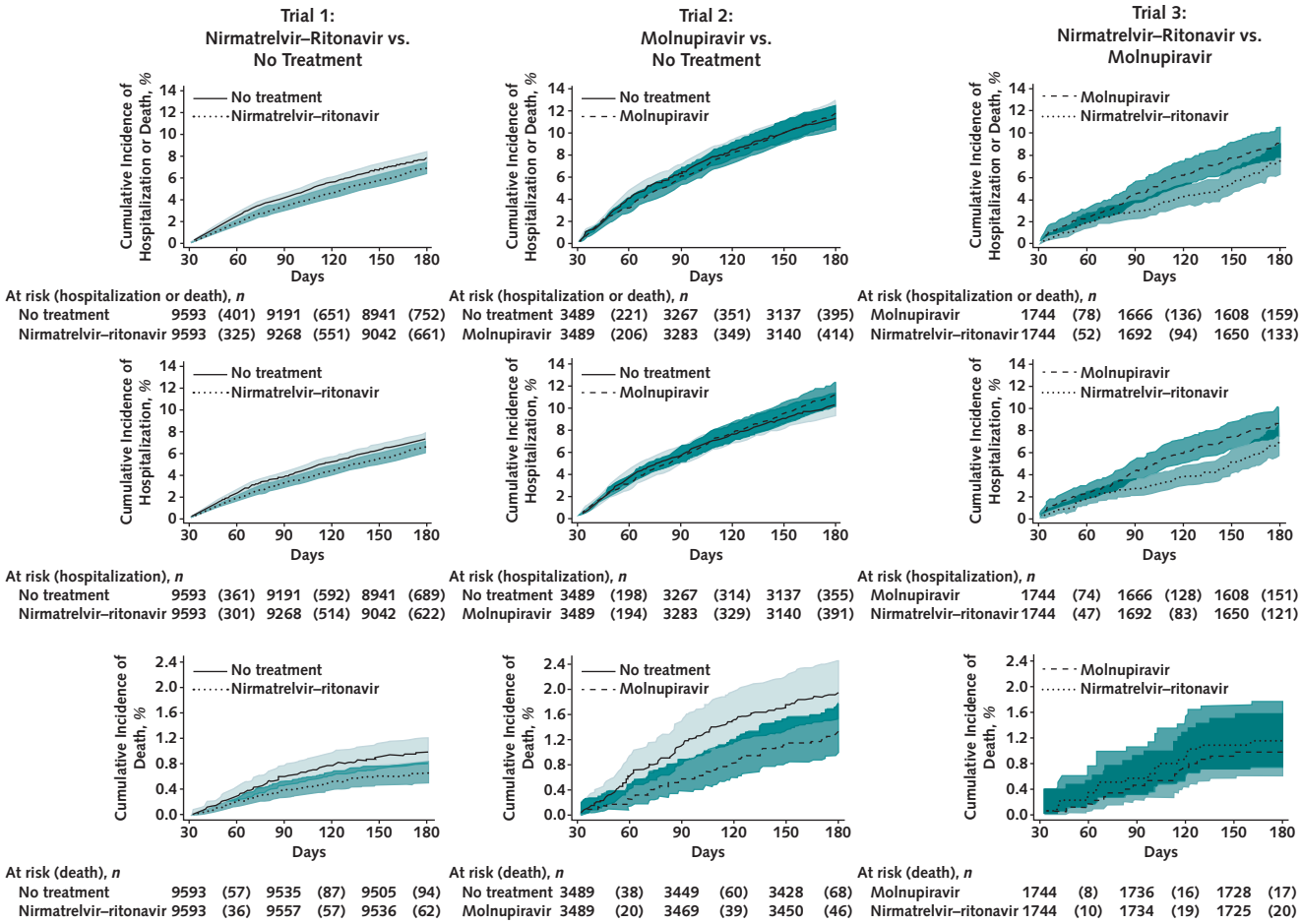
| Outcome | Trial 1: Nirmatrelvir–Ritonavir vs. No Treatment | | | Trial 2: Molnupiravir vs. No Treatment | | | Trial 3: Nirmatrelvir–Ritonavir vs. Molnupiravir | | |
|---|---|---|---|---|---|---|---|---|---|
| | Incidence, *events per 1000 persons** | | HR or SHR† (95% CI) | Incidence, *events per 1000 persons** | | HR or SHR† (95% CI) | Incidence, *events per 1000 persons** | | HR or SHR† (95% CI) |
| | Nirmatrelvir–Ritonavir (*n* = 9593) | No Treatment (*n* = 9593) | | Molnupiravir (*n* = 3489) | No Treatment (*n* = 3489) | | Nirmatrelvir–Ritonavir (*n* = 1744) | Molnupiravir (*n* = 1744) | |
| Hospitalization or death | 59.32 | 67.99 | 0.87 (0.79–0.96) | 104.76 | 100.27 | 1.04 (0.92–1.19) | 65.55 | 79.30 | 0.82 (0.64–1.06) |
| Hospitalization | 55.82 | 62.26 | 0.90 (0.79–1.02) | 98.94 | 90.02 | 1.10 (0.95–1.29) | 59.64 | 75.38 | 0.79 (0.61–1.02) |
| Death | 5.40 | 8.22 | 0.66 (0.49–0.89) | 11.05 | 16.39 | 0.67 (0.48–0.95) | 9.61 | 8.16 | 1.18 (0.58–2.39) |

HR = hazard ratio; SHR = subhazard ratio.

* Incidence was calculated for all matched groups of participants who were alive at day 31.

† SHRs, which were derived from proportional hazards regression that accounted for the competing risk for death, are presented for hospitalization outcomes. HRs are presented for the combined outcome and death.

***Figure 3.*** Cumulative 31- to 180-day incidence of hospitalization or death among outpatient veterans testing positive for SARS-CoV-2, by study group.




The figure shows comparisons of nirmatrelvir–ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir–ritonavir versus molnupiravir. Incidence was calculated among veterans who were alive at day 31. Shaded areas indicate 95% CIs.

requiring untreated matched persons to be alive and not hospitalized through the same number of days as the interval between the test-positive date and the treatment date of the paired, treated person. Second, this study was not designed to capture prior infections, which confer background immunity and may affect measured real-world effectiveness of antiviral treatments. Third, capture of outpatient COVID-19 treatments and outcomes, particularly hospitalizations, may be incomplete. To address this, we restricted the study population to veterans with a recent primary care visit who were more likely to seek care within the VHA system and integrated multiple data sources, including CMS–Medicare, to enhance ascertainment. Fourth, although we emulated a randomized target trial, there may still be residual confounding. We took care to address this in our study design by restricting the eligible population to patients receiving care at VA facilities that were actively prescribing the oral antivirals we evaluated and by including in the matching models many key patient- and facility-level factors that affected receipt of oral antivirals and health outcomes. Confounding by indication, such as illness severity at the time of COVID-19 diagnosis, was not captured, but this was unlikely to completely explain away strong associations observed between treatment and COVID-19–related outcomes. Finally, we could not verify whether veterans who were prescribed antiviral medications completed treatment as recommended. Nonadherence may have biased estimates of effectiveness toward the null for comparisons with no treatment.

In conclusion, nirmatrelvir–ritonavir seems to be an effective treatment for eligible persons with COVID-19 to reduce risk for short-term outcomes of severe COVID-19. The benefit of molnupiravir may be more limited. Further studies are needed to clarify the long-term effectiveness of oral antivirals with regard to incident post–COVID-19 conditions.

From Veterans Affairs Portland Health Care System, and Division of Infectious Diseases, Department of Medicine, Oregon Health & Science University, Portland, Oregon (K.L.B.); Research and Development, Veterans Affairs Puget Sound Health Care System,

Seattle, Washington (K.B.); Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut (E.S., Y.L.); Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, and Yale Center for Medical Informatics, Yale School of Medicine, New Haven, Connecticut (N.R., P.M.); Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, and Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut (L.Y.); Veterans Affairs Center for Medication Safety - Pharmacy Benefit Management (PBM) Services, Hines, Illinois (F.C.); Center of Innovation to Improve Veteran Involvement in Care (CIVIC), Veterans Affairs Portland Healthcare System, Portland, Oregon, and Health Management and Policy, School of Social and Behavioral Health Sciences, College of Public Health and Human Sciences, and Health Data and Informatics Program, Center for Quantitative Life Sciences, Oregon State University, Corvallis, Oregon (D.M.H.); Center of Innovation to Improve Veteran Involvement in Care (CIVIC), Veterans Affairs Portland Healthcare System, Portland, Oregon (M.R.); Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, and Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan (A.B.); Seattle Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington (E.J.B.); Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, and Schools of Medicine and Public Health, Johns Hopkins University, Baltimore, Maryland (T.J.I.); Center of Innovation to Accelerate Discovery and Practice Transformation, Durham Veterans Affairs Medical Center; Department of Population Health Sciences, Duke University School of Medicine; and Duke-Margolis Center for Health Policy, Duke University, Durham, North Carolina (M.L.M.); Veterans Affairs Palo Alto Health Care System, Palo Alto, California, and Department of Radiology, Stanford University School of Medicine, Stanford, California (T.F.O.); Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, and Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan (E.M.V.); Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, and Department of Medicine, Yale School of Medicine, New Haven, Connecticut (M.A.); Office of Research and Development, Veterans Health Administration, Washington, DC (G.D.H.); and Research and Development and Division of Gastroenterology, Veterans Affairs Puget Sound Health Care System, and Division of Gastroenterology, University of Washington, Seattle, Washington (G.N.I.).

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**Corresponding Author:** Kristina L. Bajema, MD, MSc, VA Portland Health Care System, 3710 SW US Veterans Hospital Road, Portland, OR 97239; e-mail, kristina.bajema@va.gov.

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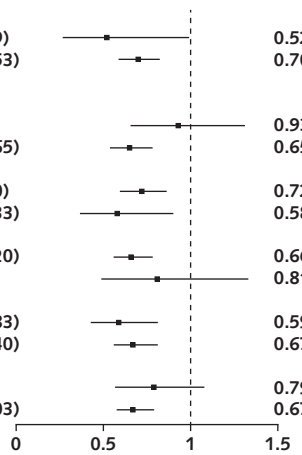
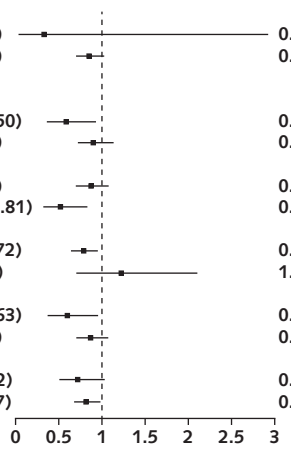
**Author Contributions:** Conception and design: K.L. Bajema, K. Berry, E. Streja, A. Bohnert, M.L. Maciejewski, M. Aslan, G.D. Huang, G.N. Ioannou.
Analysis and interpretation of the data: K.L. Bajema, K. Berry, E. Streja, N. Rajeevan, Y. Li, D.M. Hynes, M. Rowneki, A. Bohnert, E.J. Boyko, T.J. Iwashyna, M.L. Maciejewski, T.F. Osborne, E.M. Viglianti, G.N. Ioannou.
Drafting of the article: K.L. Bajema, G.N. Ioannou.
Critical revision for important intellectual content: K.L. Bajema, K. Berry, E. Streja, N. Rajeevan, F. Cunningham, D.M. Hynes, A. Bohnert, E.J. Boyko, T.J. Iwashyna, M.L. Maciejewski, T.F. Osborne, E.M. Viglianti, M. Aslan, G.D. Huang, G.N. Ioannou.
Final approval of the article: K.L. Bajema, K. Berry, E. Streja, N. Rajeevan, Y. Li, P. Mutalik, L. Yan, F. Cunningham, D.M. Hynes, M. Rowneki, A. Bohnert, E.J. Boyko, T.J. Iwashyna, M.L. Maciejewski, T.F. Osborne, E.M. Viglianti, M. Aslan, G.D. Huang, G.N. Ioannou.
Statistical expertise: K.L. Bajema, K. Berry, E. Streja, L. Yan, A. Bohnert, M.L. Maciejewski, M. Aslan, G.N. Ioannou.
Obtaining of funding: K.L. Bajema, D.M. Hynes, A. Bohnert, E.J. Boyko, T.J. Iwashyna, M.L. Maciejewski, M. Aslan, G.D. Huang, G.N. Ioannou.
Administrative, technical, or logistic support: K.L. Bajema, K. Berry, E. Streja, M. Rowneki, A. Bohnert, M.L. Maciejewski, M. Aslan, G.D. Huang.
Collection and assembly of data: K.L. Bajema, K. Berry, E. Streja, N. Rajeevan, Y. Li, P. Mutalik, M. Rowneki.

***Appendix Figure.*** Forest plots for subgroup analyses in target trials of nirmatrelvir–ritonavir versus no treatment and molnupiravir versus no treatment with respect to 30-day death or hospitalization.

| Subgroup | Incidence (95% CI) | | Risk Difference (95% CI) | Relative Risk (95% CI) | *P* Value for Interaction |
|---|---|---|---|---|---|
| | Nirmatrelvir–Ritonavir | No Treatment | | | |
| Age | | | | | <0.001 |
| 18–64 y | 7.93 (4.51 to 13.92) | 15.31 (10.76 to 21.74) | −7.38 (−14.17 to −0.59) | 0.52 (0.27 to 0.99) | |
| ≥65 y | 26.67 (23.29 to 30.53) | 38.21 (34.88 to 41.85) | −11.54 (−16.54 to −6.53) | 0.70 (0.59 to 0.82) | |
| COVID-19 vaccination status | | | | | <0.001 |
| Unvaccinated | 30.03 (22.63 to 39.76) | 32.27 (26.19 to 39.70) | −2.24 (−12.85 to 8.38) | 0.93 (0.66 to 1.31) | |
| Primary or booster | 20.57 (17.58 to 24.05) | 31.84 (28.65 to 35.36) | −11.27 (−15.89 to −6.65) | 0.65 (0.54 to 0.78) | |
| Immunocompromised | | | | | <0.001 |
| No | 21.20 (18.37 to 24.45) | 29.39 (26.48 to 32.61) | −8.19 (−12.48 to −3.90) | 0.72 (0.60 to 0.86) | |
| Yes | 44.44 (30.40 to 64.54) | 77.21 (59.37 to 99.83) | −32.76 (−58.20 to −7.33) | 0.58 (0.37 to 0.90) | |
| Timing of treatment | | | | | <0.001 |
| 0/1 d | 22.56 (19.68 to 25.86) | 34.05 (31.18 to 37.18) | −11.49 (−15.78 to −7.20) | 0.66 (0.56 to 0.78) | |
| 2–5 d | 29.01 (18.56 to 45.08) | 35.75 (28.18 to 45.26) | −6.74 (−21.98 to 8.50) | 0.81 (0.49 to 1.33) | |
| Symptoms | | | | | <0.001 |
| 0 | 18.17 (13.67 to 24.10) | 30.76 (26.66 to 35.47) | −12.60 (−19.36 to −5.83) | 0.59 (0.43 to 0.81) | |
| ≥1 | 24.39 (20.99 to 28.33) | 36.25 (32.42 to 40.52) | −11.86 (−17.32 to −6.40) | 0.67 (0.56 to 0.81) | |
| Treatment ≤5 d after symptom onset | 27.33 (20.58 to 36.19) | 34.79 (29.84 to 40.52) | −7.46 (−16.80 to 1.88) | 0.79 (0.57 to 1.08) | |
| Overall | 23.00 (20.19 to 26.20) | 34.17 (31.42 to 37.15) | −11.16 (−15.30 to −7.03) | 0.67 (0.58 to 0.79) | |




| Subgroup | Incidence (95% CI) | | Risk Difference (95% CI) | Relative Risk (95% CI) | *P* Value for Interaction |
|---|---|---|---|---|---|
| | Molnupiravir | No Treatment | | | |
| Age | | | | | <0.001 |
| 18–64 y | 3.82 (0.53 to 26.91) | 11.45 (4.54 to 28.57) | −7.63 (−20.58 to 5.32) | 0.33 (0.04 to 2.92) | |
| ≥65 y | 48.59 (41.59 to 56.71) | 57.23 (51.63 to 63.39) | −8.63 (−17.97 to 0.71) | 0.85 (0.71 to 1.02) | |
| COVID-19 vaccination status | | | | | <0.001 |
| Unvaccinated | 48.46 (32.07 to 72.60) | 82.78 (63.96 to 106.51) | −34.32 (−62.15 to −6.50) | 0.59 (0.37 to 0.93) | 2.5 |
| Primary or booster | 40.07 (33.40 to 48.01) | 44.51 (39.21 to 50.03) | −4.23 (−13.28 to 4.81) | 0.90 (0.73 to 1.13) | |
| Immunocompromised | | | | | <0.001 |
| No | 39.72 (33.34 to 47.28) | 45.88 (40.82 to 51.53) | −6.16 (−14.83 to 2.52) | 0.87 (0.70 to 1.07) | |
| Yes | 65.57 (42.59 to 99.68) | 125.41 (96.52 to 161.40) | −59.85 (−98.86 to −20.81) | 0.52 (0.33 to 0.83) | |
| Timing of treatment | | | | | 0.013 |
| 0/1 d | 43.42 (36.86 to 51.09) | 54.99 (49.64 to 60.87) | −11.56 (−20.41 to −2.72) | 0.79 (0.65 to 0.95) | |
| 2–5 d | 46.01 (27.85 to 75.10) | 37.58 (28.30 to 49.73) | 8.44 (−15.49 to 32.36) | 1.22 (0.71 to 2.10) | |
| Symptoms | | | | | <0.003 |
| 0 | 27.19 (18.12 to 40.61) | 45.41 (36.71 to 56.05) | −18.22 (−32.81 to −3.63) | 0.60 (0.38 to 0.95) | |
| ≥1 | 49.90 (42.03 to 59.16) | 57.25 (50.62 to 64.69) | −7.35 (−18.15 to 3.45) | 0.87 (0.71 to 1.07) | |
| Treatment ≤5 d after symptom onset | 45.99 (33.76 to 62.37) | 63.48 (53.31 to 75.44) | −17.49 (−35.51 to 0.52) | 0.72 (0.51 to 1.03) | |
| Overall | 43.66 (37.37 to 50.96) | 53.37 (48.40 to 58.81) | −9.70 (−18.04 to −1.37) | 0.82 (0.68 to 0.98) | |




Matched control participants not belonging to the subgroup of interest were dropped, and the remaining control participants were reweighted. Incidence is expressed as events per 1000 persons. Subgroup analyses for treatment ≤5 days after symptom onset include 1720 (nirmatrelvir–ritonavir vs. no treatment) and 848 (molnupiravir vs. no treatment) participants.

*Appendix Table.* Baseline Characteristics of Veterans Who Tested Positive for SARS-CoV-2 in the Veterans Health Administration From 1 January to 31 July 2022, Matched in 3 Emulated Target Trials of COVID-19 Antiviral Effectiveness

| Characteristic | Trial 1: Nirmatrelvir–Ritonavir vs. No Treatment | | Trial 2: Molnupiravir vs. No Treatment | | Trial 3: Nirmatrelvir–Ritonavir vs. Molnupiravir | |
|---|---|---|---|---|---|---|
| | Nirmatrelvir–Ritonavir (*n* = 9607) | No Treatment (*n* = 9607)* | Molnupiravir (*n* = 3504) | No Treatment (*n* = 3504)* | Nirmatrelvir–Ritonavir (*n* = 1750) | Molnupiravir (*n* = 1750) |
| **Median age (IQR), *y*** | 66.0 (53.0–74.0) | 66.0 (54.0–74.0) | 70.0 (60.0–75.0) | 70.0 (60.0–75.0) | 70.0 (60.0–75.0) | 70.0 (60.0–76.0) |
| **Age group, *n (%)*** | | | | | | |
| 18–49 y | 1814 (18.9) | 1765 (18.4) | 347 (9.9) | 355 (10.1) | 202 (11.5) | 184 (10.5) |
| 50–64 y | 2667 (27.8) | 2644 (27.5) | 866 (24.7) | 843 (24.1) | 397 (22.7) | 419 (23.9) |
| 65–74 y | 2903 (30.2) | 2936 (30.6) | 1210 (34.5) | 1239 (35.4) | 616 (35.2) | 572 (32.7) |
| ≥75 y | 2223 (23.1) | 2262 (23.5) | 1081 (30.9) | 1067 (30.5) | 535 (30.6) | 575 (32.9) |
| **Male, *n (%)*** | 8247 (85.8) | 8298 (86.4) | 3194 (91.2) | 3197 (91.2) | 1546 (88.3) | 1554 (88.8) |
| **Race/ethnicity, *n (%)*** | | | | | | |
| Hispanic | 898 (9.3) | 763 (7.9) | 259 (7.4) | 229 (6.5) | 158 (9.0) | 142 (8.1) |
| White | 6012 (62.6) | 6194 (64.5) | 2341 (66.8) | 2409 (68.7) | 1204 (68.8) | 1192 (68.1) |
| Black | 1850 (19.3) | 1805 (18.8) | 640 (18.3) | 615 (17.5) | 254 (14.5) | 289 (16.5) |
| Other | 305 (3.2) | 289 (3.0) | 95 (2.7) | 83 (2.4) | 61 (3.5) | 48 (2.7) |
| Unknown | 542 (5.6) | 556 (5.8) | 169 (4.8) | 168 (4.8) | 73 (4.2) | 79 (4.5) |
| **Rurality, *n (%)*†** | | | | | | |
| Rural | 2306 (24.0) | 2529 (26.3) | 999 (28.5) | 1065 (30.4) | 482 (27.5) | 467 (26.7) |
| Urban | 7228 (75.2) | 7002 (72.9) | 2482 (70.8) | 2420 (69.1) | 1261 (72.1) | 1272 (72.7) |
| Missing | 73 (0.8) | 77 (0.8) | 23 (0.7) | 19 (0.5) | 7 (0.4) | 11 (0.6) |
| **Region, *n (%)*‡** | | | | | | |
| West | 2392 (24.9) | 2392 (24.9) | 873 (24.9) | 873 (24.9) | 449 (25.7) | 449 (25.7) |
| Midwest | 1893 (19.7) | 1893 (19.7) | 529 (15.1) | 529 (15.1) | 234 (13.4) | 234 (13.4) |
| Northeast | 1968 (20.5) | 1968 (20.5) | 567 (16.2) | 567 (16.2) | 296 (16.9) | 296 (16.9) |
| South | 3354 (34.9) | 3354 (34.9) | 1535 (43.8) | 1535 (43.8) | 771 (44.1) | 771 (44.1) |
| **Facility complexity, *n (%)*** | | | | | | |
| Lower complexity (1b to 3) | 5337 (55.6) | 5337 (55.6) | 2070 (59.1) | 2070 (59.1) | 1061 (60.6) | 1061 (60.6) |
| Highest complexity (1a) | 4270 (44.4) | 4270 (44.4) | 1434 (40.9) | 1434 (40.9) | 689 (39.4) | 689 (39.4) |
| **Median Area Deprivation Index (IQR)** | 52.3 (34.3–71.3) | 53.3 (33.5–71.3) | 57.3 (38.8–75.4) | 58.3 (38.3–75.0) | 58.0 (37.3–74.3) | 55.0 (36.8–73.3) |
| **Month of test with positive result, *n (%)*** | | | | | | |
| January | 903 (9.4) | 915 (9.5) | 642 (18.3) | 639 (18.2) | 193 (11.0) | 193 (11.0) |
| February | 544 (5.7) | 529 (5.5) | 275 (7.8) | 279 (8.0) | 76 (4.3) | 76 (4.3) |
| March | 194 (2.0) | 193 (2.0) | 60 (1.7) | 60 (1.7) | 8 (0.5) | 5 (0.3) |
| April | 588 (6.1) | 556 (5.8) | 153 (4.4) | 142 (4.0) | 66 (3.8) | 59 (3.4) |
| May | 1814 (18.9) | 1811 (18.8) | 477 (13.6) | 470 (13.4) | 233 (13.3) | 249 (14.2) |
| June | 2412 (25.1) | 2381 (24.8) | 735 (21.0) | 743 (21.2) | 414 (23.7) | 404 (23.1) |
| July | 3152 (32.8) | 3223 (33.5) | 1162 (33.2) | 1171 (33.4) | 760 (43.4) | 764 (43.7) |
| **≥1 symptom, *n (%)*§** | | | | | | |
| No | 2644 (27.5) | 2765 (28.8) | 934 (26.7) | 953 (27.2) | 431 (24.6) | 437 (25.0) |
| Yes | 6963 (72.5) | 6842 (71.2) | 2570 (73.3) | 2551 (72.8) | 1319 (75.4) | 1313 (75.0) |
| **Vaccination status and time since last dose, *n (%)*‖** | | | | | | |
| No doses | 1650 (17.2) | 1721 (17.9) | 503 (14.4) | 533 (15.2) | 204 (11.7) | 187 (10.7) |
| Partial | 350 (3.6) | 334 (3.5) | 120 (3.4) | 147 (4.2) | 61 (3.5) | 52 (3.0) |
| Primary, >4 mo | 2575 (26.8) | 2513 (26.2) | 947 (27.0) | 897 (25.6) | 483 (27.6) | 481 (27.5) |
| Primary, 0–4 mo | 117 (1.2) | 93 (1.0) | 68 (1.9) | 63 (1.8) | 11 (0.6) | 18 (1.0) |
| Booster, >4 mo | 3392 (35.3) | 3490 (36.3) | 1140 (32.5) | 1152 (32.9) | 649 (37.1) | 692 (39.5) |
| Booster, 0–4 mo | 1523 (15.9) | 1456 (15.2) | 726 (20.7) | 713 (20.3) | 342 (19.5) | 320 (18.3) |
| **NIH tier, *n (%)*‖** | | | | | | |
| 1 | 1366 (14.2) | 1366 (14.2) | 617 (17.6) | 617 (17.6) | 245 (14.0) | 245 (14.0) |
| 2 | 1110 (11.6) | 1110 (11.6) | 266 (7.6) | 266 (7.6) | 109 (6.2) | 109 (6.2) |
| 3 | 4160 (43.3) | 4160 (43.3) | 1815 (51.8) | 1815 (51.8) | 966 (55.2) | 966 (55.2) |
| 4 | 2971 (30.9) | 2971 (30.9) | 806 (23.0) | 806 (23.0) | 430 (24.6) | 430 (24.6) |

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*Appendix Table*–Continued

| Characteristic | Trial 1: Nirmatrelvir–Ritonavir vs. No Treatment | | Trial 2: Molnupiravir vs. No Treatment | | Trial 3: Nirmatrelvir–Ritonavir vs. Molnupiravir | |
|---|---|---|---|---|---|---|
| | Nirmatrelvir–Ritonavir (*n* = 9607) | No Treatment (*n* = 9607)* | Molnupiravir (*n* = 3504) | No Treatment (*n* = 3504)* | Nirmatrelvir–Ritonavir (*n* = 1750) | Molnupiravir (*n* = 1750) |
| **Smoking, *n (%)*** | | | | | | |
| Never | 4099 (42.7) | 4011 (41.7) | 1343 (38.3) | 1294 (36.9) | 698 (39.9) | 709 (40.5) |
| Former | 3942 (41.0) | 3970 (41.3) | 1576 (45.0) | 1623 (46.3) | 779 (44.5) | 785 (44.9) |
| Current | 1242 (12.9) | 1296 (13.5) | 501 (14.3) | 501 (14.3) | 235 (13.4) | 208 (11.9) |
| Unknown | 324 (3.4) | 330 (3.4) | 84 (2.4) | 87 (2.5) | 38 (2.2) | 48 (2.7) |
| **Alcohol dependence, *n (%)*** | 1768 (18.4) | 1782 (18.5) | 625 (17.8) | 624 (17.8) | 272 (15.5) | 307 (17.5) |
| **Substance dependence, *n (%)*** | 331 (3.4) | 343 (3.6) | 154 (4.4) | 151 (4.3) | 57 (3.3) | 60 (3.4) |
| **Median number of underlying conditions (IQR)** | 4.0 (3.0–5.0) | 4.0 (3.0–5.0) | 5.0 (4.0–6.0) | 5.0 (3.0–6.0) | 4.0 (3.0–6.0) | 5.0 (3.0–6.0) |
| **Number of underlying conditions, *n (%)*** | | | | | | |
| 0–1 | 578 (6.0) | 744 (7.7) | 99 (2.8) | 122 (3.5) | 57 (3.3) | 60 (3.4) |
| 2–3 | 3372 (35.1) | 3350 (34.9) | 745 (21.3) | 802 (22.9) | 489 (27.9) | 442 (25.3) |
| 4–5 | 3516 (36.6) | 3270 (34.0) | 1292 (36.9) | 1258 (35.9) | 703 (40.2) | 713 (40.7) |
| ≥6 | 2141 (22.3) | 2243 (23.3) | 1368 (39.0) | 1321 (37.7) | 501 (28.6) | 535 (30.6) |
| **CAN score for mortality within 1 y at test date, *n (%)*** | | | | | | |
| 0–30 | 3171 (33.0) | 3098 (32.2) | 718 (20.5) | 685 (19.5) | 424 (24.2) | 389 (22.2) |
| 31–55 | 2662 (27.7) | 2650 (27.6) | 845 (24.1) | 878 (25.0) | 425 (24.3) | 458 (26.2) |
| 56–75 | 1926 (20.0) | 1972 (20.5) | 855 (24.4) | 887 (25.3) | 440 (25.1) | 444 (25.4) |
| 76–90 | 1333 (13.9) | 1335 (13.9) | 704 (20.1) | 671 (19.1) | 355 (20.3) | 330 (18.9) |
| 95–96 | 168 (1.7) | 161 (1.7) | 130 (3.7) | 127 (3.6) | 43 (2.5) | 51 (2.9) |
| 97–98 | 170 (1.8) | 173 (1.8) | 137 (3.9) | 138 (3.9) | 38 (2.2) | 49 (2.8) |
| 99 | 79 (0.8) | 98 (1.0) | 94 (2.7) | 97 (2.8) | 16 (0.9) | 18 (1.0) |
| Missing | 98 (1.0) | 121 (1.3) | 21 (0.6) | 22 (0.6) | 9 (0.5) | 11 (0.6) |
| **Underlying condition, *n (%)*** | | | | | | |
| Obesity (body mass index ≥30 kg/m$^2$) | 7962 (82.9) | 7934 (82.6) | 2860 (81.6) | 2862 (81.7) | 1443 (82.5) | 1447 (82.7) |
| Chronic kidney disease | 991 (10.3) | 994 (10.3) | 762 (21.7) | 724 (20.7) | 221 (12.6) | 232 (13.3) |
| Diabetes | 3148 (32.8) | 3074 (32.0) | 1484 (42.4) | 1449 (41.4) | 682 (39.0) | 718 (41.0) |
| Use of immunosuppressive medications or cancer therapies‖ | 815 (8.5) | 791 (8.2) | 399 (11.4) | 391 (11.2) | 155 (8.9) | 178 (10.2) |
| Hematologic cancer | 204 (2.1) | 193 (2.0) | 96 (2.7) | 98 (2.8) | 51 (2.9) | 52 (3.0) |
| Cancer | 1605 (16.7) | 1479 (15.4) | 707 (20.2) | 715 (20.4) | 388 (22.2) | 366 (20.9) |
| Cardiovascular disease | 3159 (32.9) | 3136 (32.6) | 1720 (49.1) | 1698 (48.4) | 725 (41.4) | 752 (43.0) |
| Chronic lung disease | 3023 (31.5) | 3000 (31.2) | 1406 (40.1) | 1381 (39.4) | 612 (35.0) | 634 (36.2) |
| Chronic liver disease | 830 (8.6) | 800 (8.3) | 346 (9.9) | 367 (10.5) | 176 (10.1) | 166 (9.5) |
| Dementia | 302 (3.1) | 313 (3.3) | 165 (4.7) | 168 (4.8) | 68 (3.9) | 69 (3.9) |
| Mental health conditions¶ | 4148 (43.2) | 4179 (43.5) | 1601 (45.7) | 1601 (45.7) | 713 (40.7) | 749 (42.8) |
| **Median number of health care encounters in prior 12 mo (IQR)** | 33.0 (19.0–52.0) | 32.0 (19.0–52.0) | 42.0 (25.0–66.0) | 40.0 (25.0–62.0) | 36.0 (23.0–55.0) | 37.5 (22.0–60.0) |
| **Number of health care encounters in prior 12 mo, *n (%)*** | | | | | | |
| 0–8 | 580 (6.0) | 619 (6.4) | 112 (3.2) | 118 (3.4) | 64 (3.7) | 65 (3.7) |
| 9–15 | 1188 (12.4) | 1214 (12.6) | 277 (7.9) | 266 (7.6) | 182 (10.4) | 166 (9.5) |
| 16–30 | 2690 (28.0) | 2713 (28.2) | 792 (22.6) | 798 (22.8) | 423 (24.2) | 464 (26.5) |
| ≥31 | 5149 (53.6) | 5062 (52.7) | 2323 (66.3) | 2323 (66.3) | 1081 (61.8) | 1055 (60.3) |

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*Appendix Table*–Continued

| Characteristic | Trial 1: Nirmatrelvir–Ritonavir vs. No Treatment | | Trial 2: Molnupiravir vs. No Treatment | | Trial 3: Nirmatrelvir–Ritonavir vs. Molnupiravir | |
|---|---|---|---|---|---|---|
| | Nirmatrelvir–Ritonavir (*n* = 9607) | No Treatment (*n* = 9607)* | Molnupiravir (*n* = 3504) | No Treatment (*n* = 3504)* | Nirmatrelvir–Ritonavir (*n* = 1750) | Molnupiravir (*n* = 1750) |
| **Days between test and treatment, *n (%)*** | | | | | | |
| 0/1 | 8952 (93.2) | – | 3178 (90.7) | – | 1719 (98.2) | 1719 (98.2) |
| 2–5 | 655 (6.8) | – | 326 (9.3) | – | 31 (1.8) | 31 (1.8) |

CAN = Care Assessment Need; NIH = National Institutes of Health.
* Baseline characteristics represent equally weighted matched control participants (up to 4 untreated persons for trials 1 and 2).
† Based on rural-urban commuting area codes.
‡ Regions are based on Veterans Integrated Services Networks (VISNs). West includes VISNs 19 to 22; Midwest includes VISNs 10, 12, 15, and 23; Northeast includes VISNs 1, 2, 4, and 5; and South includes VISNs 6 to 9, 16, and 17.
§ Any of 15 prespecified COVID-19–related symptoms present on the day the patient tested positive for SARS-CoV-2 or within the preceding 30 days.
‖ See the **Supplement** (available at Annals.org).
¶ Includes major depressive disorder, bipolar disorder, posttraumatic stress disorder, and schizophrenia.