

Impact of Oral Antiviral Therapy on Subsequent Hospital Visits and Antibacterial Use in COVID-19 Outpatients Within 28 Days

A Nationwide COVID-19 Patient Registry
from a Large Private Acute Care Hospital Network across Japan (ANCHOR-02)

Makoto Hibino, Ayumi Shintani, Hiroyuki Murayama, Nobuyuki Morikawa, Hikari Higa, Sho Nishiguchi, Eiji Monma, Bumpachi Kakii, Sadaharu Asami, Hidemitsu Nakagawa, Naoko Kudo, Yohei Maeda, Masahiro Kinoshita, Takahiro Yoden, Shogo Miyazawa, Mayuko Watamura, Shinichi Higashiue

Shonan Oiso Hospital, Osaka Metropolitan University Graduate School of Medicine, Narita Tomisato Tokushukai Hospital, Tokyo Nishi Tokushukai Hospital, **Shonan Fujisawa Tokushukai Hospital**, Shonan Kamakura General Hospital, Tokushukai Koga General Hospital, Matsubara Tokushukai Hospital, Musashino Tokushukai Hospital, Nozaki Tokushukai Hospital, Takasago Seibu Hospital, Nagoya Tokushukai General Hospital, SHIONOGI & Co., Ltd., Tokushukai Medical Corporation



Makoto Hibino

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Introduction

ANCHOR-02 study



Background

- ▶ COVID-19 (Omicron variant) symptoms are generally mild¹ but can cause
 - ✓ symptom recurrence²
 - ✓ impaired QoL³
 - ✓ reduced productivity³
 - ✓ additional antibiotic use⁴

Prior Evidence

- ▶ **ANCHOR-01: oral antivirals** were associated with a **significant reduction in PCC frequency**; primary outcome, with **adjusted RR of 0.86 (95% CI: 0.78–0.93)**⁵.

Knowledge Gap

- ▶ Impact on broader recovery unclear:
 - ✓ Re-consultations
 - ✓ Work productivity and Activity Impairment
 - ✓ Additional antibiotic use
 - ✓ Return to usual health

Objective

- ▶ **ANCHOR-02:** To evaluate secondary/exploratory outcomes and the **broader clinical benefits of oral antivirals beyond PCC**.

Methods

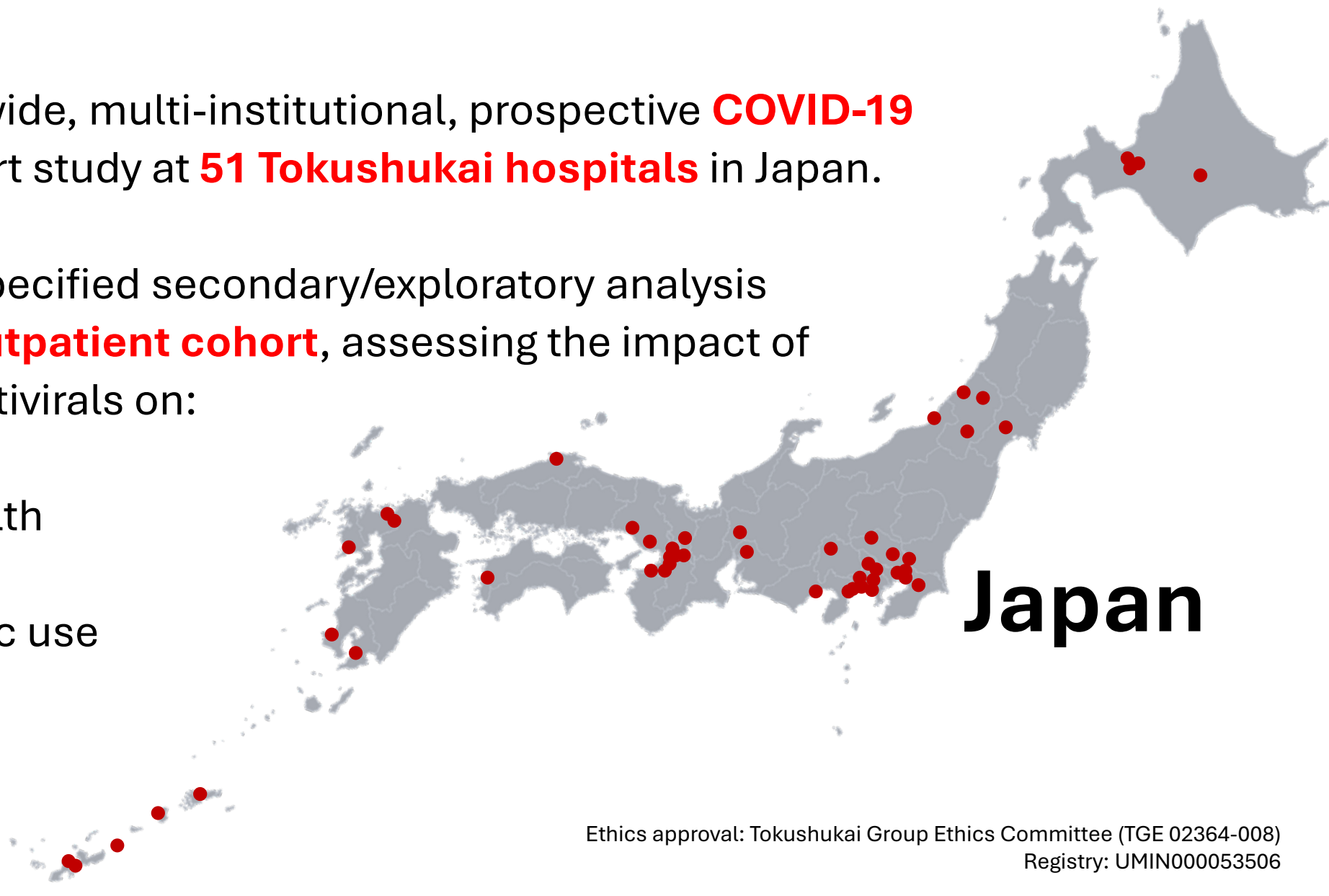
ANCHOR-02 study

Study Design and Setting

► **ANCHOR**: a nationwide, multi-institutional, prospective **COVID-19** registry-based cohort study at **51 Tokushukai hospitals** in Japan.

► **ANCHOR-02**: pre-specified secondary/exploratory analysis of the **mixed-risk outpatient cohort**, assessing the impact of acute-phase oral antivirals on:

- re-consultation
- return to usual health
- work productivity
- additional antibiotic use through Day 28





Enrollment: Feb–Oct 2024 ➡ Follow-up: until Feb 2025

Inclusion Criteria

- ▶ **Outpatients aged ≥ 12 years**
- ▶ **Symptom onset ≤ 5 days** before consent
- ▶ Confirmed SARS-CoV-2 infection (PCR or antigen test)
- ▶ Written informed consent or assent obtained

Exclusion Criteria

- ▶ Anti-SARS-CoV-2 treatment ≤ 30 days before enrollment
- ▶ Previous participation in this study
- ▶ Enrollment in another investigational trial
- ▶ Receipt of an investigational or unapproved drug ≤ 150 days before enrollment
- ▶ Using or planning to use other antiviral agents^a at entry

^aRemdesivir, casirivimab/imdevimab, sotrovimab, tixagevimab/cilgavimab, dexamethasone, baricitinib, or tocilizumab.



Antiviral treatment

- ▶ **Treatment decision:** Jointly by clinicians and patients
- ▶ **Options:** Supportive care only or oral antivirals
- ▶ **Oral antivirals:** Ensitrelvir, nirmatrelvir, molnupiravir (5-day regimen)
Covered by national health insurance
- ▶ **Guidelines:** COVID-19 management guidelines (Version 10.1, MHLW, Japan)

Data collection

- ▶ **EMR:** Tokushukai Medical Database (TMD)
- ▶ **ePRO:** Patient-reported outcomes via electronic questionnaires on Days 28 and 84
- ▶ **Both TMD and ePRO data were integrated, processed, and anonymized**

Endpoints



Secondary Endpoints



COVID-19–related
re-consultation
through Day 28

Exploratory Endpoints



Return to **usual health**
at Day 28

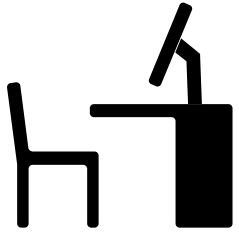


Additional **antibiotic**
use through Day 28



Work productivity and
activity impairment at
Day 28

WPAI Domains



Absenteeism (work time missed)

Hours missed due to health problems in the last 7 days/(Hours missed due to health problems in the previous 7 days + Hours actually worked in the last 7 days)

Presenteeism (impairment at work)



Degree to which health affected productivity while working in the last 7 days*/10

*Assessed using a VAS (0–10)



Overall work impairment

Absenteeism + (1 – Absenteeism) × Presenteeism

Activity impairment



Degree to which health affected regular activities in the last 7 days*/10

*Assessed using a VAS (0–10)



Sample Size Determination

- ▶ ANCHOR-02 screened eligible participants from ANCHOR enrollment during the period set to ensure sufficient sample size for statistical evaluation of PCC incidence.

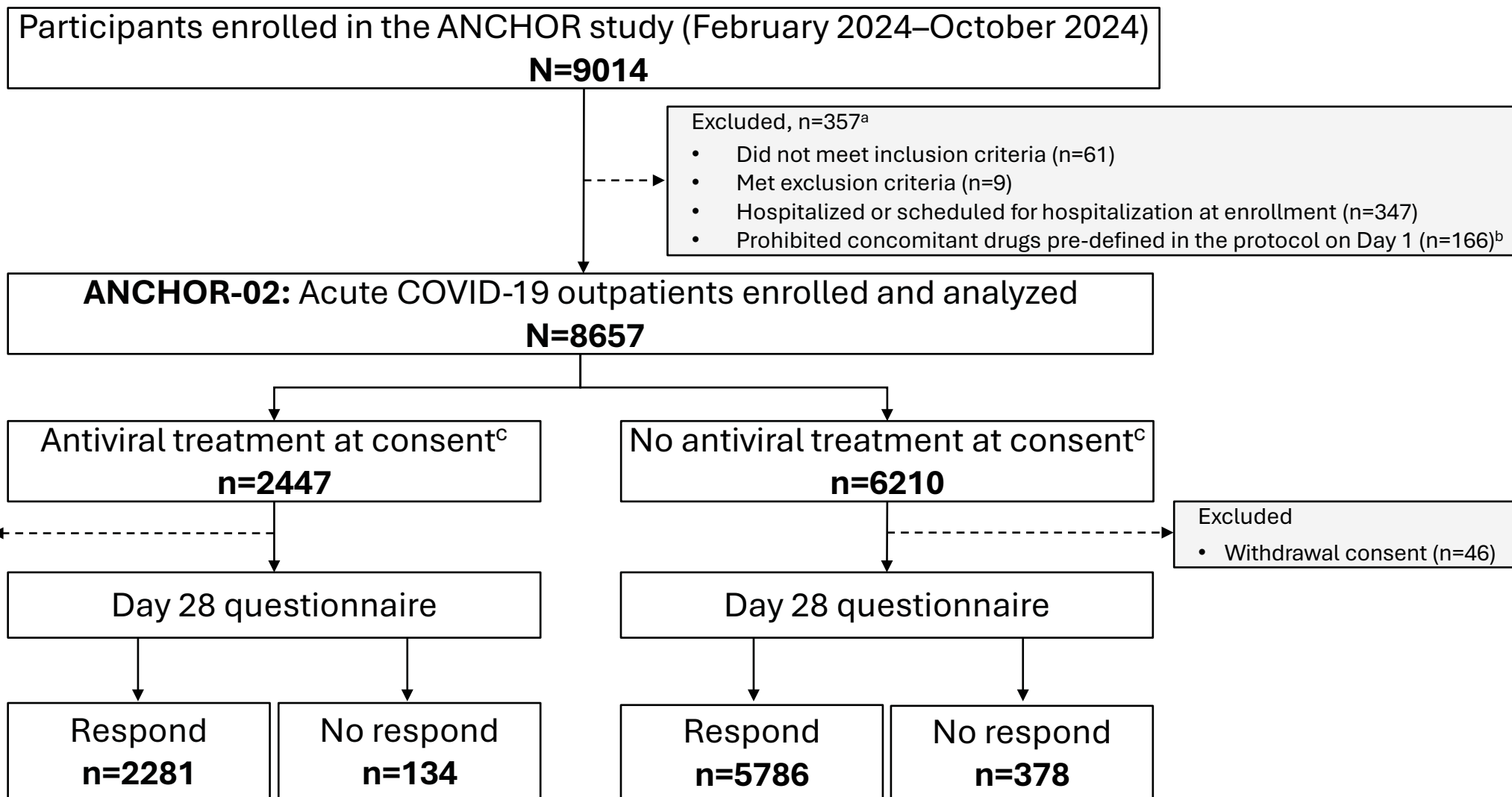
Statistical Analysis

- ▶ Approach: Complete-case multivariable analyses
- ▶ Outcomes: **Oral antivirals (ensitrelvir/nirmatrelvir/molnupiravir) vs. no treatment**
- ▶ Models: Modified Poisson and least squares regression (GEE, robust SEs)
- ▶ Adjusted for: Demographics, comorbidities, symptoms, vaccination, timing
- ▶ Significance: Two-sided $P < 0.05$ (no multiple-comparison adjustment)

Results

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Participants Flow and Disposition



^aParticipants may have more than one reason for exclusion.

^bCasirivimab-imdevimab, sotrovimab, tixagevimab-cilgavimab, dexamethasone, baricitinib, tocilizumab, or remdesivir.

^cDay 1

Characteristics	No antiviral (n=6164)	Antiviral			
		All (n=2415)	Ensitrelvir (n=1857)	Nirmatrelvir (n=117)	Molnupiravir (n=441)
Age (years), median [range]	45.0 [12–98]	59.0 [12–97]	54.0 [12–96]	72.0 [17–94]	72.0 [22–97]
Female sex, n (%)	3251 (52.7%)	1175 (48.7%)	925 (49.8%)	61 (52.1%)	189 (42.9%)
Japanese, n (%)	6099 (98.9%)	2394 (99.1%)	1841 (99.1%)	116 (99.1%)	437 (99.1%)
BMI ≤25 kg/m ² , n (%)	4471 (72.5%)	1715 (71.0%)	1332 (71.7%)	79 (67.5%)	304 (68.9%)
Smoking history, n (%)	2288 (37.1%)	970 (40.2%)	722 (38.9%)	46 (39.3%)	202 (45.8%)
Any comorbidities ^a , n (%)	1759 (28.5%)	1190 (49.3%)	751 (40.4%)	78 (66.7%)	361 (81.9%)
COVID-19 onset to enrollment: 1 to <3 days, n (%)	4270 (69.3%)	1807 (74.8%)	1410 (75.9%)	72 (61.5%)	325 (73.7%)
Mild COVID-19 ^b , n (%)	6110 (99.1%)	2354 (97.5%)	1814 (97.7%)	115 (98.3%)	425 (96.4%)

Baseline characteristics were generally well balanced among groups, except for old age and high prevalence of comorbidities in the antiviral group

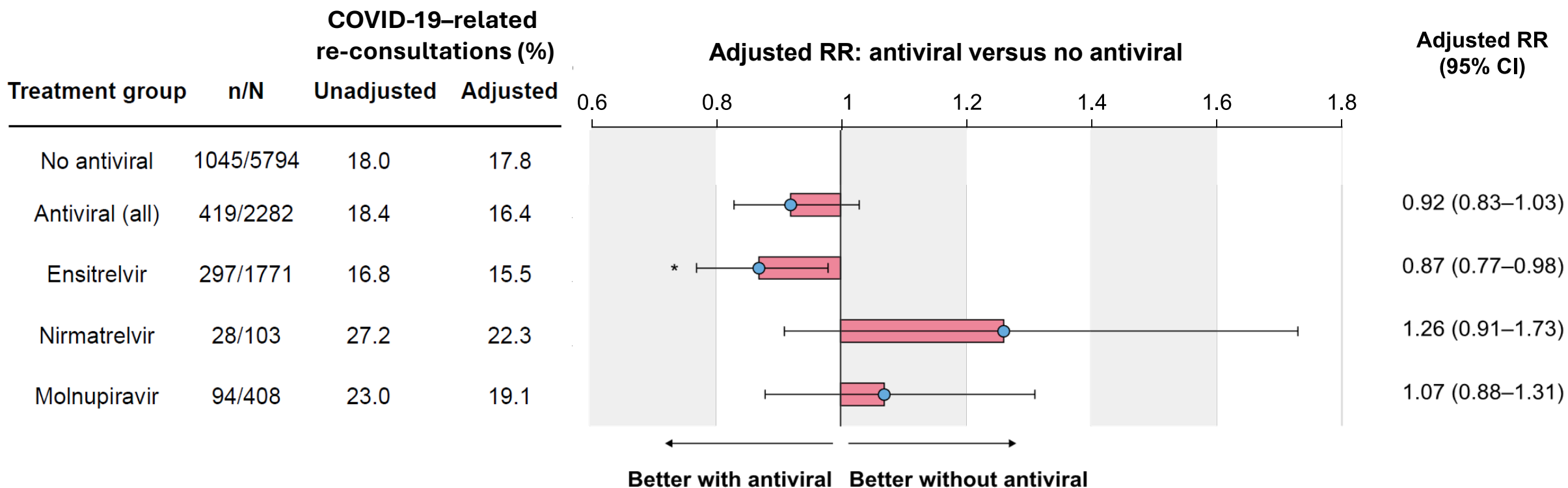
^aHypertension, diabetes, dyslipidemia, chronic kidney disease on dialysis, malignant tumor, cardiovascular disease, respiratory disease, liver disorders, genetic disorders, mental disorders, or immunodeficiency.

^bCategorized as participants with no oxygen desaturation according to the Japanese guidelines for the treatment of COVID-19, 10th edition.

BMI, body mass index; COVID-19, coronavirus disease 2019.



Risk for COVID-19–Related Re-consultations through Day 28



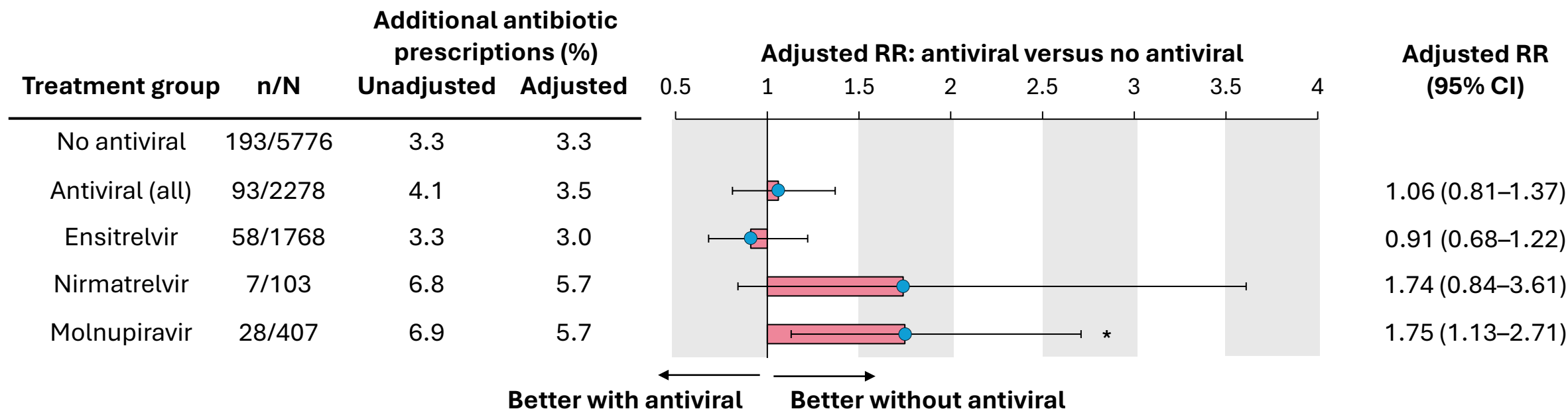
The use of ensitrelvir was associated with a significant reduction in COVID-19–related re-consultations

Participants with missing values in outcome measures or baseline covariates were excluded prior to the analysis. RR values were calculated using modified Poisson regression. Covariates included in the model-multivariate regressions were BMI, sex, smoking history, medical history (hypertension, diabetes mellitus, dyslipidemia, malignancy, cardiovascular disease, respiratory disease, and liver disease), maximum temperature from onset to Day 1, severity of Day 1 COVID-19 symptom score, presence of pneumonia on Day 1, time-to-taking from onset of COVID-19, date of last SARS-CoV-2 vaccination, and number of SARS-CoV-2 vaccinations. * $P < 0.05$ vs. no antiviral.

BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



Risk for Requiring Additional Antibiotic Prescriptions through Day 28



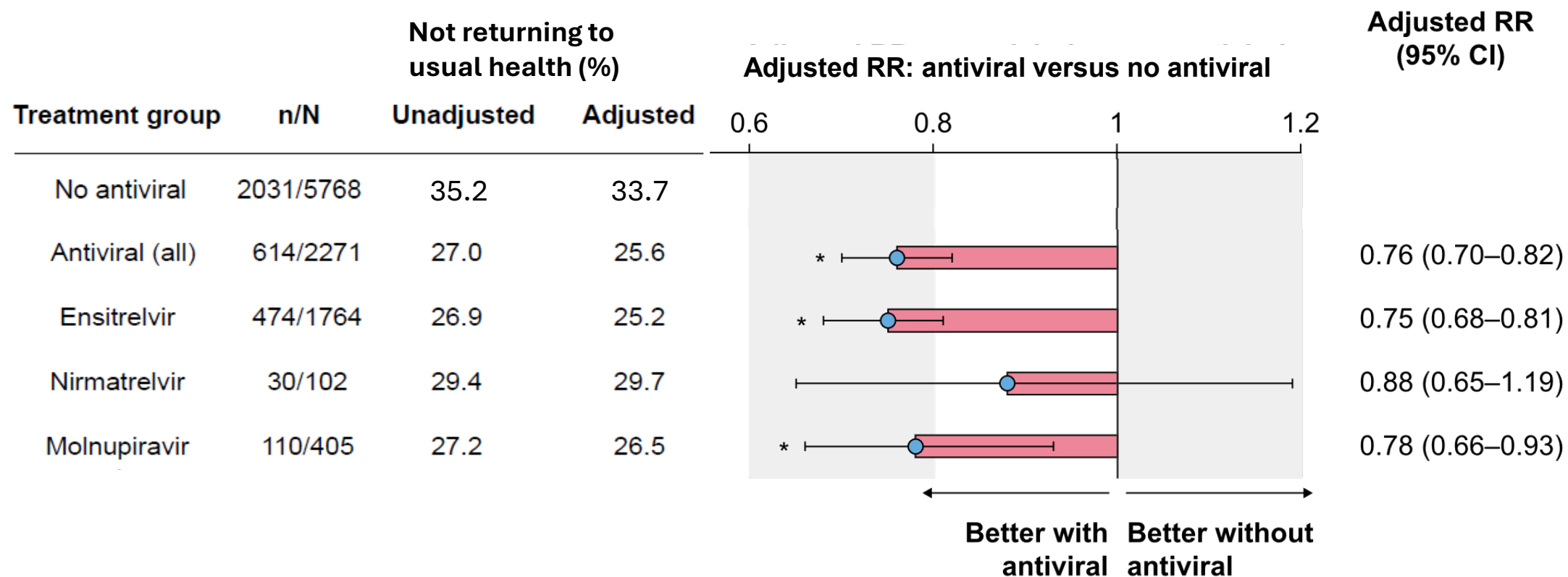
The risk for additional antibiotic use through Day 28 was numerically lower in the ensitrelvir group but higher in other groups compared with the no antiviral group, with a statistically significant increase in the molnupiravir group

Participants with missing values in outcome measures or baseline covariates were excluded prior to the analysis. RR values were calculated using modified Poisson regression. Covariates included in the model-multivariate regressions were BMI, sex, smoking history, medical history (hypertension, diabetes mellitus, dyslipidemia, malignancy, cardiovascular disease, respiratory disease, and liver disease), maximum temperature from onset to Day 1, severity of Day 1 COVID-19 symptom score, presence of pneumonia on Day 1, time-to-taking from onset of COVID-19, date of last SARS-CoV-2 vaccination, and number of SARS-CoV-2 vaccinations. * $P < 0.05$ vs. no antiviral. Boldface letter for P values indicates that the results are significant.

BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



Risk for Not Returning to Usual Health at Day 28



The risk for not returning to usual health at Day 28 was significantly lower in the all antiviral, ensitrelvir, and molnupiravir groups compared with the no antiviral group

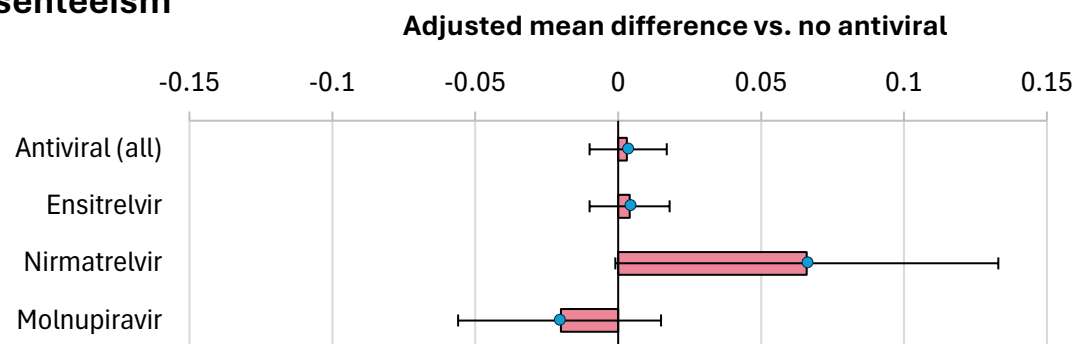
Participants with missing values in outcome measures or baseline covariates were excluded prior to the analysis. RR values were calculated using modified Poisson regression. Covariates included in the model-multivariate regressions were BMI, sex, smoking history, and history (hypertension, diabetes mellitus, dyslipidemia, malignancy, cardiovascular disease, respiratory disease, and liver disease), respectively, maximum temperature from onset to Day 1, severity of Day 1 COVID-19 symptom score, presence of pneumonia on Day 1, time-to-taking from onset of COVID-19, date of last SARS-CoV-2 vaccination, and number of SARS-CoV-2 vaccinations. * $P < 0.05$ vs. no antiviral.

BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

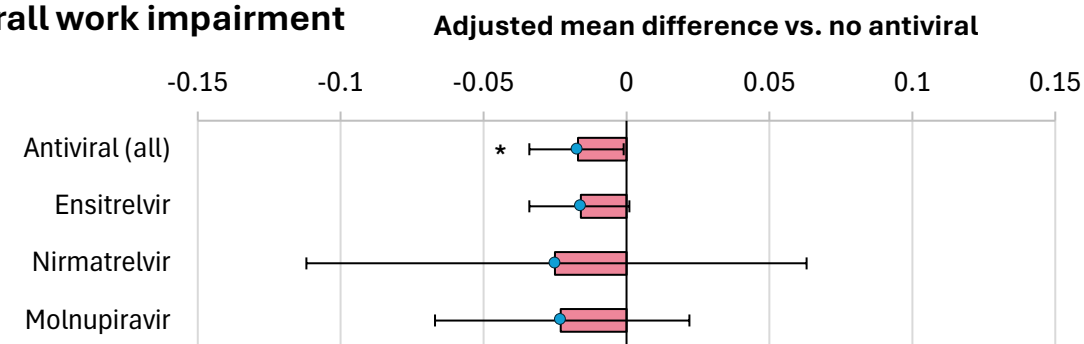


Changes in WPAI Domain Scores at Day 28

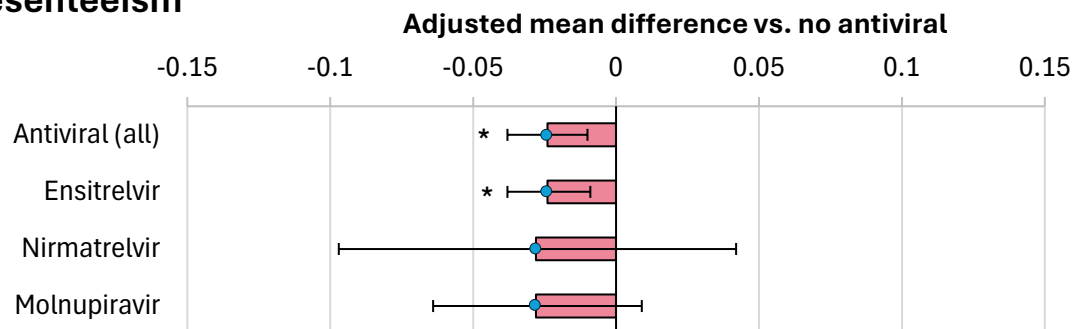
Absenteeism



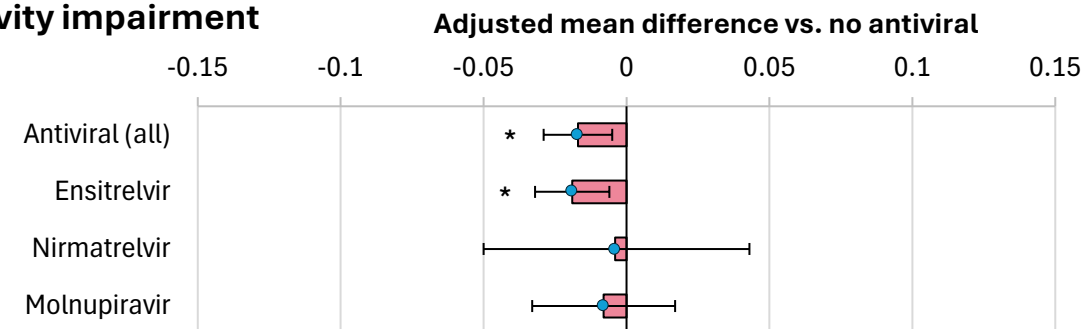
Overall work impairment



Presenteeism



Activity impairment



Antiviral treatment was associated with improvement in WPAI domain scores (except absenteeism)

SARS-CoV-2 antiviral drug-weighted mean was calculated using the generalized estimation equation for the weighted mean vs. no treatment for ensitrelvir, nirmatrelvir, and molnupiravir. Covariates included in the model-multivariate regressions were BMI, sex, smoking history, medical history (hypertension, diabetes mellitus, dyslipidemia, malignancy, cardiovascular disease, respiratory disease, and liver disease), maximum temperature from onset to Day 1, severity of Day 1 COVID-19 symptom score, presence of pneumonia on Day 1, time-to-taking from onset of COVID-19, date of last SARS-CoV-2 vaccination, and number of SARS-CoV-2 vaccinations. * $P < 0.05$ vs. no antiviral.

BMI, body mass index; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WPAI, Work Productivity and Activity Impairment.

Discussion

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The use of **ensitrelvir** was associated with a **significant reduction in COVID-19–related re-consultations**.



The risk for additional antibiotic use through Day 28 was numerically lower in the ensitrelvir group but higher in other groups compared with the no antiviral group (significantly increased in the molnupiravir group).



The risk for **not returning to usual health** at Day 28 was **significantly lower** in the **all antiviral, ensitrelvir, and molnupiravir groups** compared with the no antiviral group.



Antiviral treatment was associated with **improvement in the WPAI domain scores** (presenteeism, overall work impairment, and activity impairment).

- ▶ Building on ANCHOR-01 findings of reduced PCC, ANCHOR-02 provides new insights.
- ▶ The use of **oral antivirals generally showed a trend towards improved recovery from acute to early post-acute COVID-19** compared with non-antiviral therapy.
- ▶ **Ensitrelvir** was associated with **fewer re-consultations, better work productivity, and higher likelihood of returning to usual health** by Day 28.
- ▶ Benefits of antiviral treatment were observed despite inclusion of participants with older age and those with comorbidities.



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