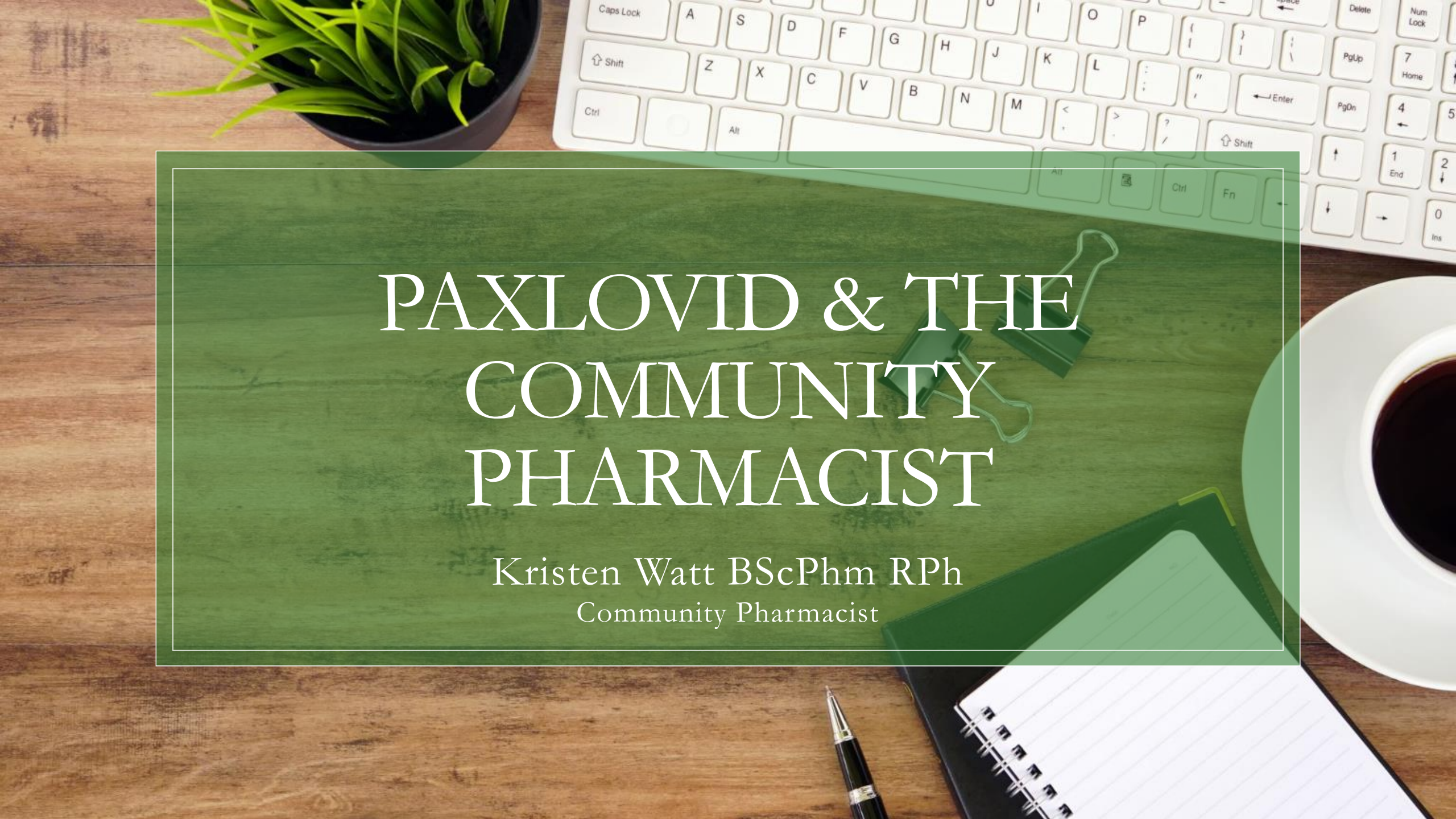


PAXLOVID & THE COMMUNITY PHARMACIST

Kristen Watt BScPhm RPh
Community Pharmacist

Me & My Conflicts

- Community Pharmacist
- UofT 1T0
- Palliative Care specialty
- Owner of Kristen's Pharmacy
- Adjunct Clinical Assistant Professor, UWaterloo School of Pharmacy
- Boards of Directors:
  - Ontario Pharmacists Association
  - PharmaChoice Canada
  - Grey Bruce Hospice
- Honoraria, payments and other affiliations from:
  - Pfizer
  - MedEssist
  - MD BriefCase
  - OPA
  - CPhA
  - PharmacyU

Me & My Conflicts

- Hospital Pharmacist
- Viral specialty
- Clinical Professor, uOttawa School of Pharmacy
- CHAP
- Editorial board of hivclinic.ca
- Organizing committee of HIV Education Day

- Honoraria, payments and other affiliations from:
  - Pfizer
  - ViiV
  - Gilead
  - Merck

The "Post Pandemic" Era

Focus on reduction of severe illness

Moving to annual vaccination (away from boosters)

Using Paxlovid to prevent severe illness in those who would benefit

How Does Paxlovid (Nirmatrelvir/Ritonavir) Work?

Nirmatrelvir prevents the long protein chains of the SARS-CoV-2 virus being cleaved into the shorter, non-structural proteins that are vital for viral replication.[1]

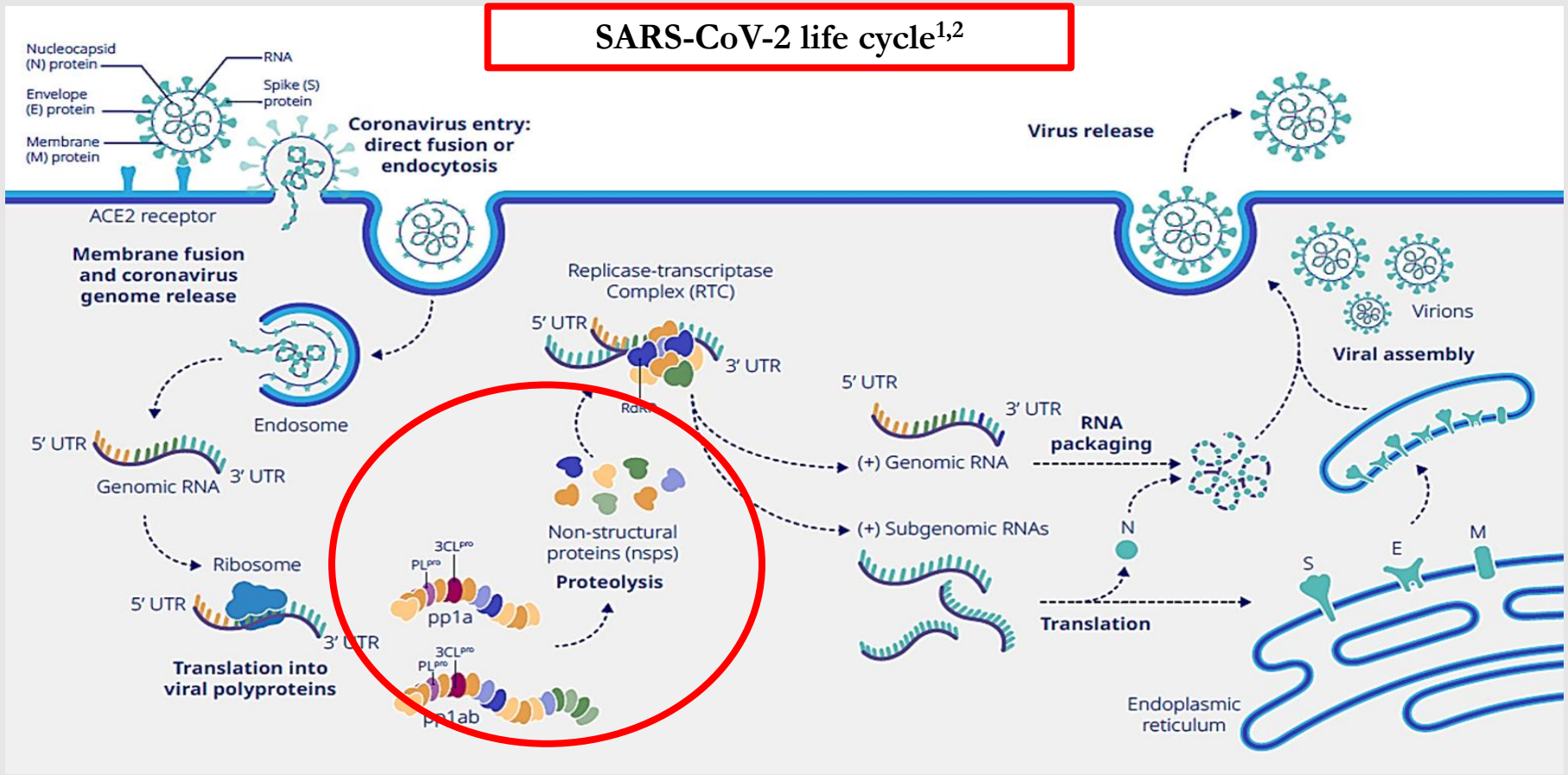


Image adapted from V'Kovski P, *et al.*, *Nat Rev Microbiol* 2021, and Owen DR, *et al.*, *Science* 2021.

References: 1. V'kovski P, Kratzel A, Steiner S, *et al.* Coronavirus biology and replication: Implications for SARS-CoV-2. *Nat Rev Microbiol* 2021;19(3):155–170. **2.** Owen DR, Allerton CMN, Anderson AS, *et al.* An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021;374(6575):1586–1593.

Paxlovid: Real World Evidence

What	Population based cohort study
When	Apr 4 – Aug 31, 2022
Who	• All residents of Ontario aged >17 years with a positive PCR test for SARS-CoV-2 • PAXLOVID-treated patients (n=8,876) and patients who were not treated (n=168,669) • 84.8% of PAXLOVID-treated patients had received ≥3 vaccine doses
Outcomes	**Hospital admission from COVID-19 or all-cause death at 1–30 days** • Occurrence of hospital admission or death was lower in the PAXLOVID group than the not-treated group (2.1% vs. 3.7%; wOR 0.56; 95% CI 0.47–0.67; p<0.001) • Occurrence of death was lower in the PAXLOVID group than the not-treated group (1.6% vs. 3.3%; wOR 0.49; 95% CI 0.40–0.60; p<0.001) • NNT for prevention of severe COVID-19 (hospitalisation or death): 62 (95% CI 43–80)

Population-based evaluation of the effectiveness of nirmatrelvir-ritonavir for reducing hospital admissions and mortality from COVID-19. Schwartz KL, et al. *CMAJ* 2023;13;195:E220–E226.

Paxlovid: Real World Evidence

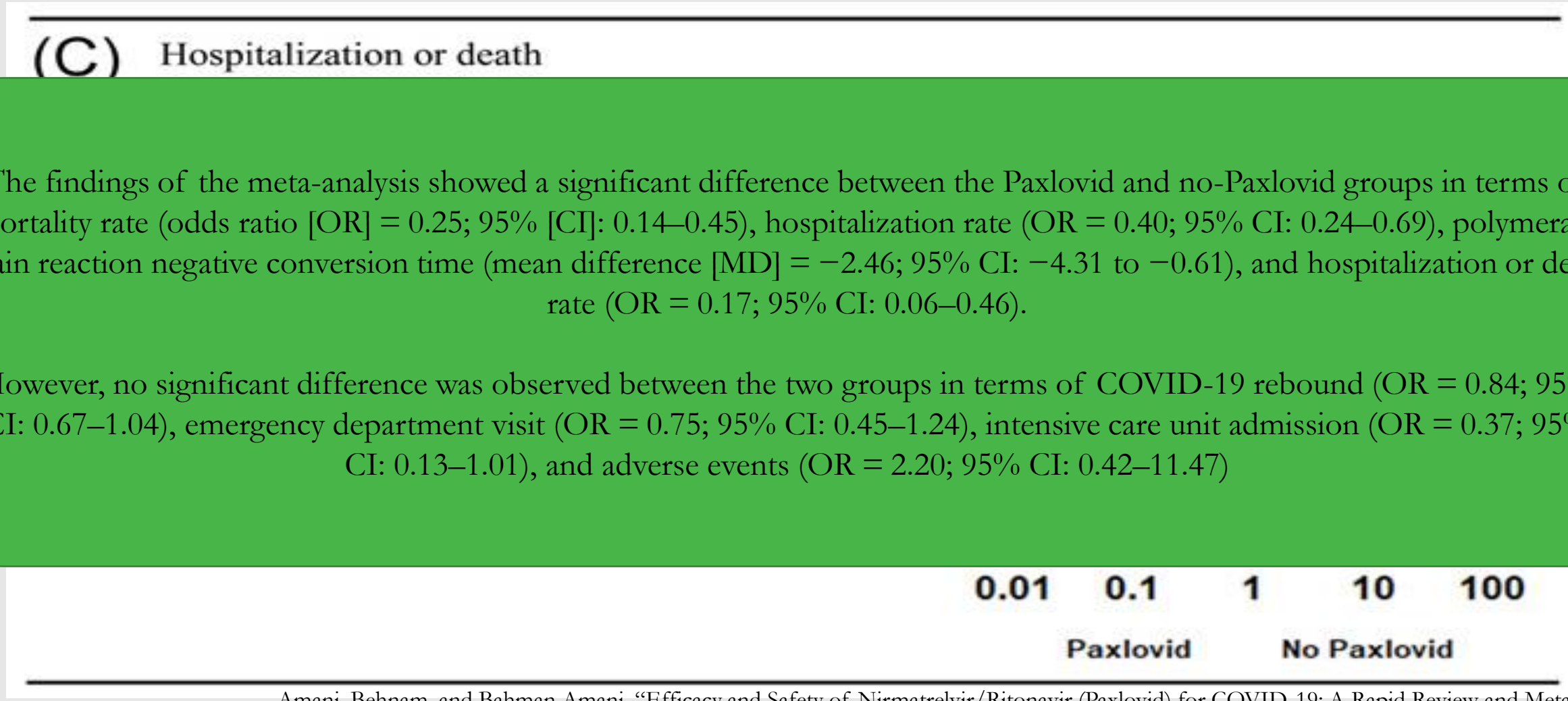
What	• Hospital Authority database
When	• 26 February 2022–26 June 2022 (Omicron BA2.2 wave)
Who	• Non-hospitalised adult patients with COVID-19 (N=1,074,856) • Molnupiravir (n=4,983) versus antiviral non-users (n=49,234)* • PAXLOVID (n=5,542) versus antiviral non-users (n=54,672)* • Molnupiravir: 88.7% aged >60 years, 16.1% fully vaccinated • PAXLOVID: 85.9% aged >60 years, 33.4% vaccinated

Outcomes	**All-cause mortality and COVID-19–related hospitalisation**
	• Compared with no antiviral treatment, molnupiravir and PAXLOVID significantly reduced mortality:
	  ○ PAXLOVID: HR: 0.34 (95% CI: 0.22–0.52)
	  ○ Molnupiravir: HR: 0.76 (95% CI: 0.61–0.95)
	• PAXLOVID was associated with a significantly lower risk of COVID-19–related hospitalisation versus no treatment; molnupiravir was not

Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study

Wong CKH, et al. *Lancet* 2022;400:1213–22

Nirmatrelvir/Ritonavir: Meta-analysis (Feb 2023)



The findings of the meta-analysis showed a significant difference between the Paxlovid and no-Paxlovid groups in terms of mortality rate (odds ratio [OR] = 0.25; 95% [CI]: 0.14–0.45), hospitalization rate (OR = 0.40; 95% CI: 0.24–0.69), polymerase chain reaction negative conversion time (mean difference [MD] = −2.46; 95% CI: −4.31 to −0.61), and hospitalization or death rate (OR = 0.17; 95% CI: 0.06–0.46).

However, no significant difference was observed between the two groups in terms of COVID-19 rebound (OR = 0.84; 95% CI: 0.67–1.04), emergency department visit (OR = 0.75; 95% CI: 0.45–1.24), intensive care unit admission (OR = 0.37; 95% CI: 0.13–1.01), and adverse events (OR = 2.20; 95% CI: 0.42–11.47)

Amani, Behnam, and Bahman Amani. "Efficacy and Safety of Nirmatrelvir/Ritonavir (Paxlovid) for COVID-19: A Rapid Review and Meta-Analysis." *Journal of Medical Virology* 95, no. 2 (2023): e28441. https://doi.org/10.1002/jmv.28441.

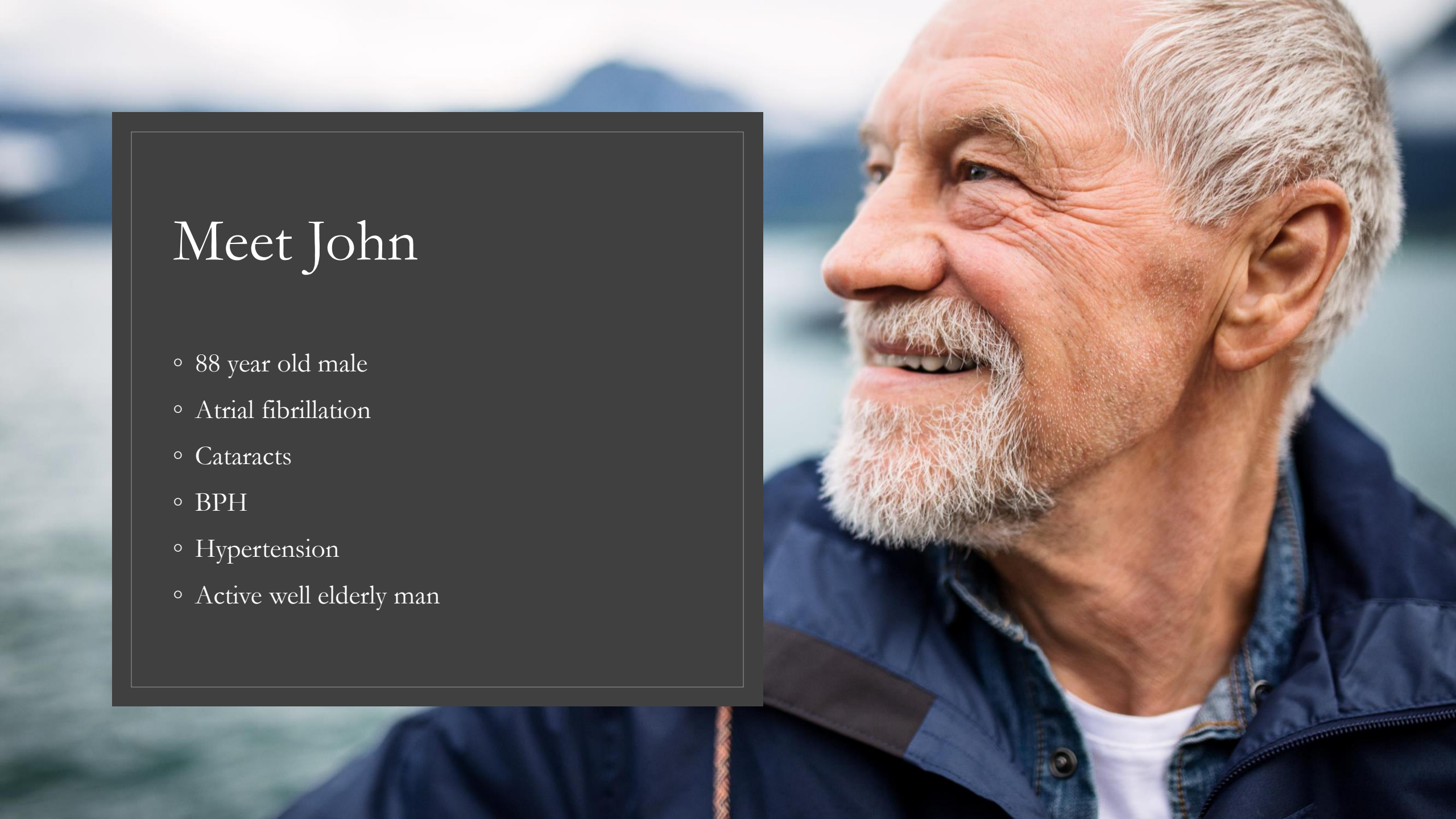
Ontario Paxlovid Eligibility Criteria

Only age	Comorbidities	Vaccination status

• 60 and older	• 18-59
	  • Immunocompromised
	  • 1 or more comorbidities that put them at higher risk of severe COVID-19
		• Unvaccinated or incomplete primary series
		• Completed primary series AND last COVID-19 vaccine dose was more than 6 months ago AND last SARS-CoV-2 infection was more than 6 months ago

Meet John

- 88 year old male
- Atrial fibrillation
- Cataracts
- BPH
- Hypertension
- Active well elderly man



April 2022: COVID+

Medication	Paxlovid Action Plan
Tamsulosin 0.4mg	HELD x 7 days
Xarelto 20mg	HALF DOSE x 7 days
Metoprolol 25mg BID	No change
Lansoprazole 30mg	No change
Candesartan 8mg	No change
MgOx 420mg	No change

PCR positive

RPh recommended Paxlovid to MD, MD authorized and collaborated directly on changes

October 2022: COVID+

Medication	Paxlovid Action Plan
Tamsulosin 0.4mg	HELD x 7 days
Xarelto 20mg	HELD x 7 days
Edoxaban 30mg	STARTED x 7 days
Metoprolol 25mg BID	No change
Candesartan 8mg	No change
MgOx 420mg	No change

RAT positive

Physician prescribed Paxlovid and managed all drug interactions without input

August 2023: COVID+

Medication	Paxlovid Action Plan
Tamsulosin 0.4mg	HELD x 7 days
Xarelto 20mg	HALF DOSE x 7 days
Diltiazem 180mg	Changed to Q2D x 7 days
Metoprolol 100mg BID	No change
Candesartan 4mg	No change
MgOx 500mg	No change
Lansoprazole 30mg	No change

RAT positive

Pharmacist prescribed Paxlovid and managed all drug interactions without input

Leveraging the Community Pharmacist

Comprehensive medication list

Managing drug drug interactions

Adapting, adjusting and managing where needed

Follow up

Editorial Comments

Data on Calcium Channel Blockers

Management DOAC Interaction

Calcium Channel Blockers

ACC.23 TOGETHER WITH WCC

2472
JACC March 7, 2023
Volume 81, Issue 8, suppl A

Complex Clinical Cases

CARDIOGENIC SHOCK DUE TO PAXLOVID INTERACTION

Restricted access | Letter | First published online December 22, 2022

A CYP3A4 Drug-Drug Interaction Between Nirmatrelvir/Ritonavir and Nifedipine Leading to Edema, Oliguria, and Acute Kidney Injury: A Case Report

Madison S. Rauser, PharmD and Ian R. McGrane, PharmD View all authors and affiliations

Volume 57, Issue 8 | https://doi.org/10.1177/10600280221143131

Case report

Pharmacokinetic interaction between verapamil and ritonavir-boosted nirmatrelvir: implications for the management of COVID-19 in patients with hypertension

Obaid Imtiyazul Haque [1,2] Samantha Mahar,[1] Shahzad Hussain,[1] Peter Sloane[1]

BMJ Case Rep 2023;16:e252677.

Calcium Channel Blockers

Health Canada

Plasma concentrations of these drugs are expected to increase by co-administration with ritonavir. Therefore, PAXLOVID should be used with caution, dose reduction of these drugs may be needed. (PM)

NIH

Closely monitor blood pressure; if hypotension occurs, reduce calcium channel blocker dose by 50% while taking Paxlovid® and for 3 days after treatment (NIH)

FDA

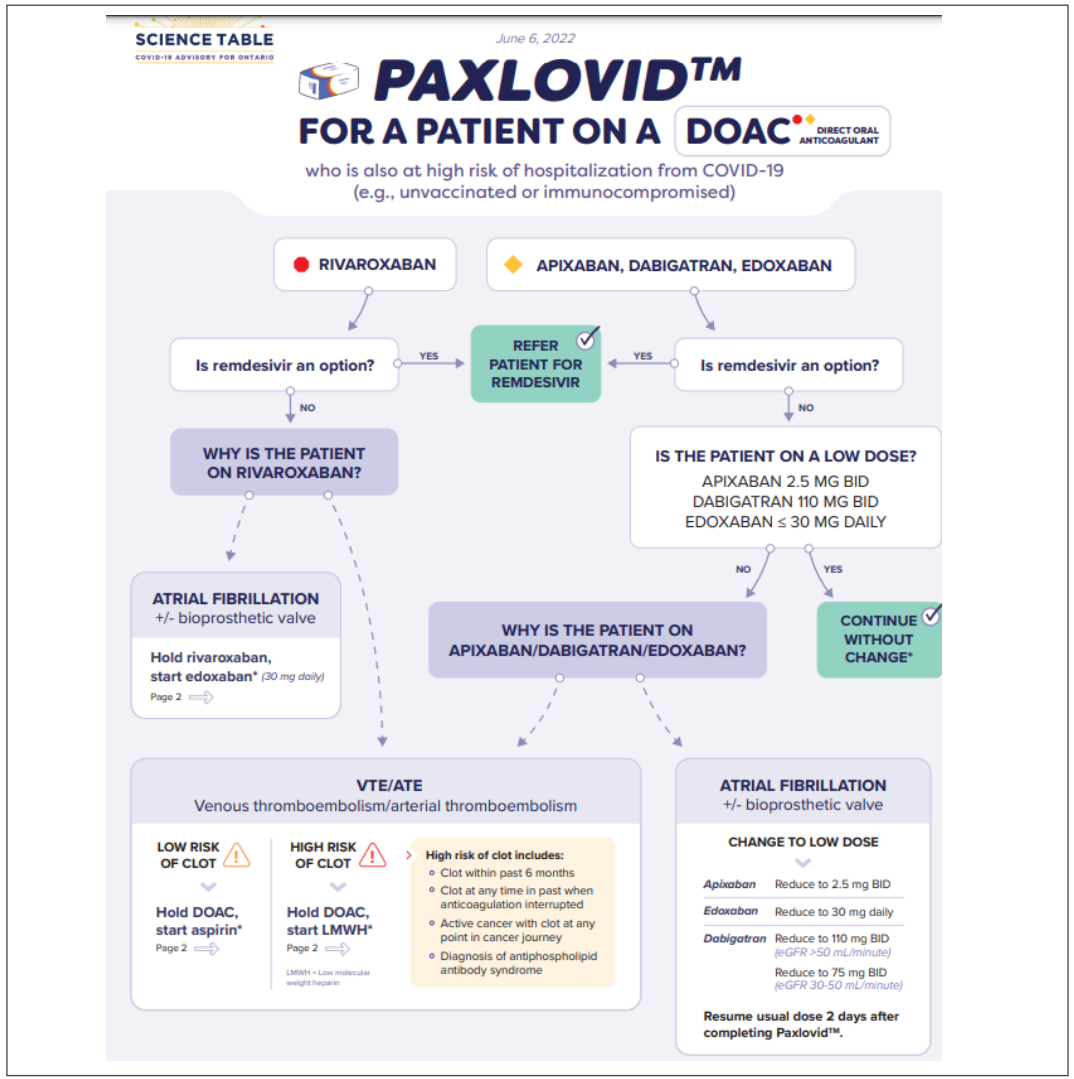
Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PAXLOVID. (FDA)

PBPK simulation study

- 50% dose reduction of amlodipine results in equivalent PK and PD effect
- Post Ritonavir inhibition gradullay weans off within 5 days (SBP increases 6mmHg)
- Higher amlodipine baseline dose is associated with greater changes (SBP 11 mmHg)

All CCB are not the same

Journal of Pharmacokinetics and Pharmacodynamics (2018) 45:443–456



DOAC

- OST algorythm
  - By agents
  - By indication
- Alternatives
  - Rivaroxaban 20mg + NRM/RTV (PBPK data)
    - Increased AUC, more profound in geriatrics & CKD
    - Dose reduction to 10mg mitigates AUC changes

    And bleeding risk by 50% in all cohorts
- Cohorts @ TOH
  - Validates safe management using OST table recommendations

Clin Pharmacol Ther, 112: 803-807

QUESTIONS?

Back up slides

- CREDIT : Clinical care options

Key Trials of Outpatient Antivirals for High-Risk Patients

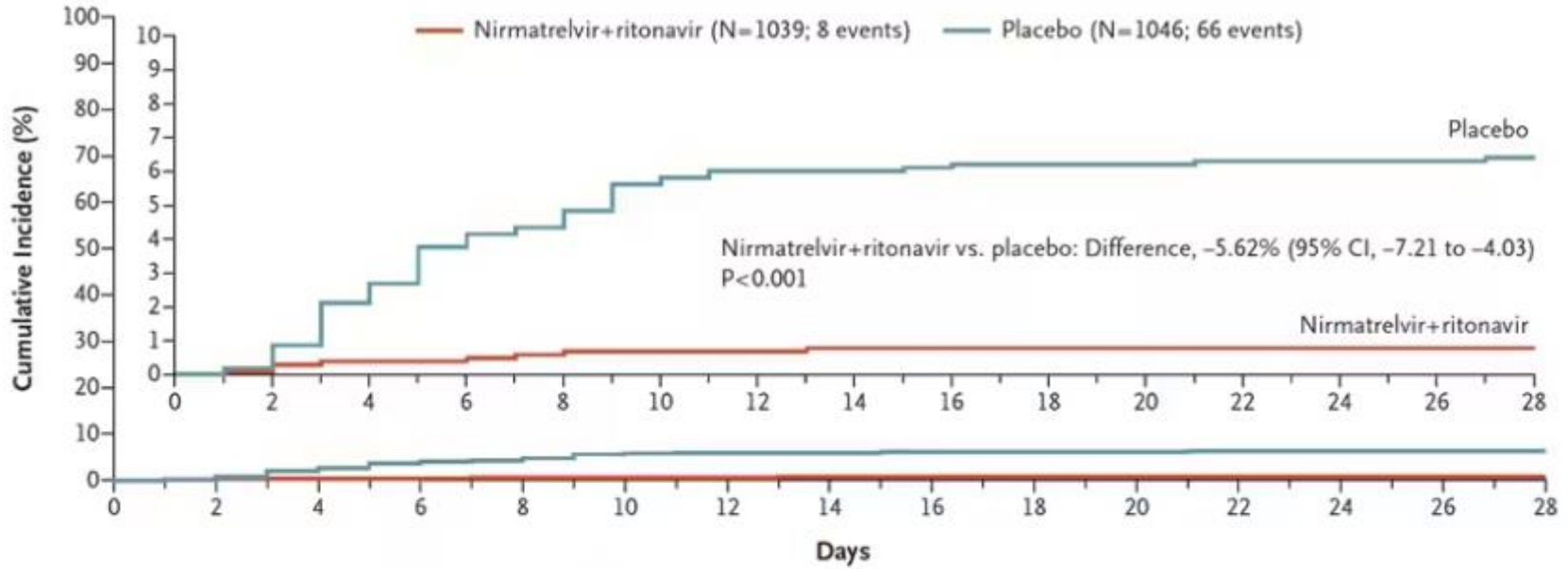
Study	Therapy	Drug Class	Participants
EPIC-HR[1]	Nirmatrelvir + ritonavir	▪ Nirmatrelvir: a SARS-CoV-2 Mpro inhibitor ▪ Ritonavir: an HIV1 protease inhibitor and CYP3A inhibitor	2246 participants: ▪ 1120 nirmatrelvir + ritonavir ▪ 1126 placebo
MOVe-OUT[2]	Molnupiravir	▪ RNA-polymerase inhibitor (cytidine nucleoside analogue)	1433 participants: ▪ 716 molnupiravir ▪ 717 placebo
PANORAMIC[3]	Molnupiravir	▪ RNA-polymerase inhibitor (cytidine nucleoside analogue)	26,411 participants: ▪ 12,821 molnupiravir ▪ 12,962 placebo
PINETREE[4]	Remdesivir	▪ RNA-polymerase inhibitor (adenosine nucleoside analogue)	562 participants: ▪ 279 remdesivir ▪ 283 placebo

CYP3A, cytochrome P450 3A; Mpro, main protease.

1. Hammond J, et al. N Engl J Med. 2022;386:1397-1408; 2. Jayk Bernal A, et al. N Engl J Med. 2022;386:509-520; 3. Butler CC, et al. Lancet. 2023;401:281-293; 4. Gottlieb RL, et al. N Engl J Med. 2022;386:305-315.

EPIC-HR: Phase 2/3 Oral Nirmatrelvir-Ritonavir in High-Risk Nonhospitalized Adults With COVID-19

COVID-19-Related Hospitalization or Death From Any Cause Through Day 28[a]



No. at Risk

NMV-r	1039	1034	1023	1013	1007	1004	1002	1000	997	995	993	993	993	993	992
Placebo	1046	1042	1015	990	977	963	959	959	955	953	951	948	948	948	945

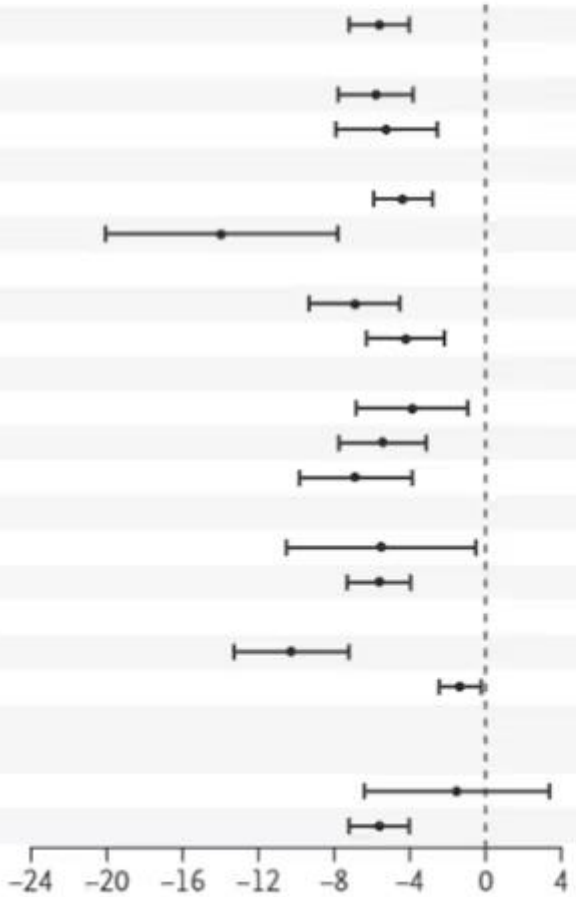
[a]Among patients treated 5 days after symptom onset.
NMV-r, nirmatrelvir-ritonavir.
Hammond J, et al. N Engl J Med. 2022;386:1397-1408.

88.9% and 87.8% relative risk reductions in COVID-19-related hospitalization or death were observed in unvaccinated patients commencing treatment within 3 days and 5 days after symptom onset, respectively

EPIC-HR
Subgroup Analyses

Treatment efficacy was consistent in the subgroup analyses of the primary endpoint

Subgroup	Nirmatrelvir+Ritonavir	Placebo	Difference from Placebo (95% CI)
	no. of events/total no.		*percentage points*
Overall	8/1039	66/1046	−5.62 (−7.21 to −4.03)
Time since symptom onset			
≤3 days	5/697	44/682	−5.81 (−7.78 to −3.84)
>3 days	3/342	22/364	−5.23 (−7.91 to −2.55)
Age			
<65 yr	7/908	46/909	−4.35 (−5.91 to −2.79)
≥65 yr	1/131	20/137	−13.93 (−20.07 to −7.80)
Sex			
Male	4/520	41/540	−6.93 (−9.32 to −4.53)
Female	4/519	25/506	−4.23 (−6.29 to −2.17)
Body-mass index			
<25	1/209	9/207	−3.88 (−6.83 to −0.94)
25 to <30	3/458	28/466	−5.44 (−7.75 to −3.13)
≥30	4/371	29/373	−6.85 (−9.82 to −3.87)
Diabetes mellitus			
Yes	2/125	9/127	−5.51 (−10.51 to −0.52)
No	6/913	57/919	−5.63 (−7.30 to −3.96)
Baseline SARS-CoV-2 serology status			
Negative	7/487	58/505	−10.25 (−13.28 to −7.21)
Positive	1/540	8/528	−1.34 (−2.45 to −0.23)
Received or expected to receive Covid-19 monoclonal antibody treatment			
Yes	1/70	2/69	−1.51 (−6.40 to 3.37)
No	8/1039	66/1046	−5.62 (−7.21 to −4.03)

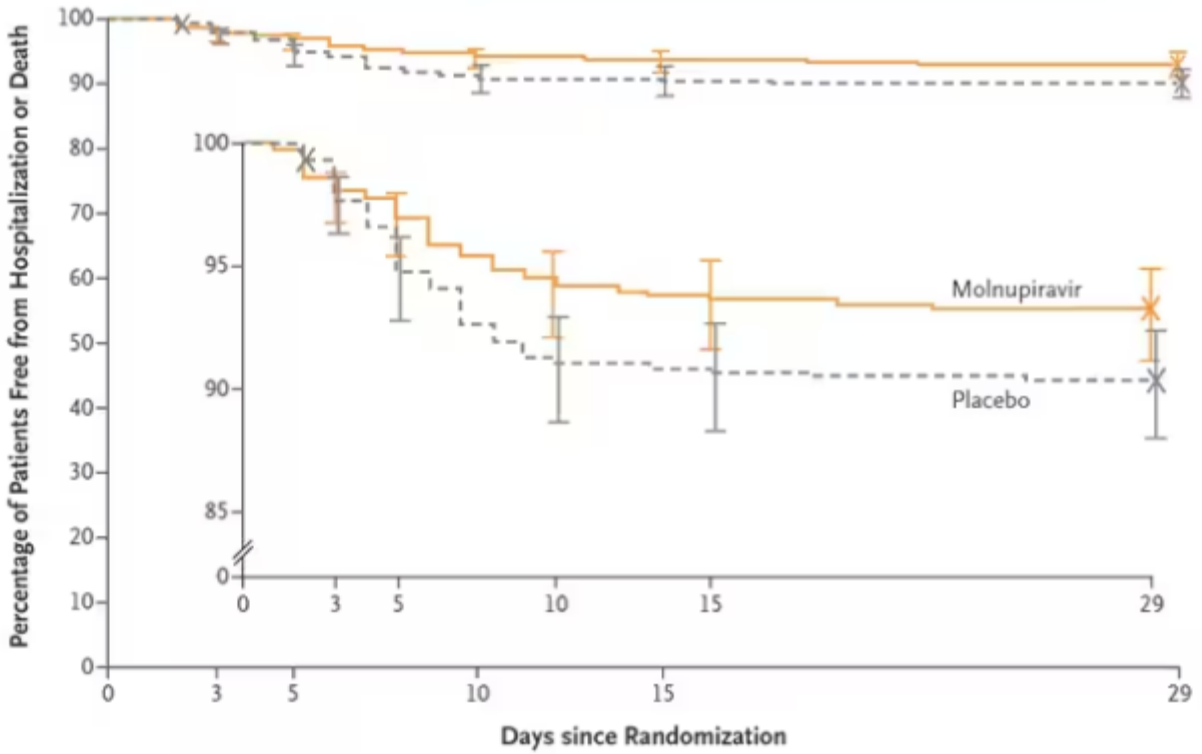


Hammond J, et al. N Engl J Med. 2022;386:1397-1408.

MOVe-OUT

Phase 3 Oral Molnupiravir in Nonhospitalized At-Risk Adults With COVID-19

Time-to-Event Analysis of Hospitalization or Death Through Day 29 in the Modified Intention-to-Treat Population



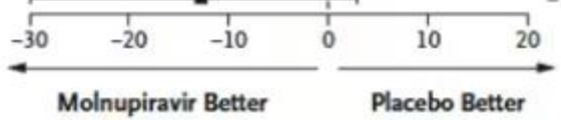
No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

Jayk Bernal A, et al. N Engl J Med. 2022;386:509-520.

Molnupiravir, initiated within 5 days after the onset of symptoms, reduced the risk of hospitalization for any cause or death in at-risk, unvaccinated adults with COVID-19

MOVe-OUT
Subgroup Analyses

Subgroup	Molnupiravir	Placebo	Absolute Risk Reduction (95% CI)
	no. of events/no. of participants		*percentage points*
Sex			
Female	16/379	27/344	−3.6 (−7.4 to −0.2)
Male	32/330	41/355	−1.9 (−6.5 to 2.8)
Days since onset of symptoms			
≤3	25/339	28/335	−1.0 (−5.2 to 3.2)
>3	23/370	40/364	−4.8 (−9.0 to −0.7)
Baseline Covid-19 severity			
Mild	19/395	27/376	−2.4 (−5.9 to 1.0)
Moderate	29/311	40/321	−3.1 (−8.1 to 1.8)
Baseline SARS-CoV-2 nucleocapsid antibody status			
Positive	5/136	2/146	2.3 (−1.7 to 7.1)
Negative	39/541	64/520	−5.1 (−8.8 to −1.6)
Risk factors for severe Covid-19			
>60 yr of age	12/118	16/127	−2.4 (−10.6 to 5.8)
Obese	29/535	46/507	−3.7 (−6.9 to −0.5)
Diabetes mellitus	17/107	17/117	1.4 (−8.2 to 11.1)
Serious heart condition	8/86	9/78	−2.2 (−12.4 to 7.5)
Race			
American Indian or Native American	18/207	21/199	−1.9 (−7.8 to 4.0)
Asian	7/25	7/23	−2.4 (not calculated)
Black	10/157	15/142	−4.2 (−11.1 to 2.2)
White	29/556	54/573	−4.2 (−7.3 to −1.2)
Baseline SARS-CoV-2 qualitative assay			
Detectable	45/614	61/613	−2.6 (−5.8 to 0.5)
Undetectable	0/54	0/51	0.0 (−7.1 to 6.7)
Unknown	3/41	7/35	−12.7 (−29.9 to 2.9)



Jayk Bernal A, et al. N Engl J Med. 2022;386:509-520.

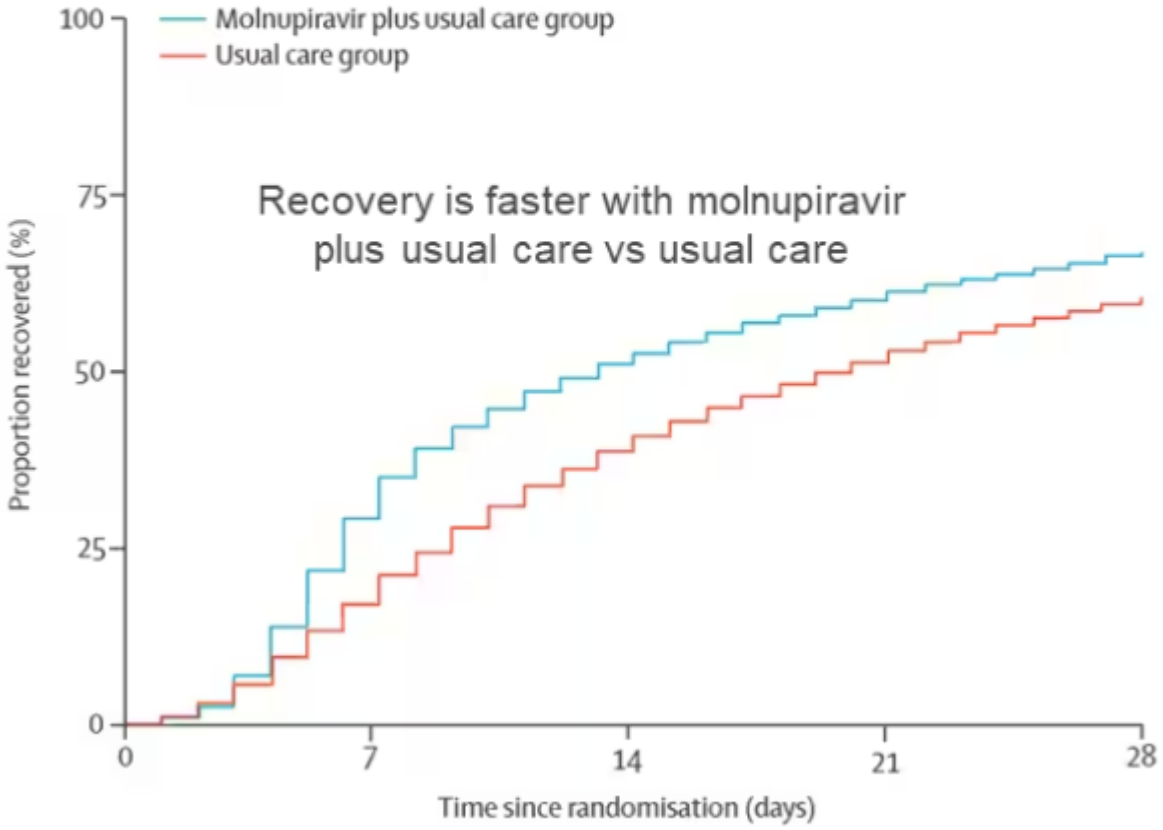
In patients with previous SARS-CoV-2 infection, low baseline viral load, or diabetes, the difference in point estimate favored placebo

PANORAMIC
Molnupiravir in Adults With COVID-19 at Increased Risk of Adverse Outcomes

26,411 patients were randomized to receive molnupiravir plus usual care or usual care only

- Largely vaccinated or naturally exposed to COVID-19
- Hospitalizations or deaths were recorded in 1% of patients in each arm

Time From Randomization to First Reported Recovery From COVID-19

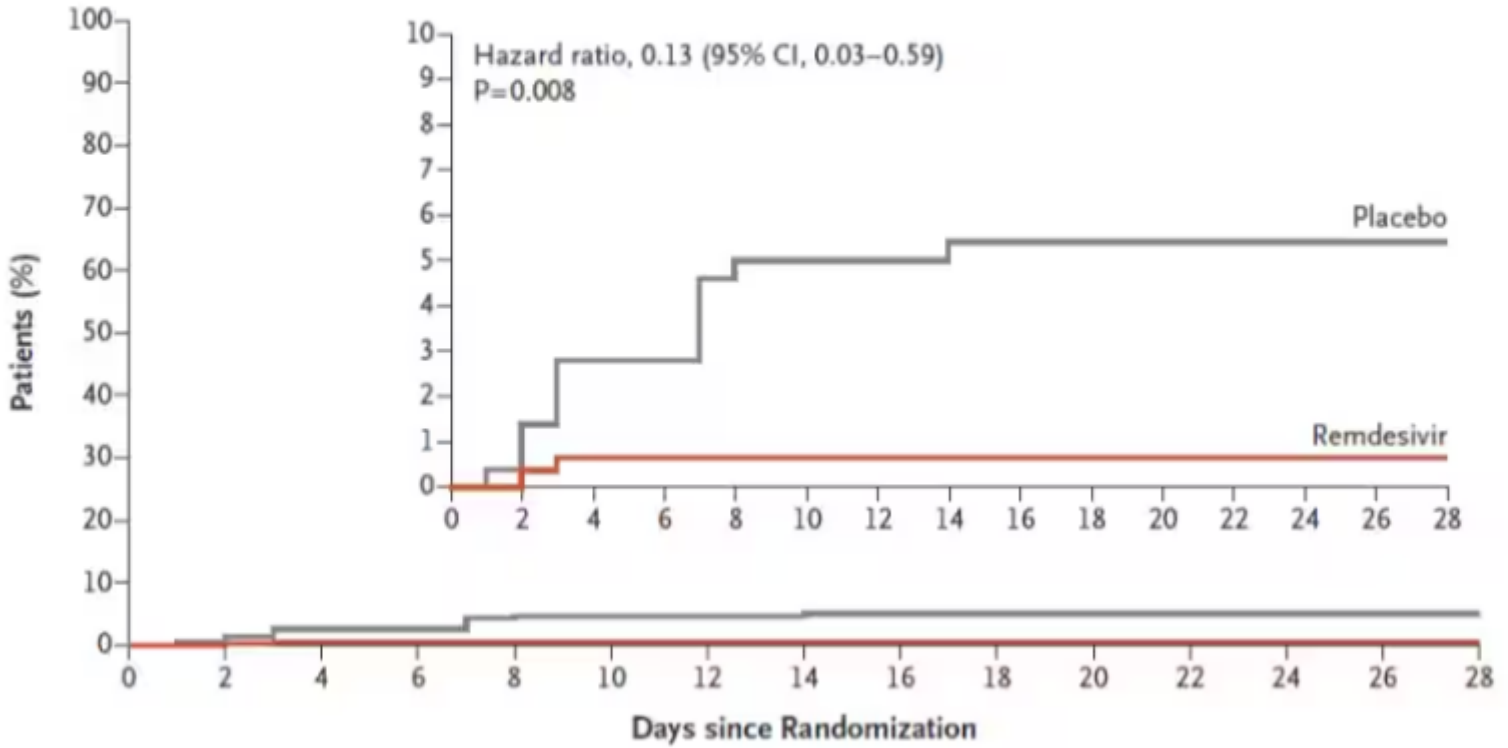


Butler CC, et al. Lancet. 2023;401:281-293.

PINETREE

Early IV Remdesivir to Prevent Progression to Severe COVID-19 in Outpatients

COVID-19-Related Hospitalization or Death From Any Cause



No. at Risk															
Placebo	283	280	272	271	265	264	264	263	262	261	261	260	256	250	227
Remdesivir	279	276	272	272	271	268	268	268	264	264	264	264	260	252	226

IV, intravenous.

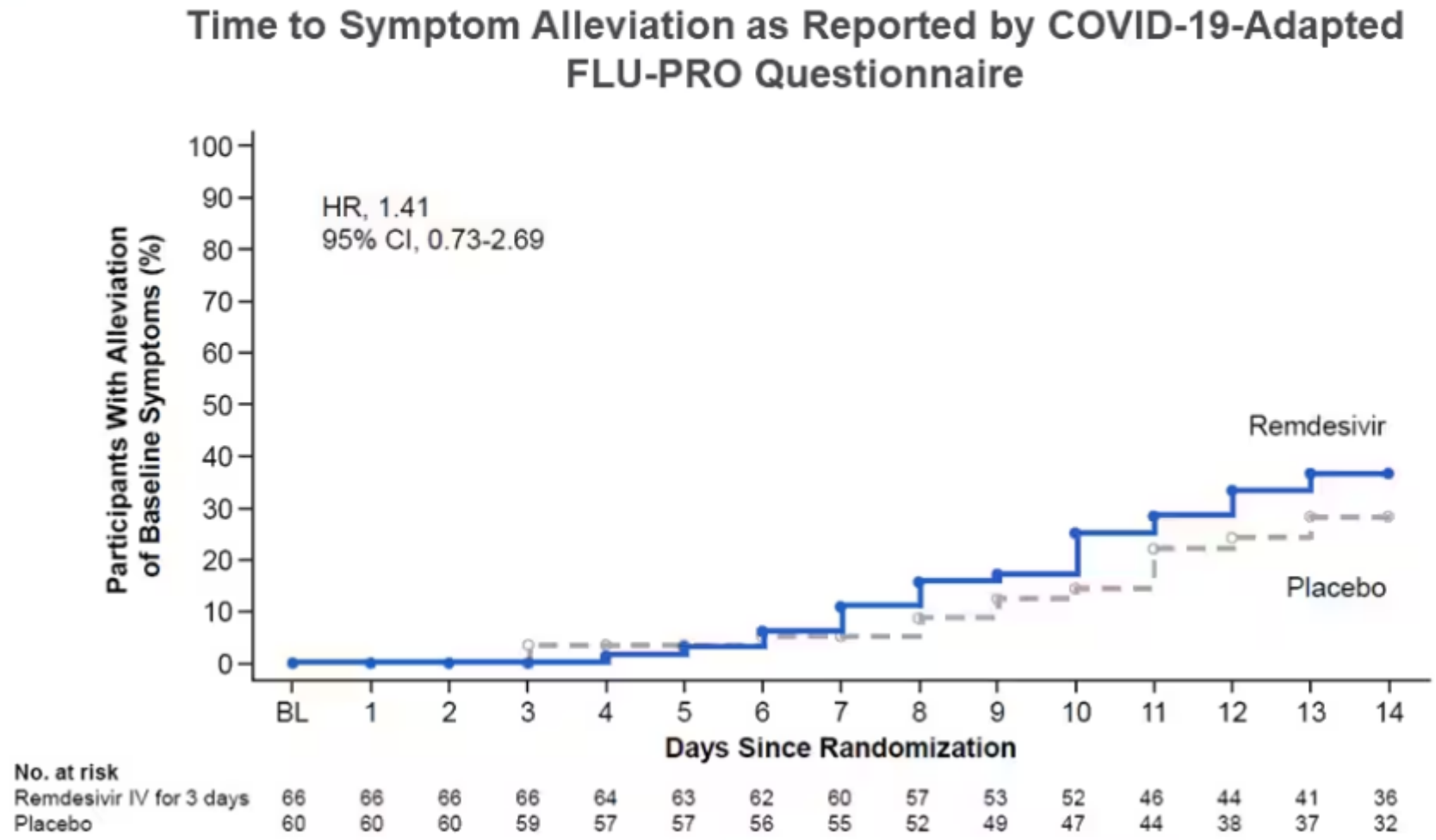
Gottlieb RL, et al. N Engl J Med. 2022;386:305-315.

562 nonhospitalized patients (symptom onset ≤ 7 days and ≥ 1 risk factor for disease progression)

Early remdesivir resulted in 87% lower risk of hospitalization or death vs placebo; no patients died by day 28

Acceptable safety profile with a 3-day course of remdesivir

PINETREE
Time to Alleviation of Symptoms



34.8% remdesivir patients and 25.0% placebo patients reported alleviation of symptoms by day 14

FLU-PRO, InFLUenza Patient-Reported Outcome.
Gottlieb RL, et al. N Engl J Med. 2022;386:305-315.

Limitations of the Antiviral Clinical Trials

EPIC-HR[1]	▪ **Restricted to unvaccinated patients** and those at high risk of progression to severe COVID-19
MOVe-OUT[2]	▪ **Restricted to unvaccinated patients,** and the potential benefit of molnupiravir for the treatment of breakthrough infections was not evaluated
PANORAMIC[3]	▪ **Open-label design** of PANORAMIC means it is not possible to estimate the proportion of the effect of molnupiravir on symptoms that might result from any placebo effect
PINETREE[4]	▪ **Excluded vaccinated patients** who had received SARS-CoV-2 vaccines ▪ Black or Asian race, chronic liver disease, chronic kidney disease, immunocompromised status, and cancer were underrepresented

1. Hammond J, et al. N Engl J Med. 2022;386:1397-1408; 2. Jayk Bernal A, et al. N Engl J Med. 2022;386:509-520; 3. Butler CC, et al. Lancet. 2023;401:281-293; 4. Gottlieb RL, et al. N Engl J Med. 2022;386:305-315.

Nirmatrelvir-Ritonavir in Reducing Severe COVID-19 and Mortality in High-Risk Patients

Israeli database: 180,351 patients were eligible to receive nirmatrelvir-ritonavir

- 4737 (2.6%) were treated; 135,482 (75.1%) had received COVID-19 vaccines

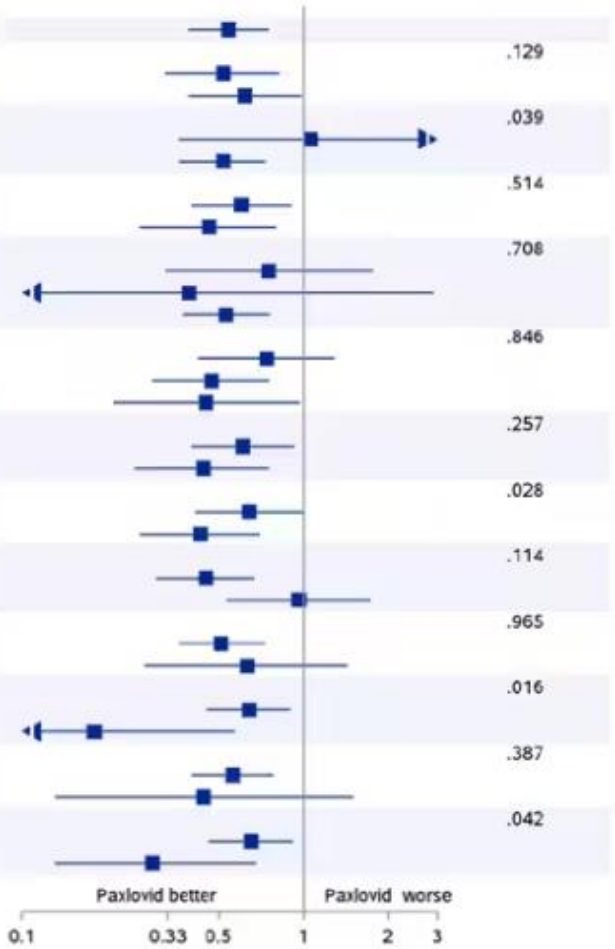
Greater efficacy was seen in older patients, those with cardiovascular or neurological disease, and those who were immunosuppressed

Magnitude of treatment effectiveness appeared to be unrelated to COVID-19 vaccination status

Najjar-Debbiny R, et al. Clin Infect Dis. 2023;76:e342-e349.

Nirmatrelvir-Ritonavir in Reducing Severe COVID-19 and Mortality in High-Risk Patients: Subgroup Analyses

Subgroup	Paxlovid No.	Non-Paxlovid No.	Hazard Ratio (95% CI)	Interaction *P* Value
Overall	4737	175 614	0.54 (.39, .75)	
Adequate COVID-19 vaccination				.129
No	1051	43 818	0.52 (.32, .82)	
Yes	3686	131 796	0.62 (.39, .98)	
Age category				.039
<60 years	973	102 040	1.06 (.36, 3.15)	
≥60 years	3764	73 574	0.52 (.36, .73)	
Sex				.514
Males	1992	71 967	0.60 (.40, .91)	
Females	2745	103 647	0.45 (.26, .80)	
Population sector				.708
Arab	300	32 758	0.75 (.32, 1.77)	
Ultra-Orthodox Jewish	202	6835	0.39 (.05, 2.89)	
General Jewish	4234	135 464	0.53 (.37, .76)	
Socioeconomic status				.846
Low	1120	62 618	0.74 (.42, 1.29)	
Middle	2090	74 928	0.47 (.29, .75)	
High	1517	37 022	0.45 (.21, .97)	
Diabetes				.257
No	2911	139 767	0.61 (.40, .93)	
Yes	1826	35 487	0.44 (.25, .75)	
Cardiovascular disease				.028
No	3231	152 121	0.64 (.41, 1.00)	
Yes	1506	23 493	0.43 (.26, .70)	
Chronic lung disease				.114
No	4238	169 385	0.45 (.30, .67)	
Yes	499	6229	0.96 (.53, 1.73)	
Chronic kidney disease				.965
No	4506	170 949	0.51 (.36, .73)	
Yes	231	4665	0.53 (.27, 1.43)	
Neurological disease				.016
No	4410	164 650	0.64 (.45, .90)	
Yes	327	10 964	0.18 (.06, .57)	
Malignancy in the prior year				.387
No	4559	174 090	0.56 (.40, .78)	
Yes	178	1524	0.44 (.13, 1.51)	
Immunosuppression				.042
No	4421	174 400	0.65 (.46, .92)	
Yes	316	1214	0.29 (.13, .68)	



Treatment effects of nirmatrelvir-ritonavir were consistent across the different subgroups

Najjar-Debbiny R, et al. Clin Infect Dis. 2023;76:e342-e349.

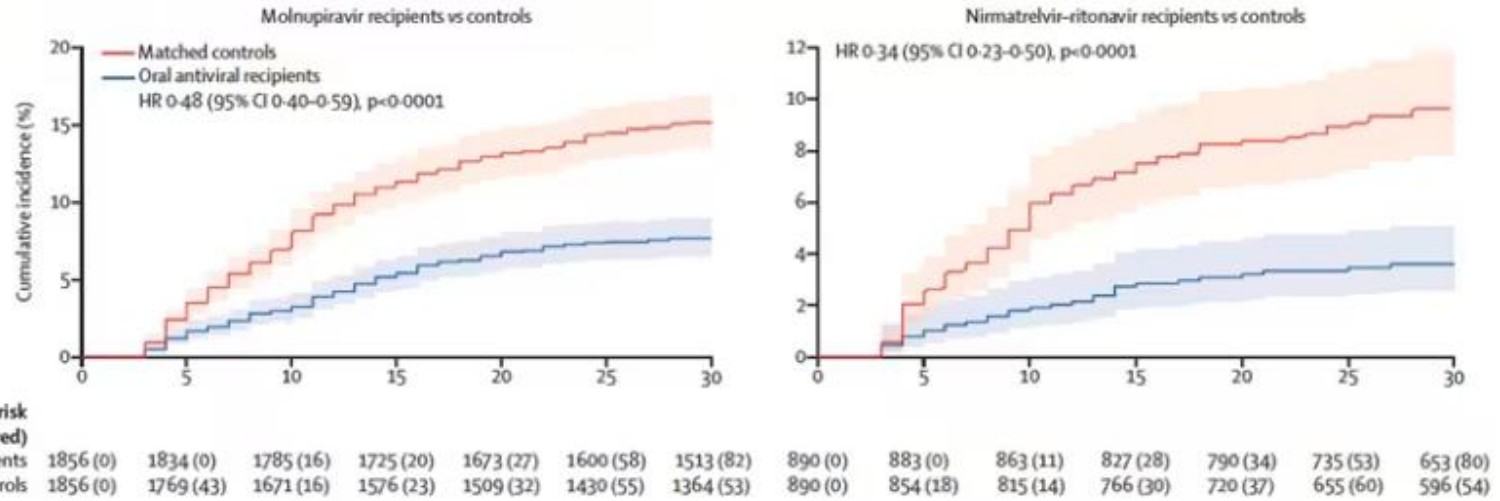
Early Molnupiravir or Nirmatrelvir-Ritonavir in Hospitalized Patients With COVID-19

- **Retrospective cohort of 40,776 patients with COVID-19 not requiring supplemental oxygen on hospitalization in Hong Kong**
- **Time to achieving low viral burden (RT-PCR cycle threshold value ≥ 30) was significantly shorter among oral antiviral recipients than matched controls**
- **Length of hospital stay among molnupiravir recipients was slightly shorter than among their matched controls**
- **Molnupiravir or nirmatrelvir-ritonavir therapy was associated with significantly lower risks of all-cause mortality and disease progression**

Wong CKH, et al. Lancet Infect Dis. 2022;22:1681-1693.

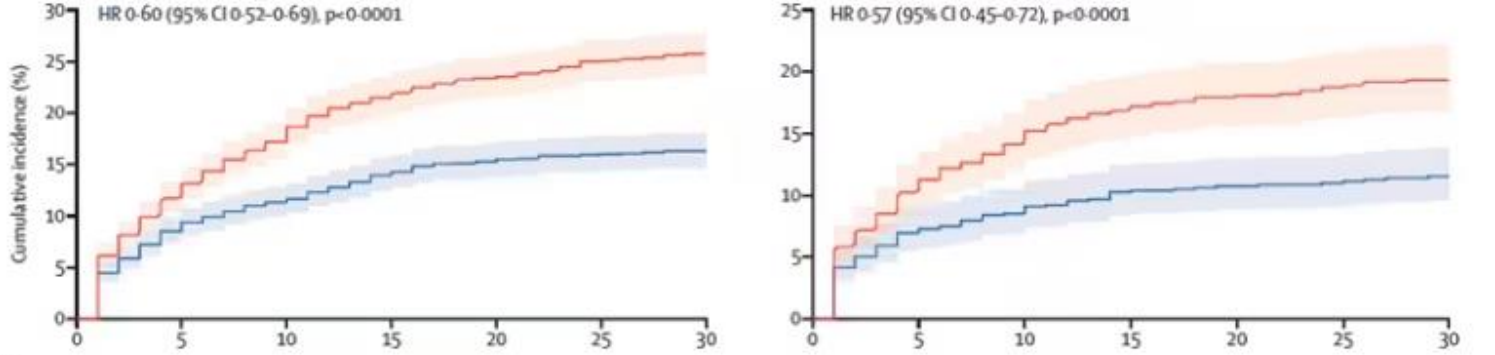
Cumulative Incidence of Mortality and Disease Progression With Molnupiravir or Nirmatrelvir-Ritonavir

All-cause death



Number at risk (number censored)														
Molnupiravir recipients	1856 (0)	1834 (0)	1785 (16)	1725 (20)	1673 (27)	1600 (58)	1513 (82)	890 (0)	883 (0)	863 (11)	827 (28)	790 (34)	735 (53)	653 (80)
Controls	1856 (0)	1769 (43)	1671 (16)	1576 (23)	1509 (32)	1430 (55)	1364 (53)	890 (0)	854 (18)	815 (14)	766 (30)	720 (37)	655 (60)	596 (54)

Composite disease progression outcome



Number at risk (number censored)														
Molnupiravir recipients	1856 (0)	1698 (0)	1630 (16)	1563 (19)	1516 (22)	1453 (51)	1373 (74)	890 (0)	828 (10)	803 (11)	763 (25)	727 (32)	676 (49)	597 (75)
Controls	1856 (0)	1602 (37)	1490 (13)	1392 (21)	1330 (29)	1255 (47	1196 (47)	890 (0)	783 (16)	738 (11)	688 (27)	645 (34)	585 (54)	531 (50)

Wong CKH, et al. Lancet Infect Dis. 2022;22:1681-1693.

Clinical and Virological Outcomes for Molnupiravir Recipients Compared With Matched Controls

	Molnupiravir Recipients (n = 1856)	Controls (n = 1856)	Molnupiravir Recipients vs Controls	
	Crude Incidence Rate per 10,000 Person-Days or Mean (95% CI)	Crude Incidence Rate per 10,000 Person-Days or Mean (95% CI)	HR or Mean Difference (95% CI)	*P* Value
All-cause mortality	19.98 (16.91, 23.45)	38.07 (33.85, 42.67)	0.48 (0.40, 0.59)	< .0001
Invasive mechanical ventilation	0.93 (0.38, 1.92)	2.20 (1.28, 3.52)	0.42 (0.17, 1.01)	.052
Intensive care unit admission	0.13 (0.00, 0.74)	0.26 (0.03, 0.93)	NA	NA
Need for oxygen therapy	31.76 (27.43, 36.59)	44.35 (39.12, 50.08)	0.69 (0.57, 0.83)	.0001
Composite disease progression outcome	44.49 (39.64, 49.76)	69.87 (63.76, 76.40)	0.60 (0.52, 0.69)	< .0001
Low viral burden	145.79 (129.04, 164.12)	100.24 (87.11, 114.79)	1.38 (1.15, 1.64)	.0005
Length of hospital stay, days	10.82 (10.41, 11.23)	11.50 (11.03, 11.98)	-0.68 (-1.31, -0.06)	.033

Wong CKH, et al. Lancet Infect Dis. 2022;22:1681-1693.

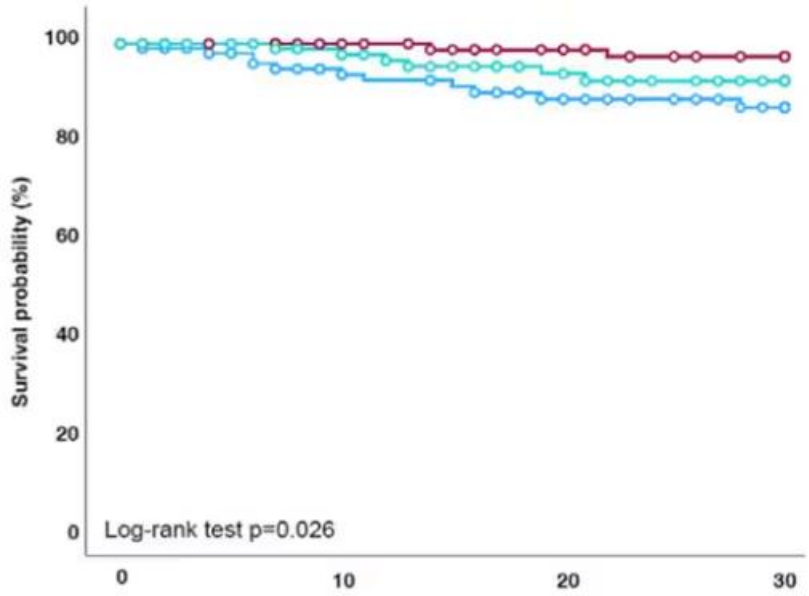
EPICOVIDEHA

Nirmatrelvir-Ritonavir in Patients With COVID-19 With Hematological Malignancies

- **1859 patients analyzed; 117 (6%) treated with nirmatrelvir-ritonavir**
- **80% had received ≥ 1 anti-SARS-CoV-2 vaccine dose before COVID-19 onset, 13% of which received a second vaccine booster**
- **Patients with hematological malignancy were more likely to receive nirmatrelvir-ritonavir when reporting extrapulmonary symptoms or second vaccine booster at COVID-19 onset, vs CPD and obesity**
- **The mortality rate in patients treated with nirmatrelvir/ritonavir was lower than in patients treated with other targeted drugs**

CPD, chronic pulmonary disease.
Salmanton-García J, et al. EClinicalMedicine. 2023;58:101939.

EPICOVIDEHA
Survival Probability by COVID-19 Treatment Strategy

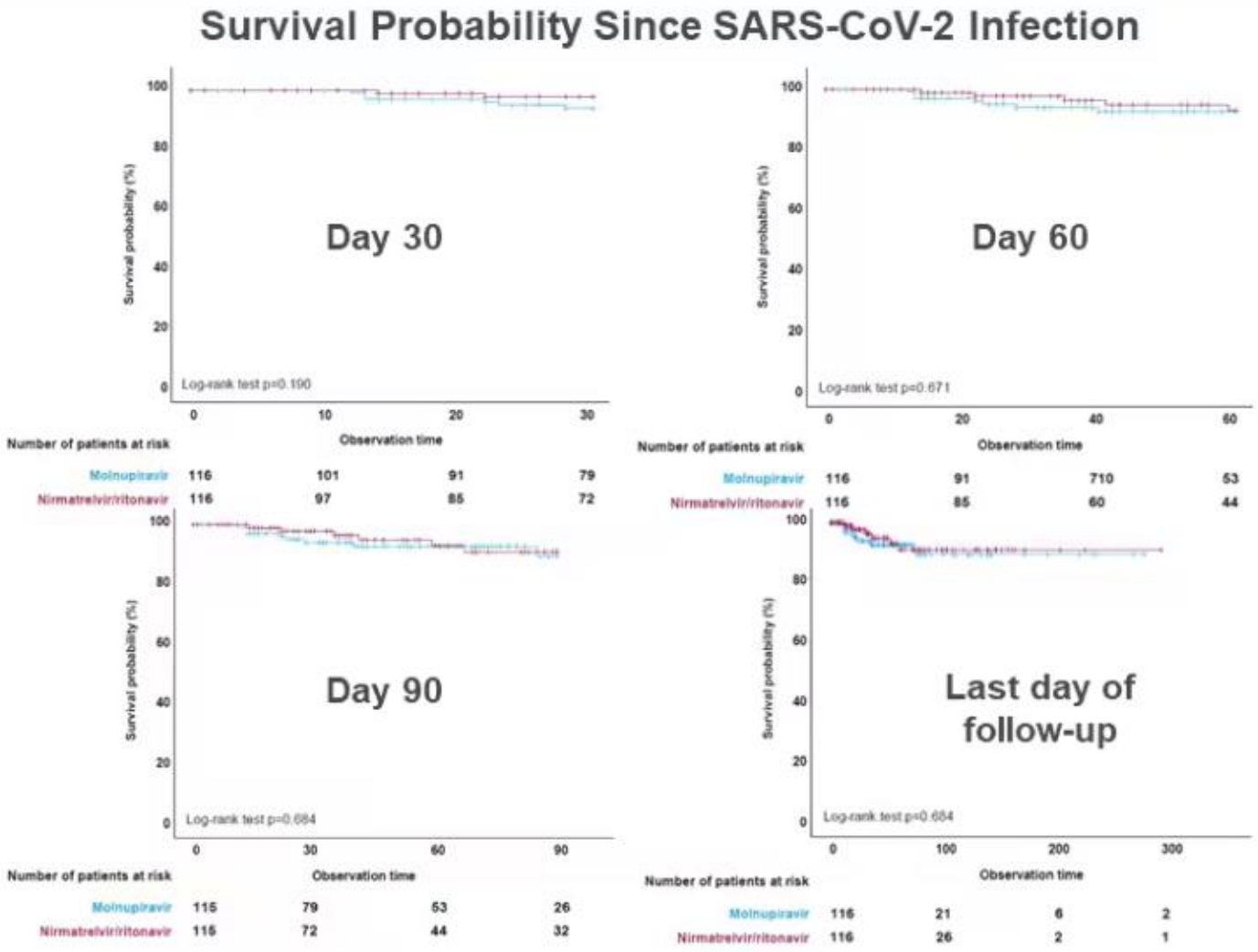


Number of patients at risk				
Directed treatment other than nirmaltrevir/ritonavir	102	79	60	49
No treatment/non-SARS-CoV-2 directed treatment	102	83	62	48
Nirmatrelvir/ritonavir	102	85	73	61

Salmanton-García J, et al. EClinicalMedicine. 2023;58:101939.

Day-30 mortality rate in patients treated with nirmatrelvir-ritonavir was 2%; in patients receiving treatments other than nirmatrelvir-ritonavir, the mortality rate was 11% (*P* = .036)

EPICOVIDEHA: Molnupiravir vs Nirmatrelvir-Ritonavir in Patients With COVID-19 With Hematological Malignancies



No statistically significant differences in survival probability on days 30, 60, and 90 after diagnosis or at last day of follow-up between molnupiravir and nirmatrelvir-ritonavir

Considerations for the Emergence of Sub-Variants

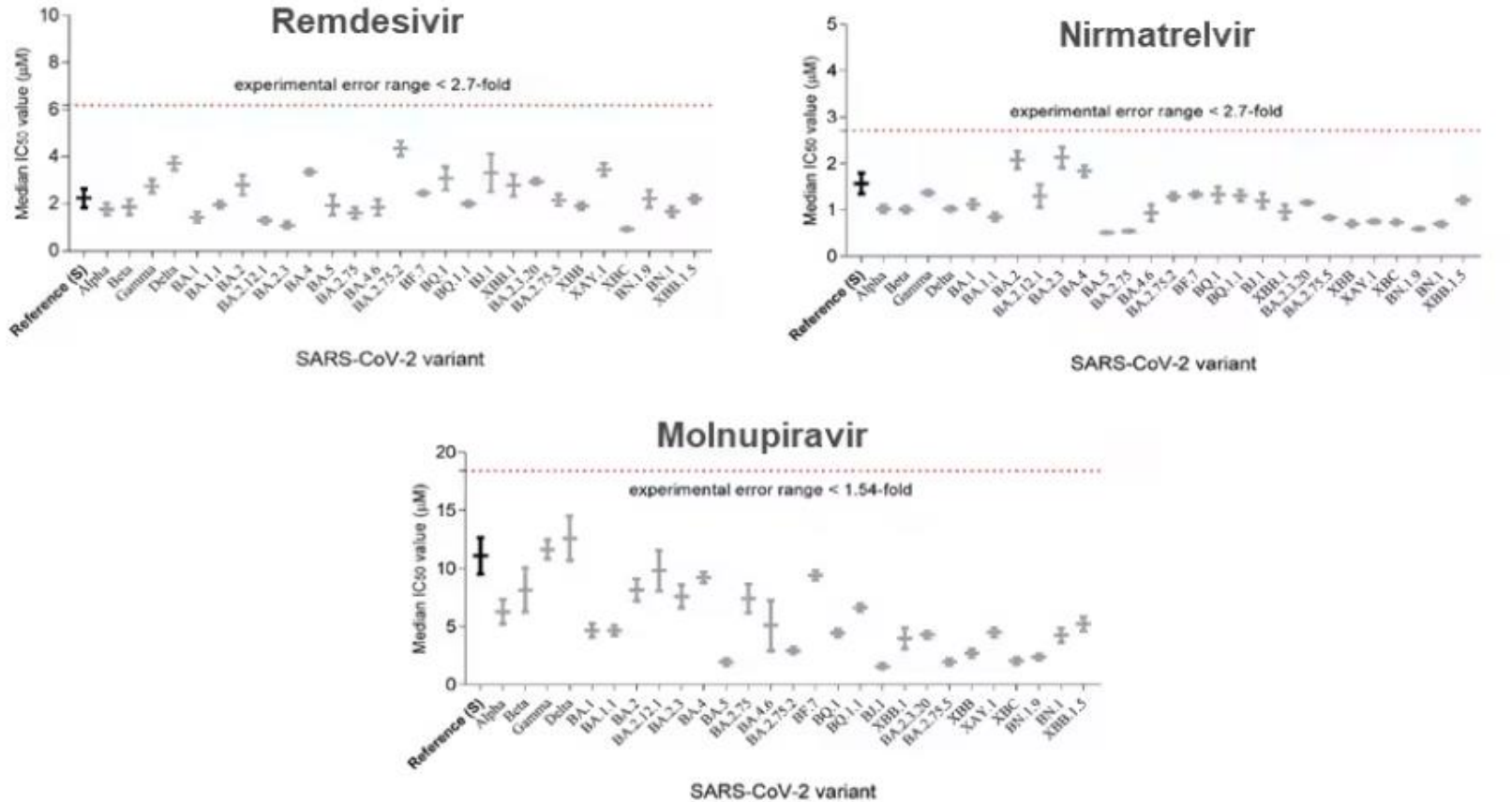
Immune pressure on the spike protein; real-world data on the impact of new variants on antivirals are needed[1]

Rebound phenomenon among oral antiviral users and non-users[2]

1. López-Cortés GI, et al. Vaccines (Basel). 2022;10:864; 2. Wang L, et al. Preprint [interim data/not peer reviewed]. medRxiv. 2022.

Efficacy of Antiviral Drugs Against Newly Emerged SARS-CoV-2 Omicron Subvariants

Median IC50 Value of the Drugs in Vero E6 Cells

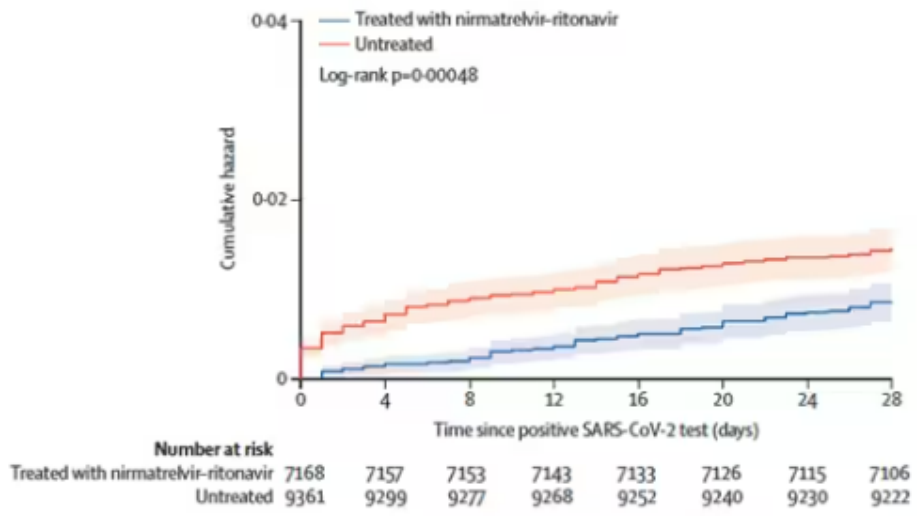


IC50, half maximal inhibitory concentration.
Cho J, et al. Antiviral Res. 2023;214:105609.

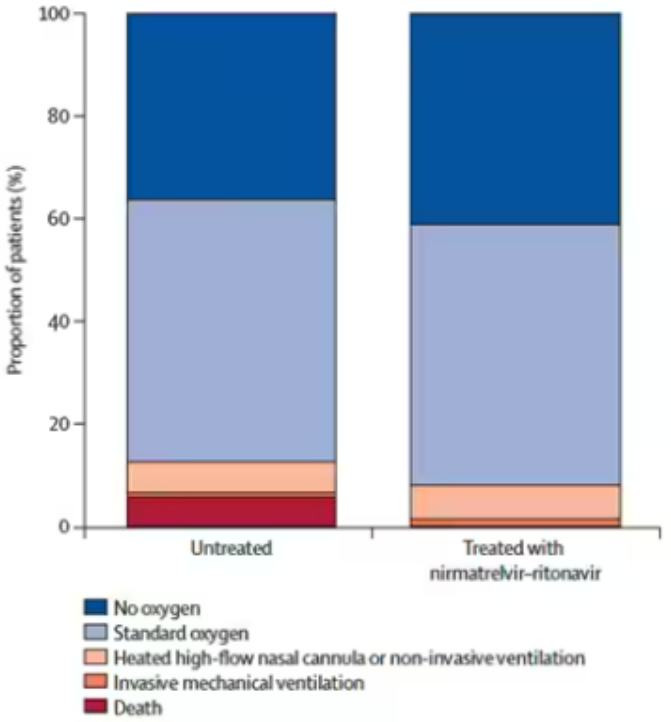
Antiviral efficacy of remdesivir, molnupiravir, and nirmatrelvir against SARS-CoV-2 variants is maintained

Real-World Use of Nirmatrelvir-Ritonavir in Outpatients With COVID-19 During the Era of Omicron Variants

All-Cause Hospitalization to Day 28 by Treatment Status



Severity of All-Cause Hospitalization to Day 28



Nirmatrelvir-ritonavir showed significantly reduced odds of 28-day all-cause hospitalization and mortality

Clinical benefit was observed during both omicron BA.2/BA.2.12.1 and BA.4/BA.5 predominant periods

Aggarwal NR, et al. Lancet Infect Dis. 2023;23:696-705.

AEs of Antivirals in High-Risk Patients

Nirmatrelvir-Ritonavir[1]

- Fewer SAEs (1.6% vs 6.6%) and AEs leading to treatment discontinuation (2.1% vs 4.2%) occurred with nirmatrelvir-ritonavir vs placebo
- Most common AEs occurring with nirmatrelvir-ritonavir were **dysgeusia, diarrhea, and vomiting**

Molnupiravir

- MOVe-OUT: similar AE rate was seen between molnupiravir and placebo (30.40% vs 33.0%)[2]
- Most common AEs related to treatment were **diarrhea nausea, and dizziness**[2]
- PANORAMIC: SAEs were recorded in 0.4% of molnupiravir vs 0.3% of usual care group[3]

Remdesivir[4]

- Fewer patients in the remdesivir group than in the placebo group had SAEs (1.8% vs 6.7%)
- Most common nonserious AEs at ≥ 5% of patients in both groups were **nausea, headache, and cough**
- AEs related to treatment occurred in 12.2% of remdesivir vs 8.8% of placebo patients

AE, adverse event; SAE, serious AE.

1. Hammond J, et al. N Engl J Med. 2022;386:1397-1408; 2. Jayk Bernal A, et al. N Engl J Med. 2022;386:509-520; 3. Butler CC, et al. Lancet. 2023;401:281-293; 4. Gottlieb RL, et al. N Engl J Med. 2022;386:305-315.