Article published online: 2022-06-23

Proposal for a Simple Algorithmic Approach to Manage Drug–Drug Interactions of Oral Anticoagulants with Nirmatrelvir/Ritonavir in COVID-19 Outpatients

John G. Rizk, RPh, MSc.[1,*] Jose G. Lazo Jr., PharmD[2,*] Aashish Gupta, MD[3] Carl J. Lavie, MD[3] Mark B. Effron, MD[3]

[1] Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, Maryland
[2] Department of Pharmacy, UCSF Medical Center, University of California San Francisco, San Francisco, California
[3] Department of Cardiology, John Ochsner Heart and Vascular Institute, Ochsner Clinical School—The University of Queensland School of Medicine, New Orleans, Louisiana

Address for correspondence John G. Rizk, RPh, MSc, Department of Pharmaceutical Health Services Research, University of Maryland, Baltimore, 220 Arch Street, 12th Floor, Room 01-409-E, MD 21201 (e-mail: john.rizk@umaryland.edu).

Semin Thromb Hemost 2023;49:85–88.

In December 2021, the U.S. Food and Drug Administration (FDA) issued emergency use authorizations (EUAs) for two oral antiviral at-home treatments for coronavirus disease 2019 (COVID-19), nirmatrelvir/ritonavir (Paxlovid [Pfizer]), and molnupiravir (Merck).[1] While their mechanisms of action somewhat differ, these agents are considered "game-changers" by some observers, since they do not require administration by intravenous infusion as monoclonal antibodies do. Initial efficacy studies suggest that nirmatrelvir/ritonavir may be more effective than molnupiravir,[1] but it also has more drug interactions of potential concern, especially related to anticoagulant therapy.[1] Molnupiravir does not have any reported interaction with anticoagulant agents.[2] Additionally, remdesivir (Veklury [Gilead]) and bebtelovimab (Lilly) are parenteral agents recently granted an EUA for use in the outpatient setting as treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death.[3] Neither of these agents have any known interaction with anticoagulants.[2]

Nirmatrelvir/ritonavir is comprised of nirmatrelvir, a SARS-CoV-2 main protease inhibitor, co-packaged with ritonavir, a protease inhibitor.[4] While ritonavir has no activity against SARS-CoV-2, its inhibition of CYP3A-mediated metabolism of nirmatrelvir increases nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication. Outpatient nirmatrelvir/ritonavir use is authorized for treatment of mild to moderate COVID-19 disease in adults and pediatric patients older than 12 and weighting more than 40 kg who are at high risk for severe progression of COVID-19.

Regarding pharmacokinetics, nirmatrelvir is primarily eliminated by the kidneys, with minimal liver metabolism.[4] However, ritonavir is known to be an inhibitor of cytochrome P450 (CYP) isoenzymes, particularly a strong CYP3A4 and weak 2D6 inhibitor, and an inhibitor of P-glycoprotein (P-gp).[5,6] Additionally, ritonavir is an inducer of CYP 1A2, 2B6, 2C19, and 2C9.[5] On that premise, the risk of drug interactions with nirmatrelvir/ritonavir and many commonly used medications, including statins and antiarrhythmic drugs, may preclude its use or need careful adjustment of dosing. Additionally, the FDA label flags two anticoagulants for nirmatrelvir/ritonavir users, rivaroxaban and warfarin, while other direct oral anticoagulants (DOACs) are not mentioned. Inhibition of CYP3A4 and P-gp leads to increased plasma levels and pharmacodynamic effects of rivaroxaban, thus potentially increasing bleeding risk (area under the curve [AUC] change 153%, maximum concentration (C_{max}) change 53%).[7]

Antiplatelet or anticoagulant therapy is not currently recommended for outpatients with COVID-19, the largest population of individuals infected.[3,8,9] The ACTIV-4B

* *These authors contributed equally (co-first authors).*

article published online June 23, 2022

Issue Theme Maintaining Hemostasis and Preventing Thrombosis in COVID-19—Part IV; Guest Editors: Emmanuel J. Favaloro, PhD, FFSc (RCPA), Leonardo Pasalic, FRCPA, FRACP, PhD, and Giuseppe Lippi, MD

© 2022. Thieme. All rights reserved.
Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0042-1750024.
ISSN 0094-6176.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Outpatient Thrombosis Prevention Trial,[10] aimed at evaluating antithrombotic therapy in outpatients with COVID-19, was a randomized, adaptive, double-blind, placebo-controlled trial that randomly assigned outpatients with COVID-19 in a 1:1:1:1 ratio to receive aspirin (81 mg orally once daily), prophylactic-dose apixaban (2.5 mg orally twice daily), therapeutic-dose apixaban (5 mg orally twice daily), or matching placebo for 45 days. Treatment with aspirin or apixaban compared with placebo did not reduce the rate of composite clinical outcomes, with risk of adjudicated primary composite outcome with placebo being 0.0% (95% CI, 0.0–2.8%), with aspirin 0.0% (95% CI, 0.0–2.6%), 0.7% in the prophylactic apixaban group (95% CI, 0.1–4.1%) and 1.4% in therapeutic apixaban group (95% CI, 0.4% –5.0%), respectively. In addition, a phase 2b placebo controlled randomized study of rivaroxaban 10 mg daily in patients with COVID-19 not currently hospitalized or under immediate consideration for hospitalization was terminated, after almost 500 of the target 600 participants were enrolled because a prespecified interim analysis of the first 200 participants in the intent-to-treat population demonstrated it would be futile to attempt to show a beneficial effect of rivaroxaban in this patient population. Disease progression rate with rivaroxaban was 20.7 versus 19.8% in placebo groups, with non-significant risk difference of –1.0 (95% confidence interval, –6.4 to 8.4%; $p = 0.78$).[11] Thus, at this time, routine anticoagulation is not recommended for patients with COVID-19 who do not need hospitalization.

Despite these findings, patients at high risk of thrombosis are usually prescribed long-term anticoagulation therapy. Moreover, COVID-19 patients who require anticoagulants for atrial fibrillation or flutter, recent surgery or immobility, heart valve replacement, ischemic stroke or other thrombotic event should be treated with oral anticoagulant (OAC) therapy. This may be a problem if they develop mild to moderate COVID-19 and are considered high risk for severe COVID-19 disease as they would then be candidates for nirmatrelvir/ritonavir.

While the package insert for nirmatrelvir/ritonavir mentions an increased bleeding risk with rivaroxaban and warns against concomitant use, it is may be reasonable to adjust the dose of apixaban, which like rivaroxaban is a substrate of both CYP3A4 and P-gp. Apixaban, edoxaban, and dabigatran have dose reduction strategies in their prescribing information for certain high bleeding risk populations that can be adopted for use with nirmatrelvir/ritonavir. For apixaban, it may be considered to reduce the dose to 2.5 mg twice daily, and in patients already taking apixaban at a dose of 2.5 mg daily, concurrent use of nirmatrelvir/ritonavir should be avoided.[12] For edoxaban, one might consider reducing the dose to 30 mg once daily.[13] Similarly, consideration of dose reduction of dabigatran to 110 mg twice daily instead of the standard dose of 150 mg twice daily[14] may allow for dabigatran use with nirmatrelvir/ritonavir. However, unlike rivaroxaban, there are no data available evaluating or demonstrating the same level of protection from thrombotic events, or less bleeding, if reduced dose strategies are used in combination with nirmatrelvir/ritonavir. There are no reported drug interactions with the use of low molecular weight heparin (LMWH) (e.g., enoxaparin), unfractionated heparin (UFH), fondaparinux, or the antiplatelet agent aspirin, with nirmatrelvir/ritonavir, and these agents can be considered better alternatives if nirmatrelvir/ritonavir is used.

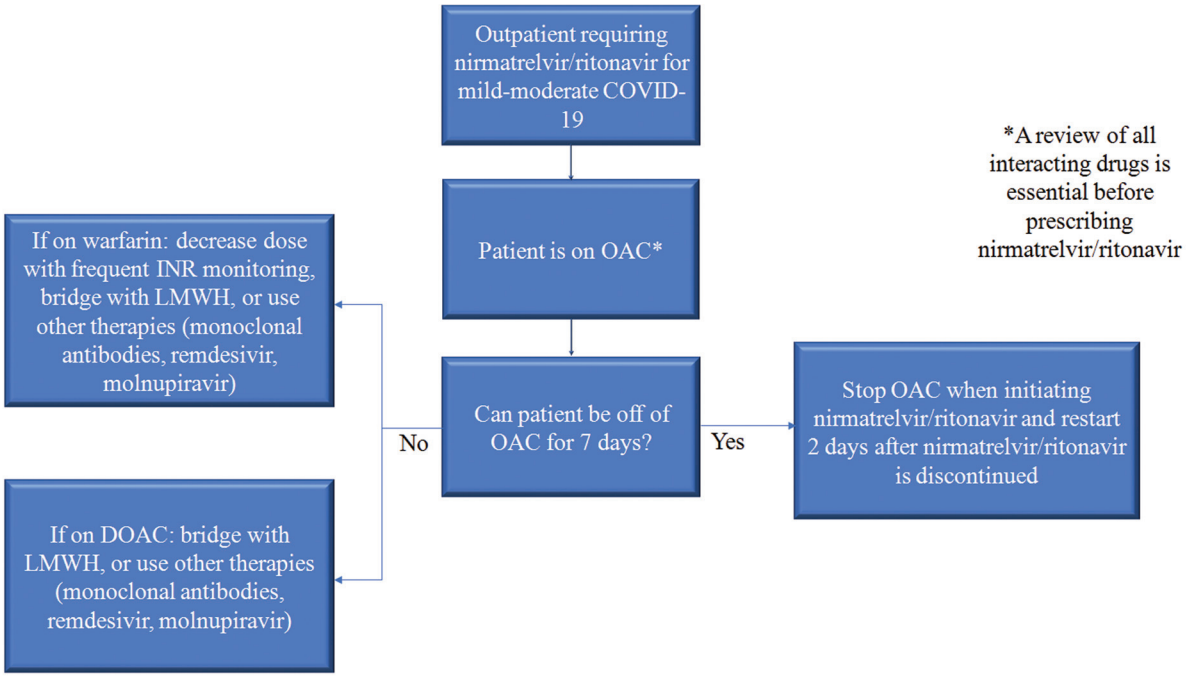

Fig. 1 Proposed algorithm for the management of oral anticoagulation therapy in COVID-19 outpatients prescribed nirmatrelvir/ritonavir. COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulant; INR, international normalized ratio; LMWH, low molecular weight heparin; OAC, oral anticoagulant.

 © 2022. Thieme. All rights reserved.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Warfarin, which is metabolized by CYP450 isozymes including CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4, also interacts with nirmatrelvir/ritonavir.[4] The S-enantiomer, which is the more potent isomer, is metabolized by CYP2C9, while the R-enantiomer is metabolized by CYP1A2 and 3A4.[15] Induction of CYP1A2 and CYP2C9 leads to decreased levels of R-warfarin while minimal pharmacokinetic effect is noted on S-warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation, therefore it is recommended that international normalized ratio (INR) is closely monitored when warfarin is administered with ritonavir.

When selecting an agent for thromboprophylaxis in COVID-19 outpatients who are already on an anticoagulant or are at high risk for arterial or venous thromboembolism (VTE), it is essential to conduct a thorough review of potential drug interactions which may diminish efficacy or increase risk of bleeding. Many of the drug interactions are manageable and should not preclude patients from taking nirmatrelvir/ritonavir. Nirmatrelvir/ritonavir is only for outpatient use prior to hospitalization for COVID-19 and the current data and recommendations are against initiating anticoagulants in these patients regardless of other treatments.[16] Moreover, the only anticoagulant warning in the nirmatrelvir/ritonavir label is for use with rivaroxaban (increased bleeding). Finally, other heparin compounds (UFH or LMWH) do not interact with nirmatrelvir/ritonavir.

An ongoing large, randomized trial of approximately 4,000 patients, PREVENT-HD, is comparing rivaroxaban 10 mg once daily with placebo in outpatients with COVID-19 (NCT04508023). The trial may provide evidence as to whether there may be a benefit for anticoagulation in outpatients. Patients who need to be on oral anticoagulation for reasons other than COVID-19 present a challenge when starting nirmatrelvir/ritonavir. If possible, the OAC should be temporarily discontinued for 5 days while the patient is taking nirmatrelvir/ritonavir and for two additional days following discontinuation, to allow washout of ritonavir.[17] If patients are not able to temporarily discontinue OAC (e.g., mechanical heart valves, recent VTE, etc.), the following recommendations should be considered. If the patient is unable to be off anticoagulation for a week, a bridging strategy using LMWH may be considered the most feasible strategy while the patient is taking nirmatrelvir/ritonavir. Otherwise, in patients who are on warfarin, the dose of warfarin should be reduced and the patient should undergo more frequent INR testing to prevent over anticoagulation. Patients currently taking rivaroxaban should either stop the drug temporarily or be bridged with LMWH before initiating nirmatrelvir/ritonavir. If a patient is on another DOAC (e.g., apixaban, dabigatran, edoxaban), consider using lower doses of these drugs; however, there is no data available on safety or efficacy of lower doses of alternative DOACs in combination with nirmatrelvir/ritonavir. If there is concern about temporarily stopping OAC, bridging with LMWH, or using lower doses of OAC, patients can be placed on other oral antivirals (molnupiravir), intravenous antivirals (remdesivir), or a monoclonal antibody (bebtelovimab)[3] instead of using nirmatrelvir/ritonavir (►**Fig. 1**) and continued on their current OAC at therapeutic doses.

Authors' Contributions

J.R. and J.G.L. contributed toward conceptualization. All the authors contributed toward data curation, writing, reviewing, and editing.

Conflict of Interest

M.B.E. has equity in and receives a pension from Eli Lilly and Company. The remaining authors do not have any conflict of interest.

References

1 Gandhi RT, Malani PN, Del Rio C. COVID-19 therapeutics for nonhospitalized patients. JAMA 2022;327(07):617–618

2 The COVID-19 treatment guidelines panel's statement on the role of bebtelovimab for the treatment of high-risk, nonhospitalized patients with mild to moderate COVID-19. Accessed Mar 30, 2022 at: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-bebtelovimab/

3 National Institute of Health. Therapeutic management of nonhospitalized adults with COVID-19. Accessed Mar 22, 2022 at: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults–therapeutic-management/

4 Paxlovid (nirmatrelvir and ritonavir) New York, NY: Pfizer; 2021. Accessed January 18, 2022 at: https://www.fda.gov/media/155050/download

5 Kumar GN, Rodrigues AD, Buko AM, Denissen JF. Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes. J Pharmacol Exp Ther 1996;277(01):423–431

6 Drewe J, Gutmann H, Fricker G, Török M, Beglinger C, Huwyler J. HIV protease inhibitor ritonavir: a more potent inhibitor of P-glycoprotein than the cyclosporine analog SDZ PSC 833. Biochem Pharmacol 1999;57(10):1147–1152

7 European Medical Agency. Paxlovid for the treatment of COVID-19. Accessed January 20, 2022 at: https://www.ema.europa.eu/en/documents/referral/paxlovid-pf-07321332-ritonavir-covid-19-article-53-procedure-conditions-use-conditions-distribution_en.pdf

8 Rizk JG, Gupta A, Lazo JG Jr, et al. To anticoagulate or not to anticoagulate in COVID-19: lessons after 2 years. Semin Thromb Hemost 2023;49(01):62–72

9 Rizk GJ, Lippi G, Rizk Y. Thromboprophylaxis in outpatients with COVID-19: a safe bet or tilting at windmills?. Minerva Cardiol Angiol 2022;70(01):1–4

10 Connors JM, Brooks MM, Sciurba FC, et al;ACTIV-4B Investigators. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. JAMA 2021;326(17):1703–1712

11 Ananworanich J, Mogg R, Dunne MW, et al. Randomized study of rivaroxaban vs. placebo on disease progression and symptoms resolution in high-risk adults with mild COVID-19. Clin Infect Dis 2022;75(01):e473–e481

12 Eliquis (apixaban) Princeton, NJBristol-Myers Squibb2012 Accessed January 20, 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf

13 Savaysa (edoxaban) Tokyo, JapanDaiichi Sankyo Co.2015 Accessed January 20, 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

14 Staerk L, Gerds TA, Lip GYH, et al. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: a nationwide cohort study. J Intern Med 2018; 283(01):45–55
15 Coumadin (warfarin) Princeton, NJBristol-Myers Squibb2011 Accessed January 20, 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf
16 Antithrombotic Therapy in Patients With COVID-19 Accessed January 4, 2022 at: https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/
17 Danner SA, Carr A, Leonard JM, et al;European-Australian Collaborative Ritonavir Study Group. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. N Engl J Med 1995;333(23):1528–1533

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

 © 2022. Thieme. All rights reserved.