Cardiovascular Drug Interactions with Nirmatrelvir/Ritonavir for COVID-19: Considerations for Daily Practice

Andrea Di Lenarda [1], Nicola Ferri [2,3], Massimiliano Lanzafame [4], Eva Agostina Montuori [5] and Luciano Pacelli [5]

1. Cardiovascular Center, Territory Specialist Department, Azienda Sanitaria Universitaria Giuliano Isontina – ASUGI, Trieste, Italy; 2. Department of Medicine, University of Padova, Padua, Italy; 3. Veneto Institute of Molecular Medicine (VIMM), Padua, Italy; 4. Medical Department, Infectious Diseases Unit, Santa Chiara Hospital, APSS, Trento, Italy; 5. Medical Department, Pfizer, Rome, Italy

Abstract

Cardiovascular disease is associated with progression to severe COVID-19 and patients with the condition are among those in whom early antiviral therapy should be warranted. The combination of nirmatrelvir/ritonavir (Paxlovid®) has been approved for clinical use by the Food and Drug Administration and European Medicines Agency. Because patients with cardiovascular disease are often on polypharmacy, physicians need to be aware of potential drug–drug interactions (DDIs) when treating COVID-19 with nirmatrelvir/ritonavir. Guidance is given for avoiding DDIs, emphasising that preventing and managing potential DDIs with nirmatrelvir/ritonavir requires thorough assessment and knowledge. The present review summarises the clinical pharmacology of nirmatrelvir/ritonavir and provides details on potential DDIs with a focus on daily practice in patients with cardiovascular disease. Particular attention is needed for drugs that are predominantly metabolised by cytochrome P450 3A4, are substrates of P-glycoprotein and have a narrow therapeutic index. Proper management of potential DDIs must balance the benefit of nirmatrelvir/ritonavir to prevent severe disease with the risk of serious adverse events.

Keywords

Cardiovascular, drug interactions, nirmatrelvir, ritonavir, COVID-19

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Correspondence: Nicola Ferri, Department of Medicine, University of Padova, 35128, Padova, Italy. E: nicola.ferri@unipd.it

While the WHO has declared that COVID-19 is no longer a global health emergency, it has also emphasised that the disease remains a global threat.[1] A number of risk factors are known to be associated with progression to severe disease, including cardiovascular disease (CVD) and related risk factors such as hypertension, diabetes and obesity.[2,3] Accordingly, special guidance for management has been issued for patients with cardiovascular risk factors and COVID-19.[4] The impact of CVD on COVID-19 is augmented by CVD being the most common cause of death globally, with more than 17 million deaths annually, accounting for more than 30% of all deaths worldwide.[5,6] In Europe alone, more than 4 million people die each year from CVD.[5,6]

In addition, multimorbidity – in particular, cardiometabolic multimorbidity – along with polypharmacy that is common in the elderly, have been associated with a higher risk of progression to severe COVID-19.[7–10] Clinicians thus require guidance for the use of medications in older adults with COVID-19, multimorbidity and polypharmacy.[11]

Like other RNA viruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continually mutates, and variants continue to be a source of concern.[12] While intense efforts were dedicated to use of vaccines to protect against COVID-19, increasing focus is being placed on antiviral therapies to treat COVID-19, given increased knowledge about the structure of the virus and its biology.[13] Early antiviral use is recommended in patients who are at increased risk for progressing to severe COVID-19 and hospital admission.[14] Among new antiviral therapies, the combination of nirmatrelvir/ritonavir (Paxlovid) has been approved for clinical use by the Food and Drug Administration and European Medicines Agency.

Patients with CVD are among those in whom early antiviral therapy should be warranted. Given that patients with CVD are often on polypharmacy, when treating COVID-19 with nirmatrelvir/ritonavir, physicians need to be aware of the potential drug–drug interactions (DDI) with this combination. This is relevant because not all prescriptions are appropriate in COVID-19 patients on polypharmacy.[15] Commonly used drugs for CVD include antiplatelet agents, anticoagulants, statins, antiarrhythmics, antianginal agents, antihypertensives and anti-inflammatories. Since the pharmacokinetic booster ritonavir is an inhibitor of cytochrome P450 (CYP) 3A4, there is the potential for interactions with many drugs.[16] This review summarises the clinical pharmacology data of nirmatrelvir/ritonavir and provides details on potential DDIs, with a focus on daily practice in patients with CVD.

Table 1: Pharmacokinetic Parameters of Nirmatrelvir and Ritonavir in Healthy Subjects

	Nirmatrelvir (Co-administered with Ritonavir)	Ritonavir
Absorption		
T_{max} (h)	3	3.98
Food effect	Test/reference (fed/fasted) ratios of adjusted geometric means AUC_{inf} and C_{max} for nirmatrelvir were 119.67 (90% CI [108.75–131.68]) and 161.01 (90% CI [139.05–186.44]), respectively.	
Distribution		
% bound to human plasma proteins	69%	98–99%
Blood to plasma ratio	0.60	0.14
C_{max} (µg/ml)	2.21	0.36
Vz/F (l), mean	104.7	112.4
Elimination		
Major route of elimination	Renal elimination	Hepatic metabolism
Half-life (h), mean	6.05	6.15
Oral clearance (CL/F) (l/h), mean	8.99	13.92
Metabolism		
Metabolic pathways	Nirmatrelvir is a CYP3A substrate but when dosed with ritonavir, metabolic clearance is minimal.	Major CYP3A, minor CYP2D6
Excretion		
% drug-related material in faeces	35.3%	86.4%
% of dose excreted as total (unchanged drug) in faeces	27.5%	33.8%
% drug-related material in urine	49.6%	11.3%
% of dose excreted as total (unchanged drug) in urine	55.0%	3.5%

The table shows pharmacokinetic parameters of nirmatrelvir and ritonavir after single oral administration of nirmatrelvir/ritonavir 300 mg/100 mg in healthy subjects. AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinity; CL/F = apparent clearance; C_{max} = maximum (peak) plasma drug concentration; CYP = cytochrome P450; T_{max} = time to reach Cmax; V_z/F = apparent volume of distribution. Source: Food and Drug Administration 2021.[22]

Table 2: The Effect on Cytochrome P450 and Drug Transporters

	Nirmatrelvir (Co-administered with Ritonavir)	Ritonavir
CYP450 metabolism	Metabolised by CYP3A4 in the absence of ritonavir	Metabolised by CYP3A4 and CYP2D6 (and is also a CYP3A4 inhibitor)
P-gp	Substrate and inhibitor	Substrate and potent inhibitor
OATP1B1	Substrate and inhibitor	No effect

The effects on CYP450 and drug transporters were determined by in vitro cultured systems. CYP = cytochrome P450; OAT1B1 = organic anion-transporting polypeptide 1B1; P-gp = p-glycoprotein. Source: Elsevier Health 2023.[23]

Nirmatrelvir/Ritonavir

Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor with potent pan-human coronavirus activity.[17] M^{pro} is an appealing target because it is essential in the viral replication cycle and has a low probability of off-target activity given the lack of human analogues.[18,19] Nirmatrelvir is primarily metabolised by CYP3A4/5 and ritonavir is used as a pharmacokinetic enhancer or booster because of its potent and irreversible inhibition of the same cytochromes, allowing for less frequent dosing of nirmatrelvir.[20] The combination has been shown to be highly effective in reducing the risk of severe COVID-19 and mortality.[21]

Pharmacokinetic and Pharmacodynamic Profile of Nirmatrelvir/Ritonavir

The main pharmacokinetic parameters are reported in *Tables 1 and 2*.[22,23] In a Phase I study, the exposure and half-life of nirmatrelvir were considerably increased by ritonavir, and allowed selection of nirmatrelvir/ritonavir 300/100 mg twice daily for Phase II/III trials, which achieved concentrations continuously above those needed for 90% inhibition of viral replication *in vitro*.[24] Following a single oral administration of nirmatrelvir/ritonavir 300/100 mg, the geometric mean C_{max} of nirmatrelvir and ritonavir were 2.21 µg/ml and 0.36 µg/ml, respectively. The AUC_{inf} of nirmatrelvir and ritonavir were 23.01 µg*h/ml and 3.60 µg*h/ml, respectively.[25] The median T_{max} were 3.0 and 3.98 hours for nirmatrelvir and ritonavir, respectively. The arithmetic mean terminal elimination half-life were 6.05 and 6.15 hours. As mentioned, ritonavir is an inhibitor of CYP3A4/5 and increases plasma concentrations of nirmatrelvir and other drugs that are primarily metabolised by CYP3A4/5. Despite being co-administered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of nirmatrelvir.[25] Moreover, given the near irreversible inhibition of CYP3A4/5 by ritonavir there is enhancement of pharmacokinetic parameters of CYP3A substrate drugs that leads to their increased bioavailability.[20] Nirmatrelvir/ritonavir can be taken with or without food.[25]

The pharmacokinetics of nirmatrelvir/ritonavir have been studied in patients with renal impairment and in those with end-stage renal

disease.[26,27] While no dose adjustments are needed for patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 to <90 ml/min 1.73 m^2), in patients with moderate renal impairment (eGFR ≥30 to <60 ml/min/1.73 m^2), the dose should be reduced to nirmatrelvir/ritonavir 150/100 mg every 12 hours for 5 days to avoid over-exposure.[25] The combination should not be used in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2), including those with end-stage renal disease on haemodialysis.

There are limited data one the use of nirmatrelvir/ritonavir during pregnancy. Animal data with nirmatrelvir have shown developmental toxicity in rabbits (lower foetal body weights), but not in rats. A large number of women exposed to ritonavir during pregnancy indicate no increase in the rate of congenital abnormalities compared with rates observed in population-based birth defect surveillance systems.[25] Animal data with ritonavir have shown reproductive toxicity.[25] At present, nirmatrelvir/ritonavir is not recommended during pregnancy or in women of childbearing potential not using contraception unless the clinical condition requires treatment with the combination.[25]

Registrational Trial

Hammond et al. performed a Phase II–III double-blind study in which 2,246 symptomatic, unvaccinated, non-hospitalised adults at high risk for progression to severe COVID-19 were randomised to receive nirmatrelvir/ritonavir 300/100 mg twice daily or placebo for 5 days.[21] The enrolment period was from 16 July 2021 to 9 December 2021. In the final analysis of 1,379 patients in the modified intention-to-treat population, there was a difference of −5.81 percentage points (95% CI [−7.78, −3.84]; p<0.001; relative risk reduction,88.9%) for COVID-19–related hospitalisation or death by day 28. Thus, compared with placebo, nirmatrelvir/ritonavir reduces progression to severe COVID-19 by 89% in unvaccinated, high-risk symptomatic patients. There were 13 deaths, all of which were in the placebo group. Moreover, viral load was lower with nirmatrelvir/ritonavir versus placebo at day 5 of treatment, with a similar incidence of adverse events between groups.[21]

Meta-analyses

Souza et al. carried out a meta-analysis of 16 observational studies on the efficacy of nirmatrelvir/ritonavir.[28] Compared with standard treatment without antivirals, nirmatrelvir/ritonavir reduced the risk of death by 59% (OR = 0.41) and the risk of hospital admission by 53% (OR = 0.47). For a composite outcome of hospitalisation and/or mortality, nirmatrelvir/ritonavir reduced the risk by 56% (OR = 0.44). In a subgroup of patients aged <60 years, it appears there was no difference between treatment with nirmatrelvir/ritonavir compared with standard treatment (OR 0.48; 95% CI [0.09–2.50]); treating patients aged >60 years with nirmatrelvir/ritonavir suggested greater protection against the risk of death (OR 0.47; 95% CI [0.40–0.55]). On the other hand, nirmatrelvir/ritonavir reduced the risk of hospitalisation both those in aged <60 years (OR 0.45; 95% CI [0.25–0.82]) and those aged >60 years (OR 0.30; 95% CI [0.13–0.70]), without a significant difference between the two groups

Chen et al. carried out a network meta-analysis of randomised controlled trials of oral small molecule drugs (azvudine, molnupiravir, nirmatrelvir/ritonavir, VV116 and placebo) that included nine trials on over 30,000 patients with COVID-19.[29] The analysis found that nirmatrelvir/ritonavir significantly reduced both mortality (OR = 0.11) and hospitalisation (OR = 0.06) in patients with COVID-19, and was the drug that had the highest probability of being the best management strategy in patients with COVID-19.

Potential for Drug–drug Interactions with Nirmatrelvir/ritonavir

As mentioned, ritonavir has been used as a pharmacokinetic booster of other protease inhibitor antivirals predominantly because of its potent inhibition of CYP3A4.[16] Given this, nirmatrelvir/ritonavir has a high potential to cause harm from DDIs with other drugs metabolised through this pathway.[25,30] Cox et al. observed that co-administration of strong CYP3A4 inhibitor with a strong CYP3A inhibitor such as ritonavir was associated with small increases in plasma nirmatrelvir; co-administration of a strong inducer decreased systemic nirmatrelvir and ritonavir exposures.[31] Additionally, *in vitro* studies showed that ritonavir also inhibits CYP2D6, which may determine an increase in the exposure of drugs metabolised by this cytochrome.[23]

Anticoagulants

Exposure of P-glycoprotein (P-gp) substrates, such as direct oral anticoagulants (DOACs), may be increased by ritonavir.[32] In healthy volunteers it has been noted that nirmatrelvir/ritonavir increased systemic exposure of dabigatran.[33] In particular, nirmatrelvir/ritonavir increases the area under the concentration-time curve (AUC) and maximum (peak) plasma drug concentration (C_{max}) of dabigatran by 94% and 133%, and by 153% (AUC) and 53% (C_{max}) for rivaroxaban.[25] Similar effects can be predicted for apixaban and edoxaban given that they are substrates of CYP3A4, and thus an interaction can be expected as for other DOACs.[34]

According to the Summary of Product Characteristics, monitoring of anticoagulation parameters is recommended during co-administration with warfarin.[25] Muse et al. examined internal normalized ratio (INR) levels in a series of 29 patients treated with nirmatrelvir/ritonavir.[35] While slight small changes in INR trends were observed, it was believed that these were related to the acute viral infection and not to treatment with nirmatrelvir/ritonavir. Notwithstanding, none of the patients had a severe infection requiring hospitalisation and thus INR changes due to an effect of the drug could not be ruled out.

Antiplatelet Agents

Among antiplatelet agents, ritonavir can theoretically increase aspirin metabolism, but no increase of clinical adverse events has been reported.[36] Similarly, CYP3A4 and CYP2B6 are responsible for the bioactivation of prasugrel, a prodrug. Although there is a twofold decrease in the maximum concentration (C_{max}) of prasugrel in patients on ritonavir, its antiplatelet activity does not seem to be affected.[37] Thus, the co-administration of aspirin and/or prasugrel with nirmatrelvir/ritonavir should be considered safe.

Conversely, ritonavir decreases the production of the active metabolite of clopidogrel, reducing its platelet inhibition by 20%.[37] Ticagrelor is a CYP3A4 substrate, and co-administration of nirmatrelvir/ritonavir is associated with an increased risk of bleeding.[38] Thus, ticagrelor or clopidogrel should be replaced by prasugrel, or, alternatively, prescribing nirmatrelvir/ritonavir should be avoided and alternative COVID-19 therapies considered.

Antianginal Agents

With the exception of ranolazine, clinical effects and safety of antianginal agents (i.e. β-blockers and nitrates) are not significantly affected by nirmatrelvir/ritonavir. Ranolazine is a CYP3A4 and P-gp substrate.[39] Its plasma concentration is exponentially increased in the presence of CYP450 inhibitors, thereby increasing the risk of QT prolongation and torsades de pointes. Therefore, co-administration of nirmatrelvir/ritonavir is contraindicated.[22]

Antiarrhythmic Drugs

Antiarrhythmic drugs (amiodarone, dronedarone, flecainide, propafenone and quinidine) are metabolised by CYP3A4 and co-administration with ritonavir is expected to significantly increase their exposure.[25] For amiodarone and flecainide, co-administration should not be used unless a multidisciplinary consultation is obtained to safely guide it.[25] Caution is warranted and monitoring of therapeutic concentration is recommended for disopyramide if available.[25] Administration of dronedarone, propafenone and quinidine is contraindicated. Digoxin is expected to interfere with nirmatrelvir/ritonavir via direct inhibition of P-gp, and its administration can be managed by monitoring digoxin levels.[25]

Drugs for Heart Failure

Regarding heart failure drugs, angiotensin-converting enzyme inhibitors, 'sartans', spironolactone, sodium-glucose cotransporter 2 inhibitors and diuretics do not show significant interactions with nirmatrelvir/ritonavir. Thus, their continuation is allowed and safe with close blood pressure monitoring. A weak inhibition of the hepatic uptake transporter organic anion-transporting polypeptide 1B1 (OATP1B1) by nirmatrelvir/ritonavir may increase the concentration of both valsartan and the active metabolite of sacubitril, warranting close blood pressure monitoring and possibly dose reduction or temporary withdrawal of sacubitril/valsartan while on nirmatrelvir/ritonavir.[40]

Among mineralocorticoid receptor antagonists used to treat heart failure, eplerenone is primarily eliminated by CYP3A4,[41] and concurrent nirmatrelvir/ritonavir administration can significantly increase the risk of hyperkalaemia and therefore is contraindicated.

Finally, ivabradine is a CYP3A4 substrate. Co-administration with nirmatrelvir/ritonavir may cause significant bradycardia and therefore co-administration with ivabradine is contraindicated.[25]

Antihypertensive Agents

Among antihypertensive agents, amlodipine, nifedipine and felodipine are metabolised by CYP3A4. Thus, the significant increase of blood levels may require dose adjustment and close monitoring of adverse effects, which may warrant temporary discontinuation of treatment while on ritonavir.[22] Similarly, diltiazem and verapamil are metabolised by CYP3A4 and CYP2D6. Careful monitoring for adverse effects such as bradycardia, dizziness and hypotension, which may warrant dose adjustment or temporary discontinuation, is recommended when administered with nirmatrelvir/ritonavir.[22]

Finally, α-blockers, such as doxazosin and terazosin, are also metabolised by CYP3A4, and co-administration with nirmatrelvir/ritonavir can increase plasma concentration of these agents causing hypotension.[42] Alfuzosin is contraindicated because of a risk of profound hypotension.[22]

Statins

The HMG-CoA reductase inhibitors simvastatin and lovastatin are highly dependent on CYP3A metabolism and are expected to have markedly increased plasma concentrations when co-administered with ritonavir.[43] Thus, the combination of these drugs with ritonavir is contraindicated since they predispose patients to myopathies and rhabdomyolysis. Metabolism of atorvastatin is less dependent on CYP3A4, while rosuvastatin is independent from this pathway.[43] However, elevation of rosuvastatin and atorvastatin plasma levels have been reported with ritonavir, potentially due to the inhibition of P-gp and OATP1B1.[44] Thus, when used with ritonavir, the lowest possible doses of atorvastatin or rosuvastatin should be used.[25]

In summary, many classes of drugs can interfere with nirmatrelvir/ritonavir with a clinically relevant effect, and the potential entity of DDIs is large. In fact, it has been estimated that approximately one-third of the US population would be at risk for a major or contraindicated DDI should they receive a ritonavir-containing regimen, with the risk increasing significantly among individuals aged ≥60 years and with comorbidities, such as serious heart conditions, chronic kidney disease, diabetes and HIV.[45] A Danish study reported that among drugs likely to interact with nirmatrelvir/ritonavir, anticoagulants that are contraindicated during nirmatrelvir/ritonavir treatment were being used by 20% of the population aged ≥65 years and 30% of those aged ≥80 years.[46]

It is essential not only that clinicians are aware of drugs that are contraindicated with nirmatrelvir/ritonavir, but also recognise which drugs can be safely co-administered.

Case Reports of Drug–drug Interactions with Nirmatrelvir/Ritonavir

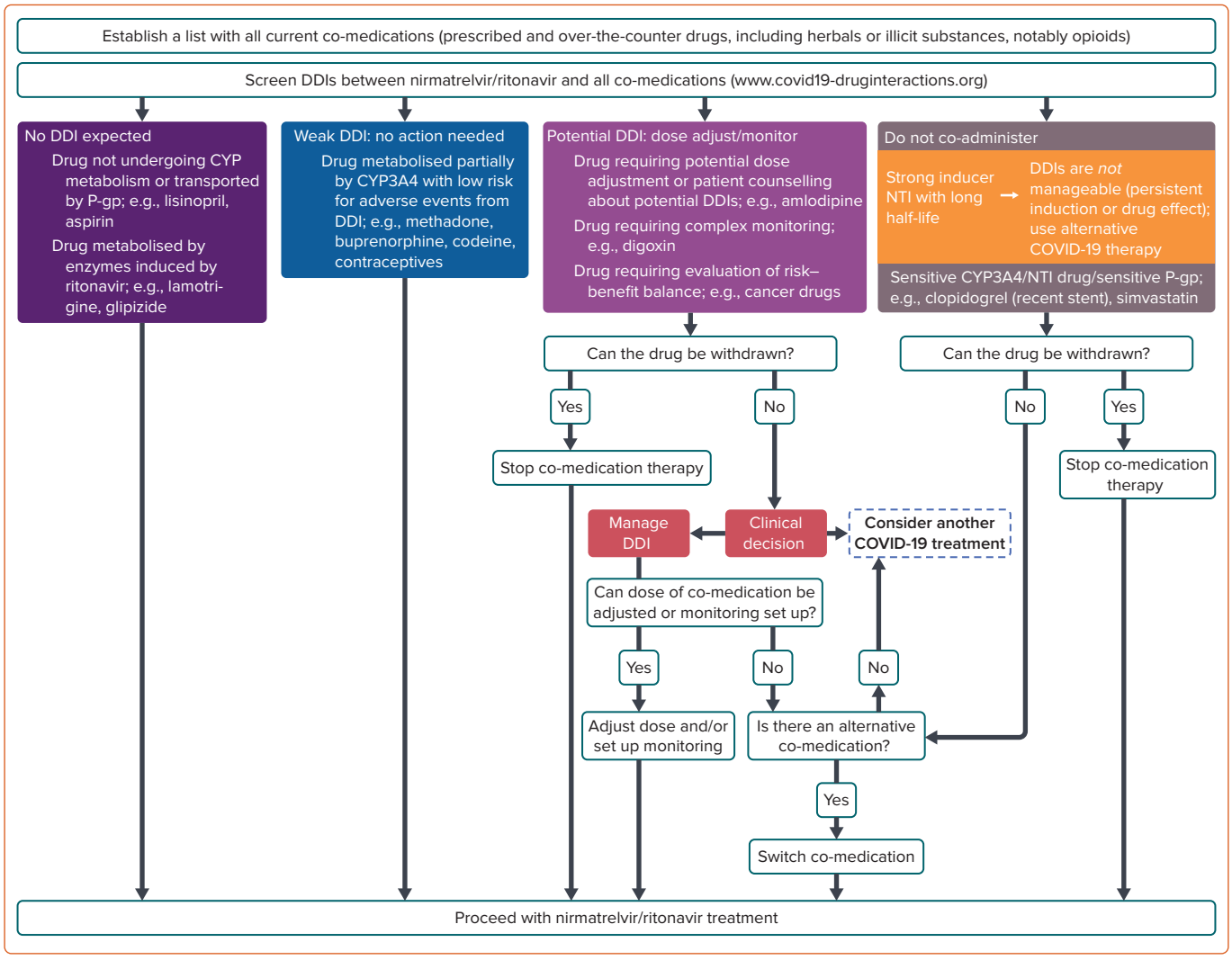
Several case reports have documented diverse DDIs with nirmatrelvir/ritonavir and several drugs. Rauser et al. published the case of a patient experiencing a DDI between nirmatrelvir/ritonavir and nifedipine that gave rise to oedema, oliguria and acute kidney injury.[47] The 79-year-old woman with multiple comorbidities (moderate-to-severe chronic kidney disease, type 2 diabetes, hypertension and congestive heart failure) on polypharmacy presented with cough and a positive test for SARS-CoV-2. Among her medications, colchicine and rosuvastatin were temporarily discontinued upon initiation of nirmatrelvir/ritonavir. However, the patient returned 3 days later with peripheral oedema and decreased urine output. Suspecting a DDI, nirmatrelvir/ritonavir and nifedipine were discontinued after which the oedema and renal function normalised within 2 days.[47]

Haque et al. reported on an elderly woman who presented with acute onset of generalised weakness, lethargy and altered mental state.[48] Investigations led to findings of hyperglycaemia, bradycardia and metabolic acidosis. A DDI was suspected between nirmatrelvir/ritonavir and verapamil. After discontinuation of nirmatrelvir/ritonavir the patient's symptoms subsided within 4 days.[48] Amiodarone has been cited among drugs that are contraindicated with nirmatrelvir/ritonavir. Sluijters et al. reported on the case of a 72-year-old patient with follicular lymphoma treated with rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone, and persistent AF treated with amiodarone and receiving apixaban who had remained positive for SARS-CoV-2 for 3 months.[49] Amiodarone was discontinued for 48 hours before initiating nirmatrelvir/ritonavir and restarted 96 hours after completion of the 5-day course of antiviral treatment. Nirmatrelvir/ritonavir was considered to be well tolerated and the patient was negative for SARS-CoV-2 after testing at day 7. Prospective simulations have hinted that any DDI between amiodarone and nirmatrelvir/ritonavir is possibly inflated and warrants more comprehensive clinical evaluation.[50] However, at present, it is emphasised that combining nirmatrelvir/ritonavir with antiarrhythmics such as amiodarone, dronedarone, flecainide, propafenone and quinidine may have severe and potentially fatal consequences.[25]

A Focus on Statins

Management of risk factors for CVD is crucial and hypercholesterolaemia – one of the most important modifiable cardiovascular risk factors – is still highly prevalent in the general population.[51] Considering this, statins are one of most widely prescribed drug classes.[52] While most authors recommend discontinuing statins, there is some controversy. Marzolini et al. recommend discontinuing statins for at least 3–5 days following

Figure 1: Flow Diagram to Assess Management of Nirmatrelvir/ritonavir Drug–drug Interactions



CYP = cytochrome P450; DDI = drug–drug interaction; NTI = narrow therapeutic index; P-gp = p-glycoprotein. Source: Marzolini et al. 2022.[57] Reproduced with permission from American College of Physicians.

treatment with nirmatrelvir/ritonavir.[30] These authors consider that temporarily discontinuing statins during nirmatrelvir/ritonavir therapy will not have any relevant therapeutic effects, but could potentially lower the risk of adverse DDIs.[30] However, Abraham et al. consider that simvastatin and lovastatin have an absolute contraindication, while dose adjustments or temporary discontinuation are needed for atorvastatin and rosuvastatin.[53] In contrast, pravastatin, fluvastatin and pitavastatin can be considered safer to co-administer with nirmatrelvir/ritonavir. Vuorio et al. are more cautious and consider that there may be a risk associated with temporarily withholding a statin in patients ≥65 years.[54] These authors recommend substituting simvastatin or lovastatin with either pravastatin or fluvastatin.

Guidance for Avoiding Drug–drug Interactions with Nirmatrelvir/Ritonavir

The University of Liverpool has provided an updated online tool and mobile app to search for DDIs with drugs used to treat COVID-19, including nirmatrelvir/ritonavir, and a large number of co-medications.[36] This easy-to-use tool provides an extremely useful resource for clinicians to check for potential DDIs with nirmatrelvir/ritonavir.[36]

Several societies have issued specific recommendations to guide clinicians in avoiding DDIs with nirmatrelvir/ritonavir. The American College of Cardiology published a list of DDIs with nirmatrelvir/ritonavir and commonly used cardiovascular medications.[55] The guidance notes that shared decision-making should be used to consider the risks/benefits of nirmatrelvir/ritonavir therapy, while considering factors such as the risk of severe COVID-19, age, comorbidities and prior infection, as well as the possible risks of changing the cardiovascular therapy. If risk is likely to result, then it would be worthwhile to consider alternative treatment options for COVID-19.

The French Society of Pharmacology and Therapeutics has also provided recommendations for administration of nirmatrelvir/ritonavir with commonly used drugs.[56] While the guidance notes that nirmatrelvir/ritonavir is a first-line option for oral treatment of patients developing COVID-19 and at risk of severe disease, it is further acknowledged that the drug has some limitations due to safety. When a DDI is expected, possible alternatives to nirmatrelvir/ritonavir include sotrovimab and remdesivir.

Marzolini et al. have provided specific recommendations for DDIs between nirmatrelvir/ritonavir and many drugs and drug classes.[30] In line with other guidance, antiarrhythmics are not recommended with nirmatrelvir/ritonavir. It is also mentioned that potential DDIs can be expected with oxycodone requiring dose reduction. The same authors have also proposed an algorithm to assess management of nirmatrelvir/ritonavir DDIs (*Figure 1*).[57] The algorithm takes into consideration that the inhibitory effect of ritonavir requires several days to resolve. Accordingly, if a co-medication is paused,

Table 3: Drug–drug Interactions with Selected Cardiovascular Drug Classes and Nirmatrelvir/ritonavir According to the Summary of Product Characteristics

Drug Class	Drug	Comment
α_1-adenoreceptor antagonists	Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated
	Tamsulosin	Extensively metabolised, mainly by CYP3A4 and CYP2D6, both of which are inhibited by ritonavir. Avoid concomitant use with nirmatrelvir/ritonavir
Antianginal	Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. Concomitant administration with ranolazine is contraindicated
Antiarrhythmics	Amiodarone, flecainide	Given the risk of substantial increase in amiodarone or flecainide exposure and thus of its related adverse events, co-administration should not be used unless a multidisciplinary consultation could be obtained to safely guide it
	Digoxin	This interaction may be due to modification of P-gp-mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer. Digoxin drug concentration is expected to increase. Monitor digoxin levels if possible and digoxin safety and efficacy
	Disopyramide	Ritonavir may increase plasma concentrations of disopyramide, which could result in an increased risk of adverse events such as cardiac arrhythmias. Caution is warranted and therapeutic concentration monitoring is recommended for disopyramide if available
	Dronedarone, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of dronedarone, propafenone and quinidine and is therefore contraindicated
Anticoagulants/ antiplatelets	Apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with nirmatrelvir/ritonavir depend on the apixaban dose. Refer to the apixaban SmPC for more information
	Clopidogrel	Co-administration with clopidogrel may decrease levels of clopidogrel active metabolite. Avoid concomitant use with nirmatrelvir/ritonavir
	Dabigatran	Concomitant administration of nirmatrelvir/ritonavir is expected to increase dabigatran concentrations resulting in increased risk of bleeding. Reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran SmPC for further information
	Rivaroxaban	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of Rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of nirmatrelvir/ritonavir is not recommended in patients receiving rivaroxaban
	Ticagrelor	Given the risk of substantial increase in ticagrelor exposure and thus of its related adverse events, co-administration should not be used unless a multidisciplinary consultation could be obtained to safely guide it
	Warfarin	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little 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 anticoagulation parameters are monitored when warfarin is co-administered with ritonavir
Calcium channel agonists	Amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when amlodipine, diltiazem, felodipine, nicardipine, nifedipine or verapamil are concomitantly administered with ritonavir
	Lercanidipine	Co-administration of lercanidipine and nirmatrelvir/ritonavir should be avoided
HMG Co-A reductase inhibitors ('statins')	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	Statins which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated. Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with a statin is indicated, pravastatin or fluvastatin is recommended
Lipid-modifying agents	Lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of nirmatrelvir/ritonavir with lomitapide is contraindicated (see prescribing information for lomitapide)
Mineralocorticoid receptor antagonists	Eplerenone	Co-administration with eplerenone is contraindicated due to the potential for hyperkalaemia
	Finerenone	Co-administration contraindicated due to potential for serious adverse reactions including hyperkalaemia, hypotension and hyponatremia
Other cardiovascular agents	Aliskiren (renin antagonist)	Avoid concomitant use with nirmatrelvir/ritonavir
	Bosentan (endothelin receptor antagonist)	Co-administration with nirmatrelvir/ritonavir is not recommended. Co-administration of nirmatrelvir/ritonavir for 5 days may result in significant increases bosentan trough concentrations. The US product label advises to discontinue bosentan at least 36 h prior to initiation of nirmatrelvir/ritonavir
	Cilostazol (quinolone derivative)	Dosage adjustment of cilostazol is recommended. Refer to the cilostazol SmPC for more information
	Ivabradine (I_f inhibitor)	Co-administration with ivabradine is contraindicated due to the potential for bradycardia or conduction disturbances

CYP = cytochrome P450; I_f = funny current; P-gp = p-glycoprotein; SmPC = summary of product characteristics. Source: European Medicines Agency 2024.[25]

therapy should be restarted 3 days after the last dose of nirmatrelvir/ritonavir. The algorithm is based on the premise that clinically relevant DDIs with nirmatrelvir/ritonavir can be managed in four ways: pre-emptive discontinuation of the co-medication; monitoring/dose adjustment of co-medications, even if this is usually not practicable; counselling of patients on possible symptoms and self-withdrawal of medications; or choosing an alternative treatment to nirmatrelvir/ritonavir.

Abraham et al. provide extensive guidance on cardiovascular DDIs with nirmatrelvir/ritonavir.[53] The guidance also includes an algorithm to aid in decision-making when nirmatrelvir/ritonavir is needed in patients with COVID-19. In drugs with a potential interaction or contraindication with nirmatrelvir/ritonavir, temporary discontinuation should be considered. If this is not possible, alternatives to nirmatrelvir/ritonavir should be considered. If temporary discontinuation is possible and safe, then the cardiovascular drug should be stopped, or the dose reduced, upon initiation of nirmatrelvir/ritonavir and restarted 3 days after stopping nirmatrelvir/ritonavir.

Rizk et al. have proposed an algorithm to manage DDIs with nirmatrelvir/ritonavir specifically for anticoagulants.[58] Briefly, if the patient is on an oral anticoagulant, it must first be decided if the patients can be off the anticoagulant for 7 days. If yes, the anticoagulant should be stopped when initiating nirmatrelvir/ritonavir and reinitiated 2 days after the combination is discontinued. If the anticoagulant cannot be reasonably stopped, if on warfarin the dose should be decreased with frequent INR monitoring or an alternative therapy to nirmatrelvir/ritonavir used such as monoclonal antibodies, remdesivir and molnupiravir. If the patient is on a DOAC, the patient can be bridged with low molecular weight heparin or an alternative antiviral can be used.

Finally, Rubina, et al. have summarised the risk of DDIs of nirmatrelvir/ritonavir with cardiovascular drugs by compiling data from six databases.[59] Information on DDIs was collected on all drugs used to treat COVID-19 and antihyperglycemic agents, cardiovascular drugs and antihypertensives.

Drug–drug Interactions with Nirmatrelvir/Ritonavir in Daily Practice

DDIs remain one of the most significant factors in achieving therapeutic efficacy with nirmatrelvir/ritonavir.[59] *Table 3* summarises the DDIs with several relevant cardiovascular drug classes. Avoiding and managing potential DDIs with nirmatrelvir/ritonavir requires thorough assessment and knowledge, which is particularly relevant in patients with CVD who are likely to be older and on polypharmacy. In addition, cardiovascular drugs for which no DDIs or weak DDIs are expected with nirmatrelvir/ritonavir according to the Liverpool Tool are listed in *Table 4*. There are many excellent resources upon which clinicians can rely to guide therapy with nirmatrelvir/ritonavir or, when needed, an alternative antiviral. Any doubts or concerns should be resolved by consulting the Summary of Product Characteristics.[25] The decisional algorithm proposed by Marzolini et al. is also an excellent tool for clinicians to assist decision-making (*Figure 1*).[57]

Table 4: Drugs with Weak or No Drug–drug Interactions with Nirmatrelvir/Ritonavir According to the Liverpool Tool

Drug Class	No DDIs Expected	Weak Interaction Expected but No Action Needed
α_1-adenoreceptor antagonists	Prazosin	Doxazosin
β-blockers	Atenolol Bisoprolol Carvedilol Metoprolol Nebivolol Propranolol Sotalol Timolol	
Angiotensin receptor blocker	Candesartan Captopril Cilazapril Enalapril Eprosartan Fosinopril Lisinopril Olmesartan Perindopril Quinapril Ramipril Telmisartan Trandolapril	Irbesartan Losartan
Anticoagulants/antiplatelets	Dalteparin Dipyridamole Enoxaparin Heparin Prasugrel Tinzaparin Aspirin	-
Diuretics	Amiloride Furosemide Hydrochlorothiazide	Torasemide
HMG Co-A reductase inhibitors ('statins')	Fluvastatin Pivastatin Pravastatin	-
Lipid-modifying agents	Clofibrate Alirocumab Evolocumab Fenofibrate	Ezetimibe Gemfibrozil Bempedoic acid
Mineralocorticoid receptor antagonists	Spironolactone	
Other cardiovascular agents	Ambrisentan (endothelin receptor antagonists)	Macitentan
	Hydralazine (vasodilator)	
	Iloprost (prostacyclin receptor antagonist)	

The table shows drugs for which no DDIs with nirmatrelvir/ritonavir are expected and those for which weak interaction is expected but no action is needed according to the Liverpool Tool. DDI = drug–drug interaction. Source: University of Liverpool, 2024.[36]

Conclusion

DDIs are a clinically relevant issue for the treatment of COVID-19 with nirmatrelvir/ritonavir. Particular attention is needed for drugs that are predominantly metabolised by CYP3A4, are substrates of P-gp and have a narrow therapeutic index. The management of nirmatrelvir/ritonavir therapy is simplified by the short treatment course, a factor that may justify pausing the co-medication therapy. However, only a few therapies can be paused, so decisional algorithms have been proposed to manage treatment. Nevertheless, such guidance is mainly based on predicted DDIs that take into consideration *in vitro* preclinical data of drug metabolism and substrate recognition to drug transporters. Relevant help comes from the two decades of experience of HIV specialists with ritonavir boosting. Thus, knowledge of the pharmacokinetic characteristics of co-administered drugs represents the starting point for proper management of potential DDIs that must balance the benefit of nirmatrelvir/ritonavir to prevent severe disease against the potential risk of serious adverse events. ❑

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