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Drug interaction risk between cardioprotective drugs and drugs used in treatment of COVID-19: A evidence-based review from six databases

Shini Rubina S K, Pharm.D^a, Anuba P A, Pharm.D^a, Swetha B, Pharm.D^a,
Kavya Priya kalala, Pharm.D^a, Aishwarya PM, MD^b, Sarvesh Sabarathinam, Ph.D^{a,*}

^a Department of Pharmacy Practice, SRM College of Pharmacy, SRM IST, Kattankulathur, 603203, Kancheepuram, Tamil Nadu, India

^b Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, 600044, India

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ABSTRACT

Background and aims: This Review discusses the potential drug interactions risk between Drugs used in treating COVID-19 infection and Drugs used in treating comorbid conditions (Diabetes, hypertension, cardiovascular illness).

Method: Six Databases were consulted a) Micromedex drug interaction b) Medicine complete.com c) Liverpool Drug Interaction Group for COVID-19 therapies d) Epocrates e) Medscape f) drugs.com. To acquire information on possible interaction effects between drugs used for COVID-19 treatment such as atazanavir, lopinavir/ritonavir, remdesivir, molnupiravir, paxlovid(nirmatrelvir/ritonavir), dexamethasone, azithromycin, chloroquine, and FDA approved monoclonal antibodies with primarily used anti-diabetic drugs, antihypertensive drugs, and drugs acting on the cardiovascular system.

Results: Potential interaction effects such as worsening glycemic control were prominent with lopinavir/ritonavir and the primarily used antidiabetic drugs, which needs dosage adjustment and close monitoring. The risk of hypotension and irregular heart rhythm is the potential interaction effects with concomitant use of drugs for COVID-19 treatment and antihypertensive drugs. Caution is advised with drugs such as atazanavir and lopinavir/ritonavir when concomitantly used in treating comorbid conditions. Drugs such as remdesivir, molnupiravir, and some monoclonal antibodies are safer in use with drugs used in treating the comorbid condition.

Conclusions: Drug-drug interaction remains one of the significant factors in altering the therapeutic efficacy. Drugs used to manage comorbid conditions may influence the COVID-19 treatment with potential interaction effects. These enhance the view on safety concerns about the drug interaction risk in managing COVID-19 infection in patients with comorbid conditions. This primary evidence may concern preventing potential or unintentional effects resulting from Drug-drug interaction, Improving patient quality of life.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease triggered by severe acute respiratory syndrome coronavirus 2 strain (Sars cov-2), which constitutes the pandemic of the century [1,2]. The number of people affected by COVID-19 infection

worldwide is over 32 million and rapidly increasing, emphasizing the importance of symptom management and treatment knowledge for general practitioners and other clinicians [3]. COVID-19 infection targets the lungs primarily, causing interstitial pneumonitis and intense ARDS (acute respiratory distress syndrome) [4]. With increasing age, comorbidities, and underlying conditions, the intensity of the infection and fatality get increases [5]. Patients over 60 years of age with a medical history, such as cardiovascular disease, are at the highest risk of developing severe disease as a result of COVID-19 [6]. Under FDA-issued emergency use authorization, antiviral pharmaceuticals (e.g., Remdesivir), anti-inflammatory

* Corresponding author. Department of Pharmacy Practice, S.R.M. College of Pharmacy, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur, 603 203, Kancheepuram, Tamil Nadu, India.
E-mail address: sarveshtvg@gmail.com (S. Sabarathinam).

medications, anti-SARS-CoV-2 monoclonal antibodies, and immunomodulatory therapy are accessible as an option for pharmacological management [7,8]. Treatment of complex diseases frequently necessitates the use of multiple drugs simultaneously. Polypharmacy raises the risk of drug-drug interaction and reduces patient compliance. Drug combination therapy can be very effective, but it is also associated with drug-drug interactions. COVID-19 Patients with underlying diseases are more likely to have drug interactions as they frequently require multiple medications. Drug interactions may put the patient at risk of severe adverse effects and reduce treatment safety and efficacy. Therefore, there must be a significant concern in managing their conditions. This Review discusses the potential interaction effects between the drugs used in COVID-19 treatment and drugs primarily used for cardiovascular and comorbid conditions such as diabetes and hypertension.

2. Drugs used in treatment of COVID 19 infections

Developing research and clinical data on the virologic SARS-CoV-2 suggest a possible list of repurposed drugs with suitable pharmacological effects and therapeutic efficacies in managing COVID-19 patients. Antiviral drugs such as atazanavir, lopinavir/ritonavir, and remdesivir are significant in treating the COVID-19 infection [9]. Atazanavir inhibits the protease activity of SARS-CoV-2 which results in inhibition of viral replication. Viral replication is also hampered by the drug lopinavir/ritonavir by its action of inhibiting the protease activity of the virus. The drug remdesivir induces the termination of viral protein synthesis by inhibiting RNA polymerase. Many repurposed antiviral drugs are being investigated, and some are still in the initial stages of regulatory approval. Recently U.S. Food and Drug Administration (FDA) has approved antiviral drugs such as molnupiravir, paxlovid (nirmatrelvir/ritonavir), which gives concern to the new strains of SARS-Cov-2. Molnupiravir is a prodrug of *N*-hydroxycytidine (NHC) with activity against SARS-CoV-2 and other RNA viruses and a high barrier to resistance development [10]. Molnupiravir found to follow "error catastrophe" mechanism, which is built on the concept that increasing the rate of mutation in the viral genome beyond a biologically tolerable threshold will render the virus lethal and lead to its extinction [11]. Paxlovid is a brand name for a combination therapy that includes nirmatrelvir and ritonavir. Nirmatrelvir is a SARS-CoV-2 protease inhibitor. Coadministration of nirmatrelvir with a low dose of ritonavir (commonly used in combination with other protease inhibitors as part of antiretroviral therapy for HIV infection) slows hepatic metabolism of nirmatrelvir, allowing it to remain active in the body for a more extended period. Corticosteroids are also used to treat COVID-19 infection which shows their effectiveness in suppressing multiple inflammatory genes. Glucocorticoids, such as dexamethasone, have been used as anti-inflammatory and immunosuppressive medications. Dexamethasone prevents the entry of SARS-CoV-2 spike pseudo typed virus into host cells by preventing the binding of angiotensin converting enzyme-2 (ACE-2) receptors to the spike protein [12]. Azithromycin is the potential antibiotic used in the treatment of COVID-19 infection, and it exhibits antiviral activity by reducing viral entry into host cells and also exhibits its immunomodulatory effect by inhibiting the release of cytokine mainly involved in COVID 19 infection [13]. Anti-parasitic drugs involved in the treatment of COVID-19 infection are chloroquine, hydroxychloroquine, and ivermectin. Chloroquine prevents the entry of SARS-CoV-2 into host organisms by preventing glycosylation of ACE-2 receptors. Glycosylation of ACE-2 receptors gets activated when the virus binds to ACE-2 receptors, providing entry of the virus to the host cell. Chloroquine also works by inhibiting endosome and lysosome acidification, causing the virus to stall inside endosomes and

preventing the viral RNA genome from being released into the cytosol [14]. The cytokine storms activated by the overproduction of proinflammatory cytokines were observed in COVID-19 patients. In such conditions, proinflammatory cytokines such as interleukin 1 (IL-1) and interleukin 6 (IL-6) levels are typically elevated. Drugs that inhibit the biological activity of IL-1 and its downstream product, IL-6, may help treat SARS-CoV-2 infection [15]. Currently, the COVID-19 treatment guidelines have recommended using two drugs such as Sarilumab and Tocilizumab. Anti-SARS-CoV-2 monoclonal antibodies that target the spike protein were shown to be clinically effective in treating COVID-19 infection. These involve drugs such as Bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab, which received emergency use authorization to treat mild to moderate COVID-19 in nonhospitalized patients.

3. Method

We consulted six Databases.

- a) Micromedex drug interaction
- b) Medicine complete.com
- c) Liverpool Drug Interaction Group for COVID-19 therapies
- d) Epocrates
- e) Medscape
- f) drugs.com.

To acquire information on possible interaction effects between drugs used for COVID-19 treatment such as atazanavir, lopinavir/ritonavir, remdesivir, molnupiravir, paxlovid (nirmatrelvir/ritonavir), dexamethasone, azithromycin, chloroquine, and FDA approved monoclonal antibody with primarily used antidiabetic drugs, antihypertensive drugs, and drugs acting on the cardiovascular system.

4. Potential interaction risk between drugs used in treatment of COVID-19 and drugs used in treating comorbid conditions

Potential interaction effects between antidiabetic drugs and covid treatment drugs involve hypoglycemia, lactic acidosis, and worsening glycemic control. The majority of the databases showed Significant interactions between lopinavir/Ritonavir and metformin. Chloroquine interacts with all the antidiabetic drugs, of which moderate interaction risk was seen with atazanavir and dexamethasone. These prominent effects have been conveyed from more than three databases, as shown in Table 1. Drug paxlovid, a combination of nirmatrelvir and ritonavir, was found to interact with all the listed antidiabetic drugs, significantly with glimepiride and glipizide.

The potential interaction effect of increased risk of bleeding with major severity is conveyed by more than three databases between paxlovid (nirmatrelvir/ritonavir) and drugs acting on the cardiovascular system (ticagrelor, warfarin, and rivaroxaban). Rhabdomyolysis, myopathy remains a possible potential interaction effect between lopinavir/ritonavir, paxlovid, atazanavir, and atorvastatin. Other drugs such as dexamethasone, chloroquine, and monoclonals such as sarilumab and tocilizumab provide moderate interaction with cardioprotective drugs that need caution and monitoring. Azithromycin potentially interacts with cardiovascular drugs such as warfarin and rivaroxaban conveyed from more than three databases as shown in Table 2. However, monitoring is mandatory in all conditions.

Hypotension and irregular heart rhythm are the possible interaction effects between drugs used in COVID-19 treatment and primarily used antihypertensive drugs (enalapril, Lisinopril,

Table 1
Drugs used in treatment of COVID-19 and anti diabetic drug.

	METFORMIN	LINA GLIPTIN	SITA GIPTIN	GLI MEPIRIDE	GLIPIZIDE	ACARBOSE
ATAZANAVIR	◆	◆	◆	◆	△	△
LOPINAVIR/RITONAVIR	◆	◆	△	△	△	
REMSDESIVIR						
MOLNUPIRAVIR						
PAXLOVID	▲	▲	▲	◆	◆	▲
DEXAMETHASONE	◆	◆	◆	◆	◆	◆
AZITHROMYCIN						
CHLOROQUINE	▲	◆	◆	◆	◆	◆
SARILUMAB						
TOCILIZUMAB						
CASIRIVIMAB/IMDEVIMAB						
ETESEVIMAB/BAMLANIVIMAB						
SOTROVIMAB						

Green-No interaction; Yellow- Moderate interaction which requires caution and close monitoring; Red- Major interaction which needs monitoring, dosage adjustment or alteration of drugs.

△-denotes drug interaction reported from single database

▲-denotes drug interaction reported from two databases

◆ -denotes drug interaction reported from three or more than three databases

Olmesartan, telmisartan, propranolol, and atenolol). Interactions with major severity are found to be with the drug atazanavir. These Interactions are conveyed from more than three databases. Dexamethasone was found to produce potential interaction effects with all antihypertensive drugs with moderate severity. Other drugs such as azithromycin chloroquine were found to moderately interact with some antihypertensive drugs that need monitoring of parameters, as explained in Table 3. As drug interaction potentially results in toxicity effects or therapeutic failure, concern on the coadministration of drugs is mandatory. These interactions may or may not affect therapy based on the individual patient's pharmacokinetics and pharmacodynamics. Therefore, There is a need for health care professionals to be aware of potential effects associated with drug interactions.

5. Discussion

5.1. Drugs used in treatment of COVID-19 and antidiabetic drugs

Drug interactions may produce unwanted effects during pharmacological treatment, which is common among patients receiving more drugs. Polypharmacy remains a significant cause for drug-drug interactions. These drug-drug interactions result in either toxicity effects or therapeutic failure. In this Review, we have analyzed six databases to check possible interaction effects

between drugs used in COVID-19 treatment and primarily prescribed drugs for comorbid conditions such as hypertension, diabetes, and cardiovascular illness, which remain major mortality risk factors during the COVID-19 pandemic. Green, yellow, red explains the severity of the interaction effects. Green indicates no interactions, yellow and red refer to moderate and major severity, respectively. The interactions effects are discussed between COVID-19 treatment drugs and antidiabetic, antihypertensive, and drugs acting on the cardiovascular system. In this Review, one drug from each category has been chosen as all drugs in the same class possess a similar mechanism of action. This mechanism of action remains significant for checking out interactions.

Diabetes mellitus is managed by drugs that belong to biguanides (metformin), sulfonylurea (glimepiride and gliclazide), Dipeptidyl peptidase (DPP) 4 inhibitors (linagliptin and sitagliptin), alpha1 glucosidase inhibitors (acarbose). These drugs are primarily chosen to check interactions with drugs used in COVID-19 treatment. Potential effects such as worsening glycemic control, hypoglycemia, increased risk of lactic acidosis are the possible interaction effects with drugs used in COVID-19 treatment. The results of the interaction are conveyed in Table 1. Interaction with major severity is found with drugs lopinavir/ritonavir and chloroquine. The significant possible effect found between lopinavir/ritonavir and metformin is increased risk of lactic acidosis, so concurrent administration is not recommended in renal or hepatic impairment

Table 2
Drugs used in treatment of COVID 19 and drugs acting on cardiovascular system.

	ASPIRIN	CLOPI DOGREL	TICAGRE LOR	WAR FARIN	RIVA ROXABAN	ATORVA STATIN
ATAZANAVIR			◆	◆	◆	◆
LOPINAVIR/ RITONAVIR		▲	◆	◆	◆	◆
REMDESIVIR						△
MOLNUPIRAVIR						
PAXLOVID		◆	◆	◆	◆	◆
DEXAMETHASONE	◆	△	◆	◆	▲	◆
AZITHROMYCIN			△	◆	◆	◆
CHLOROQUINE		△			△	
SARILUMAB		△	▲	◆	▲	◆
TOCILIZUMAB	△	△	△	◆	▲	◆
CASIRIVIMAB/ IMDEVIMAB						
ETESEVIMAB/ BAMLANIVIMAB						
SOTROVIMAB						

Green-No interaction; Yellow- Moderate interaction which requires caution and close monitoring; Red- Major interaction which needs monitoring, dosage adjustment or alteration of drugs.

△-denotes drug interaction reported from single database

▲-denotes drug interaction reported from two databases

◆-denotes drug interaction reported from three or more than three databases

patients. Symptom monitoring is always recommended. Chloroquine produced significant interaction with all antidiabetic drugs as listed on Table 1. Chloroquine enhances the hypoglycemic effect when co-administered with antidiabetic drugs due to the synergistic effect. Hence the possible impact found to be the risk of hypoglycemia. The antagonistic effect is seen with concomitant use of dexamethasone and antidiabetic drugs. Dexamethasone was found to antagonize the effectiveness of hypoglycemic agents. Monitoring the glycemic level of the patient is mandatory during treatment. Nirmatrelvir/ritonavir can alter the effect of antidiabetic drugs by enzyme induction when used for an extended period. However, the risk is low, monitoring blood glucose levels is recommended during treatment. These interaction effects, as mentioned above, may or may not be at a higher risk in all patients. However, monitoring the patient's glycemic level is essential as these interactions can produce toxicity effects or result in therapeutic failure.

5.2. Drugs used in treatment of COVID-19 and drus acting on cardiovascular system

Drugs acting on the cardiovascular system discussed in this Review belong to a category such as Anticoagulants (warfarin, rivaroxaban), anti-platelets (aspirin, clopidogrel, ticagrelor), and dyslipidemic agents (atorvastatin), and these drugs checked for interaction with the drug used in COVID-19 treatment. The results

were analyzed from six databases, as shown in Table 2. Significant interactions were possible with atazanavir and ticagrelor, which likely may increase the risk of bleeding, which involves the mechanism of enzyme inhibition by the drug atazanavir. Monitoring of hematological parameters is mandatory. It has been recommended that the use of drugs that belongs to potent CytochromeP450 3A4 (CYP3A4) inhibitors (E.g., atazanavir) can be avoided while it is necessary for receiving ticagrelor. Another significant interaction is seen with atazanavir and atorvastatin, which explains the potential effect of enhanced exposure of drug atorvastatin which has a high capability of resulting in toxicity. The combination drugs such as Lopinavir/ritonavir and nirmatrelvir/ritonavir (paxlovid) potentially interact with clopidogrel, ticagrelor, warfarin, and rivaroxaban resulting in increased exposure to clopidogrel, ticagrelor, warfarin and rivaroxaban, respectively indicating the risk of bleeding. At such conditions, dosage adjustment and routine monitoring of hematology profile are recommended. The risk of myopathy and rhabdomyolysis, a condition associated with a muscle injury, is indicated with concomitant use of Lopinavir/ritonavir with atorvastatin. Monitoring toxicity symptoms are recommended for this kind of effect. If so seen, dosage adjustment or frequency adjustment has to be initiated. Increased risk of rhabdomyolysis is also seen with concomitant use of azithromycin with atorvastatin. The drugs with a higher risk of producing drug interaction are atazanavir and lopinavir/ritonavir, and nirmatrelvir/

Table 3

Drugs used in treatment of COVID 19 and antihypertensive drugs.

	ENALA PRIL	LISINO PRIL	OLMESAR TAN	TELMISAR TAN	PROPRANO LOL	ATENO LOL	AMLO DIPINE
ATAZANAVIR					◆	◆	◆
LOPINAVIR/ RITONAVIR					△	△	◆
REMDESIVIR							
MOLNUPIRAVIR							
PAXLOVID					▲		◆
DEXAMETHASONE	▲	▲	▲	▲	▲	▲	▲
AZITHROMYCIN					△	△	△
CHLOROQUINE					△	△	△
SARILUMAB							▲
TOCILIZUMAB							◆
CASIRIVIMAB/ IMDEVIMAB							
ETESEVIMAB/ BAMLANIVIMAB							
SOTROVIMAB							

Green-No interaction; Yellow- Moderate interaction which requires caution and close monitoring; Red- Major interaction which needs monitoring, dosage adjustment or alteration of drugs.

△-denotes drug interaction reported from single database

▲-denotes drug interaction reported from two databases

◆-denotes drug interaction reported from three or more than three databases

ritonavir. These are to be made under consideration during administration. Increased risk of bleeding is indicated with concomitant use of warfarin and rivaroxaban with azithromycin. Hematological parameters to be monitored regularly during the treatment. Other drugs of COVID-19 therapy are found to produce moderate interactions, which needs monitoring, but patients are not found to be at higher risk; however, monitoring is always required. Effects that remain possible with moderate interactions are increased risk of bleeding and elevated INR (international normalized ratio) values.

5.3. Drugs used in treatment of COVID 19 and antihypertensive drugs

Hypertension is pharmacologically treated Primarily with beta-blockers (atenolol, propranolol), Angiotensin converting enzyme (ACE) inhibitors (enalapril, Lisinopril), Angiotensin receptor blockers (Olmesartan, telmisartan), and calcium channel blockers (Amlodipine), interaction of these drugs with drugs used in COVID 19 treatment are shown in Table 3. Hypotension, irregular heart rhythm, electrocardiographic (ECG) changes are the potential effects of drug interaction with COVID-19 treatment drugs and antihypertensive drugs. Interaction with major severity is found between atazanavir and beta-blockers (propranolol, atenolol),

resulting in irregular heart rhythm or additive PR interval prolongation. Concurrent use is not recommended, In case of necessity, their ECG parameters are to be monitored during treatment. More than three databases conveyed Possible interactions with Amlodipine and atazanavir. Its effect remains with major severity, increasing risk of cardiotoxicity PR interval prolongation are considered to be the effects of major severity. Therefore, Routine ECG monitoring is required. The same interaction effect is also seen with lopinavir/ritonavir with major severity. Dexamethasone interacts with all the antihypertensive drugs with moderate severity producing an impact of antagonization of antihypertensive effect resulting in therapeutic failure. This interaction is at low risk as they are conveyed from a single database. These interaction effects need consideration for frequency adjustment. Other drugs such as azithromycin chloroquine showed potential interaction with antihypertensive drugs, resulting in ECG changes and prolongation of PR or QT interval; therefore, caution is advised for the concomitant use of these drugs with atenolol, propranolol, and Amlodipine. Nirmatrelvir/ritonavir enhances plasma drug concentration of calcium channel blockers by enzyme inhibition resulting in hypotension. Monitoring for symptoms related to hypotension is strictly recommended. If concurrent use of the drug mentioned above is unavoidable, renal function, ECG parameters, and blood pressure are to be routinely examined to prevent potential effects that

results from drug-drug interactions.

5.4. Drug interaction with monoclonal antibody

One of the proposed COVID-19 therapeutic options is a monoclonal antibody. Anti-SARS-CoV-2 monoclonal antibodies are among the most recent investigational COVID-19 treatments permitted for emergency use authorization (EUA) by the US Food and Drug Administration (FDA). A clinical perspective of drug-drug interactions with a monoclonal antibody are unlikely to occur. Interleukin 6 inhibitor monoclonals such as sarilumab, Tocilizumab, recommended for COVID-19 treatment, was found to interact with drugs acting on the cardiovascular system. These drugs were found to suppress the action of co-administered cardioprotective medications by affecting the expression of drug-metabolizing enzymes that may result in therapeutic failure. Although the interaction potential is less prominent as conveyed from fewer databases, therapeutic monitoring of effects is recommended during treatment. Tocilumab and sarilumab were found to moderately interact with antihypertensive drugs such as Amlodipine and found that these drugs reduce the efficacy of Amlodipine by affecting the drug-metabolizing enzymes. It is less risky however therapeutic monitoring of effect is required. The FDA-approved Anti-SARS-CoV-2 monoclonal antibodies such as casirivimab/imdevimab, etesevimab/bamlanivimab, sotrovimab are not found to interact with antidiabetic, antihypertensive, or with drugs acting on the cardiovascular system. The absence of interaction is detected with these monoclonals however these drugs are recommended for patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 infection and are at high risk for progressing to severe disease.

6. Limitations

The major limitation of this study is; as it does not include clinical evidence or a systematic review. This review has been carried out from evidence based primary sources in the view of to address the caution behind the use of drug during COVID-19 treatment.

7. Conclusion

Management of comorbid conditions is unavoidable. Patients with underlying diseases receive complex drugs risking drug interaction. Drug-drug interactions remain one of the challenging issues during treatment, as they may develop either toxicity or therapeutic failure, which may influence the patient's treatment efficacy. Since the Safety concern of patients remains mandatory during their treatment, this review highlights the possible effects of drug interactions between drugs used in COVID-19 treatment and drugs used primarily for comorbid conditions when used simultaneously. Therefore, this primary evidence may concern preventing potential or unintentional effects resulting from a Drug-drug interaction, Improving patient quality of life.

CRedit authorship contribution statement

SRSK, APA: Methodology and Writing. SB, KKP: Data curation and Review. APM: Investigation and Resource. SS: Writing, Editing, Conceptualization and Supervision.

Ethics approval and consent to participate

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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