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Clinical Relevance of Drug-Drug Interactions in COVID-19 with Comorbid Cardiovascular Disease and Diabetes: A Systematic Review

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ABSTRACT

Background: The WHO has declared COVID-19 as a global pandemic. The cause of mortality in COVID-19 is not limited to the infection alone, the pre-existing comorbid conditions and their treatments in the infected patient play a vital role in determining the disease outcome. Thus, knowledge on possible drug-drug interactions is an absolute necessity, which may help in avoiding preventable DDIs and drug related harm to patients. **Method**: A systematic search of Pubmed was conducted using suitable search terms and other relevant articles were identified by cross referencing and snowballing technique. **Results:** Drugs repurposed for treatment of COVID-19 including chloroquine, hydroxychloroquine, azithromycin and lopinavir-ritonavir carry risk of significant DDIs leading to adverse consequences such as cardiac conduction abnormalities, drug toxicities with digoxin, ivabradine and statins, significant alterations in therapeutic effects of anticoagulants, antiplatelet drugs and several other DDIs with varying levels of significance. **Discussion:** Drug interactions and their adverse outcomes may be time-dependent, dose-dependent and specific to certain risk factors. Analyzing the clinical relevance of theoretical risks and previously documented DDIs is needed for decision-making in routine clinical practice. Further, prospective studies are needed to analyze the clinical effects of these DDIs and safety profile of the repurposed drugs, specific to use in patient with COVID-19.

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been declared by WHO as a global pandemic.

Till date there are no specific therapies for SARS – CoV – 2. Several agents are being used under clinical trial and compassionate use protocols, based on in-vitro activity and on limited clinical experience. Some of the therapeutic agents understudy for COVID-19 include chloroquine, hydroxychloroquine, azithromycin, Lopinavir-Ritonavir, remdesivir, favipiravir, tocilizumab, ribavirin, interferons and COVID-19 convalescent plasma.[1,2]

Elderly and those with pre-existing medical conditions such as diabetes and heart disease appear to be more vulnerable to become severely ill with COVID-19.[3]In India, more than 20 % of population suffer from chronic illnessesand on treatment with some long-term medications.[4] Thus, an important aspect to be looked into the treatment of COVID-19 is to evaluate the possible drug-drug interactions(DDIs) which can be cause of major but preventable adverse drug reactions.

Drugs proposed for treatment of COVID-19 such as chloroquine, hydroxychloroquine or azithromycin carry the risk of potential drug interactions leading to adverse cardiovascular outcome which is of more concern when the patient also has an underlying cardiovascular disease. Lopinavir-Ritonavir, an antiretroviral drug which is currently being studied for treatment of COVID-19 is well-known for its influence on enzyme induction and inhibition of the common drug metabolizing enzymes which would lead to numerous drug-drug interactions.

Hence, in this article, we aim at understanding the drug-drug interaction (DDIs) of chloroquine, hydroxychloroquine, azithromycin and lopinavir-ritonavir, with the drugs widely used for comorbid illnesses such as diabetes, hypertension and other cardiovascular diseases. The clinical relevance of these drug-drug interaction specific to COVID-19 management is also critically analyzed and discussed in this review.

PHARMACOTHERAPY OF COVID 19

According to WHO, currently, there is no proven evidence to recommend a specific anti COVID-19 treatment. The WHO announced an international clinical trial called

SOLIDARITY which compares between four treatment groups (remdesivir, chloroquine/hydroxychloroquine, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon-β). The rationale behind this single randomized global mega trial is to facilitate the rapid worldwide comparison of these unproven treatments.[5] Lately, WHO decided not to randomize patients to the hydroxychloroquine (HCQ) arm as data from trials showed that has HCQ does not seem to reduce mortality in COVID-19 patient.

Based on evidence from in-vitro studies, chloroquine and hydroxychloroquine are found to be effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and they may act by blocking entry of virus into host cells.[6,7]In vitro study have shown that combined use of azithromycin and hydroxychloroquine has synergistic effect against SARS-COV-2.[8]These drugs also have anti-inflammatory and immunomodulatory effects which may help attenuate lung inflammation in COVID-19.[9] But current recommendations are against use of these drugs for COVID-19 except in context of clinical trials or under national emergency use programmes.

Some of the therapeutic agents which are candidates of ongoing clinical trials for COVID-19 treatment are listed in Table 1. Current evidence on these drugs show contradicting results and there is uncertainty in the benefits and risks of using these drugs for treatment of COVID 19.

Table No. 1: Recommendations on available treatment options for COVID-19

TREATMENT OPTION (dose mentioned below is commonly used in investigations/ trials for treatment of COVID-19)	**CURRENT EVIDENCE FOR USE IN TREATMENT OF COVID 19**	
Chloroquine Oral:1 g on day 1, followed by 500 mg OD, Duration: 4 to 7 days Oral: 450 mg twice daily for 1 day, followed by 450 mg once daily for 4days **Hydroxychloroquine** Oral:800 mg OD or 400 mg BD on day 1, followed by 200 BD or 400 mg OD Duration: 4 to 7 days	Current recommendations are against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 except in the context of a clinical trial. It is recommended to avoid use of high-dose chloroquine (600 mg twice daily for 10 days) for COVID-19 treatment.	Infectious Disease Society of America (**IDSA**), NIH guidelines
	It is recommended to avoid HCQ in patients with severe disease and if QTc interval is >500 ms. HCQ should only be used after shared decision making with the patients, and early in the disease course.	Clinical Management Protocol: COVID-19Ministry of Health & Family Welfare-Goverment of India (**MoHFW- GoI**)
Hydroxychloroquine + Azithromycin Hydroxychloroquine: 400 mg BD on day1, followed by 200 BD (4 days)+Azithromycin: 500 mg OD (5 days)	Combined use of Hydroxychloroquine and Azithromycin combination is not recommended except in the context of a clinical trial. In view of their long half lives, caution is recommended even for sequential use of HCQ and azithromycin.	Infectious Disease Society of America (**IDSA**), NIH guidelines
Lopinavir-Ritonavir 400 mg/100 mg twice daily for up to 14 days	Until sufficient evidence for use in COVID-19 is available, lopinavir-Ritonavir should be used only as a part of clinical trial.	**IDSA**, NIH guidelines
Remdisevir 200 mg intravenously on day 1, followed by100 mg IV OD (infused over 30–60 minutes) Duration:5 days	It is an investigational drug developed for Ebola outbreak. Use of Remdesivir for treatment of COVID-19 is recommended in hospitalized patients with SpO2 ≤94% on ambient air or those who require supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO). There is insufficient data to make recommendations for or against use of remdesivir in the treatment of patients with mild or moderate COVID-19.	ClinicalTrials.gov. NIH guidelines

	Remdesivir may be considered in patients with moderate disease requiring oxygen support, in the absence of contraindications such pregnancy, lactation, children (age <12 years), AST/ALT greater than 5 times the normal upper limit, severe renal impairment.	Clinical Management Protocol: COVID-19 (**MoHFW- GoI**)
Corticosteroids Not to exceed the dose **equivalent** to Methylprednisolone 1-2mg/kg/day. Should use only for a short duration of 3 to 5 days.[10]	Guideline recommendations are against routine use of systemic corticosteroids in COVID-19 treatment, except in situations such as refractory shock.	IDSA, NIH guidelines
	It is recommended that glucocorticoids can be used **only** in patients with progressive deterioration of oxygenation indicators, rapid worsening on imaging and excessive activation of inflammatory response.	Clinical Management Protocol: COVID-19 (**MoHFW- GoI**)
Convalescent plasma Dose is variable ranging from 4 to 13 ml/kg (usually 200 ml single dose given slowly over not less than 2 hours) [10]	Convalescent plasma are antibody-rich products collected from eligible donors who have recovered from COVID-19. Due to insufficient data, no recommendations are made for or against use of COVID-19 Convalescent plasma	NIH guidelines
	The off-label use of convalescent plasma may be considered in patients with moderate disease in whom the oxygen requirement is progressively increasing and not improving even with use of steroids.	Clinical Management Protocol: COVID-19 (**MoHFW- GoI**)

METHODOLOGY:

We searched PubMed for published articles using search terms "ritonavir", "lopinavir", "hydroxychloroquine", "chloroquine", "azithromycin", and using relevant MeSH terms for drug interactions combined by "AND" or "OR". Manual searching in Google scholar was carried out by using a search strategy of combining the interacting drug names with Boolean operator "AND". All type of publications irrespective of the study design were included. We reviewed the title and abstract of the articles and selected those relevant to the objective of our review. We also searched for relevant articles by cross referencing and by using snowballing technique. Quality of available evidence on each drug interaction were critically analyzed and their clinical relevance is discussed in this review.

RESULTS:

A total of 56 articles were included for the final review. The findings of the studies are discussed under suitable subheading.

DRUG-DRUG INTERACTION IN PATIENTS WITH CARDIOVASCULAR DISEASE

1. ARRYTHMIAS AND CONDUCTION ABNORMALITIES:

1.1Augmented QT Prolongation Effect

Many drugs are reported to cause prolongation of QT interval, but not all patients treated with QT prolonging medications develop Torsades de pointes(TdP).[11] Clinically significant risk of Tdp is when the QTc interval is greater than 500 ms or it becomes prolonged > 60 ms compared with the pretreatment value. Patients receiving multiple QT prolonging drugs are at increased risk of TdP. Hence monitoring for such drug interactions is very important.[12]

Antiarrhythmic drugs such as amiodarone, quinidine, sotalol and many noncardiac drugs including macrolide antibiotics, antifungals, antihistamines, tricyclic antidepressants, antipsychotics, opiates are reported to have risk of causing torsade de poites(Tdp).[13]Combined use of these drugs with chloroquine, hydroxychloroquine or azithromycin in COVID-19 patients may substantially increase risk of complications related to QT prolongation. The risk is further increased when the patient also has an underlying cardiovascular disease.

Cardiac consequences due to chloroquine and hydroxychloroquine are generally long term effects as a result of cumulative toxicity. QT prolongation and QRS widening may occur in case of acute toxicity due to overdose or with rapid intravenous administration of Chloroquine, moreover, these cardiac adverse effects are rare but can be life-threatening.[14]he mechanism of QT prolongation with chloroquine, hydroxychloroquine and macrolide antibiotics is by the inhibition of the rapid component of delayed rectifier potassium current (IKr), otherwise called as hERG current in the cardiac myocytes, which leads to prolonged repolarization.[15]

Azithromycin is only a weak inhibitor of hERG current and unlike other macrolide antibiotics, Tdp and cardiac arrhythmias are rare with azithromycin.[16]Though available

evidence is inconclusive and contradicting, azithromycin should be used with caution especially in elderly and in presence of risk factors such as pre-existing cardiovascular disease and use of concomitant QT-prolonging drugs.[17]

In case of Lopinavir-Ritonavir, an antiviral drug being trialed for COVID-19, there is no sufficient evidence to show any significant effect on QT interval.[18]Theoritical model suggests that Lopinavir is expected to produce a prolongation of QT_C interval of <5ms by a small degree of hERG Blockade.[19]Despite, it must used with caution in patients with cardiovascular disease because of its enzyme inhibition properties. In that regard, another potential drug interaction to consider is the inhibition of CYP-3A4 mediated metabolism of the antiarrhythmic amiodarone by ritonavir/lopinavir which leads to significant increase in QT prolongation effect of amiodarone.[20]

1.2 Effects on PR interval

In a randomized placebo-controlled study, it was found that increase in PR interval due to Lopinavir/Ritonavir was clinically insignificant at a dose of 400/100 mg given twice daily.[21]According to the product monograph, caution and monitoring is recommended especially in patients with pre-existing heart disease or conduction abnormalities and during co-administration of Lopinavir-Ritonavir with other drugs that prolong the PR interval (including calcium channel blockers, digoxin, beta-adrenergic blockers).[22] The effect on PR interval during combined use of these drugs with Lopinavir-Ritonavir is a theoretical risk and require further evaluation.

Lopinavir- Ritonavir, by inhibiting enzyme CYP3A4 may increase the plasma concentration of calcium channel blockers such as diltiazem and verapamil and may lead to elevated PR interval. However, in a retrospective observational study, PR alteration was not observed during concomitant use of these drugs.[23]But the results of this study have limitations as it includes only a small number of patients taking each calcium channel blocker. In view of these drug-drug interactions, ECG monitoring becomes necessary with the use of Lopinavir-Ritonavir in COVID-19 treatment.

2. HEART FAILURE

Pharmacotherapy of heart failure includes digoxin, beta-blockers, loop diuretics, ACE inhibitors or angiotensin receptor blockers. Following are the potential pharmacokinetic interactions to consider when a patient taking these drugs acquire COVID-19.

2.1. Life-Threatening Digoxin Toxicity

Digoxin for its positive inotropic effect is mainly used for the treatment of congestive heart failure. It has a narrow therapeutic and a wide drug interaction range.[24]Digoxin AUC was found to increase in patients receiving ritonavir boosted lopinavir[25]Digoxin clearance is primarily mediated by P-glycoprotein efflux transporter(P-gp) in kidneys.[26]P-gp is also present in the intestine and it is evident that inhibition of intestinal P-gp can increase systemic exposure of digoxin.[27]Ritonavir is found to decrease digoxin clearance both at renal and non renal levels.[28]Ritonavir has a time dependent mixed induction-inhibition effect on P-gp. It initially has an inhibitory effect on P-gp followed by mild induction at steady state, but the net effect is found to be inhibition of P-gp and thereby cause decrease in the clearance of digoxin.[29]Hence, due to risk of digoxin toxicity, monitoring serum digoxin level is required during concomitant use of Ritonavir-Lopinavir and digoxin.

Evidence from a case report, in vitro study and animal studies, support the risk of interaction between Chloroquine/hydroxychloroquine and digoxin, which may lead to digoxin toxicity.[30]There is no sufficient information on mechanism of this effect and it may be possibly due to inhibition of p-glycoprotein efflux transporter.[31]In a study conducted by Mcelnay et al, on dogs it was shown that on the 3rd day of chloroquine administration, there was an increase of 77% peak plasma concentration of digoxin which was present before the administration of Chloroquine.[32]Product monograph of hydroxychloroquine recommends monitoring of serum digoxin levels in situations of concomitant use with digoxin. Though more evidence is required, chloroquine/hydroxychloroquine for treatment of COVID 19, should be used cautiously when the patient is on digoxin.

Azithromycin, when compared to other macrolides, is found to have lesser influence on P-gp mediated digoxin absorption or excretion and it can be considered as the safest macrolide to use with oral digoxin.[33]But the possibility of risk cannot be ruled out and more studies are required, hence azithromycin also should be used with caution in patients receiving digoxin.[34]

2.2 Ivabridine Toxicity

Ivabradine, a drug used in the treatment of angina and heart failure acts by direct inhibition of spontaneous depolarization of sinus node and thereby causing decrease in the heart rate. Ivabradine is metabolized by CYP3A4 isoenzyme which indicates its risk of potential pharmacokinetic interactions.[35] Ivabradine at toxic dose is thought to cause severe bradycardia and acute heart failure. The potent CYP3A4 inhibitors like ketoconazole increased ivabradine mean plasma exposure by 7 to 8 fold and hence its use is contraindicated with strong CYP3A4inhibitors.[36]So, when Lopinavir-Ritonavir is used in COVID-19 treatment, it is important to consider the fact that Ritonavir being a strong CYP3A4 inhibitor may increase exposure to ivabradine, leading to its toxicity.

2.3 Statin Toxicity

Drug interactions can significantly contribute to risk of statin related myopathy and rhabdomyolysis, mainly due to competition for hepatic metabolism of statins. Simvastatin and lovastatin are mainly metabolized by the CYP3A4 isoenzymes, and atorvastatin to a lesser extent whereas CYP450 isoenzymes are not much involved in rosuvastatin clearance.[37]When strong CYP3A4 inhibitors like ritonavir are to be given with statins, the following recommendation should be considered for selection and dosing of statins.[12]

Table No. 2: Recommended dose of Statins with strong CYP3A4 inhibitors

Drug	**Recommended dose with strong CYP3A4 inhibitors**
Simvastatin and lovastatin	Avoid
Atorvastatin	10 mg/day
Rosuvastatin	10 mg/day
Pravastatin, pitavastatin	dose adjustment not required
Fluvastatin	no data available

Macrolide antibiotics such as erythromycin and clarithromycin are found to cause increased exposure to statins by inhibition of the enzyme CYP3A4 and OAT1B transporter. However unlike other macrolides, Azithromycin does not affect statin exposure and so, it is safe to use with statins.[38]

3. HYPERTENSION

For a COVID-19 patient who is a known hypertensive, it is vital to look into possible drug interactions. Hydroxychloroquine may increase the bioavailability of metoprolol, a selective β1 receptor blocker which is used in treatment of hypertension.[39]The proposed mechanism is that hydroxychloroquine may inhibit the CYP2D6 mediated hepatic metabolism of metoprolol. However, further studies are needed to evaluate the clinical significance of this interaction. Beta blockers such as carvedilol, propranolol and metoprolol are dependent on CYP2D6 for their metabolism. Though ritonavir is a known inhibitor of CYP2D6 isoenzyme, at low boosting dose (lopinavir 400mg/ritonavir 100 mg), CYP2D6 inhibition is negligible and hence it may not affect the metabolism of beta-blockers.[40]There is a theoretical risk of increase in PR interval when lopinavir-ritonavir is combined with betablockers, but clinical significance is not known.

Macrolide antibiotics are generally known to increase plasma concentration of calcium channel blockers by CYP3A4 inhibition, but azithromycin, which is only a weak CYP3A4 inhibitor does not have this effect and is safe to use with calcium channel blockers.[41]Ritonavir being a strong CYP3A4 inhibitors, inhibits the metabolism of calcium channel blockers(CCBs) including amlodipine, nifedipine and nimodipine, leading to increased plasma concentration of CCBs.[23]Clinical effects of this interaction such as hypotension or prolonged PR interval is not clearly known and hence caution and monitoring is recommended. However, in a case report of a patient in whom nifedipine was coadministered with Lopinavir-Ritonavir, the patient subsequently developed hypotension, generalised edema and renal failure.[42]

ACE inhibitors or Angiotensin receptor blockers (ARBs) do not have any clinically significant drug interaction with any of the therapeutic agents proposed for management of COVID-19. There is a theoretical risk of increased valsartan exposure when co-administered with ritonavir, due to inhibition of hepatic efflux transporter MRP2,[43] but there is no evidence to support the clinical significance of this effect.

4. CORONARY ARTERY DISEASE/ ISCHEMIC HEART DISEASE

Anticoagulants and antiplatelet drugs are the mainstay of pharmacotherapy in the short term and long term management of coronary artery disease. Drugs proposed for treatment of COVID-19 alter the metabolism of these drugs, leading to either loss of therapeutic effect or

drug toxicity. DDIs with other drug classes such as beta blockers, statins and calcium channel blockers are discussed in the previous sections.

4.1 Altered antiplatelet effect:

Dual antiplatelet therapy, used as standard treatment for management of acute coronary syndrome involve combination of aspirin with a P2Y12 receptor inhibitor. Among the P2Y12 receptor inhibitors, prasugrel and clopidogrel are prodrugs and they require bioactivation by cytochrome P450 enzymes. Ritonavir is a strong CYP3A4inhibitor and may influence this bioactivation process and decrease the antiplatelet effect. In a randomized crossover clinical trial, pharmacokinetics of clopidogrel and prasugrel in combination with ritonavir boosted antiretroviral therapy was evaluated and it was found that antiplatelet effect of clopidogrel was decreased but prasugrel retained its effect.[44]This could be possibly due to bioactivation of prasugrel by other enzymes such as CYP2B6 which is not inhibited by Lopinavir-Ritonavir.[45]

In contrast, ticagrelor does not require bioactivation as majority of antiplatelet effect is due to the parent drug and its equipotent active metabolite contributes to some extent. Thus, overall antiplatelet effect is not decreased by inhibition of ticagrelor metabolism, but an increase in antiplatelet effect may be observed.[46] When coadministered with ritonavir, the CYP3A4 mediated metabolism of ticagrelor is inhibited and its level is substantially increased which may lead to risk of bleeding.[47]In the approved prescribing information of ticagrelor, it is stated that its use with strong CYP3A4 inhibitors is contraindicated.

Thus prasugrel is the preferred alternative to clopidogrel and ticagrelor for patients who are on ritonavir.

4.2 Altered Anticoagulant Effect

Anticoagulant drugs for cardiovascular diseases is mainly given in case of atrial fibrillation as prophylaxis for thromboembolic events and in other conditions of hypercoagulable state. Lopinavir-Ritonavir is reported to cause a significant decrease in the anticoagulant effect of warfarin and acenocoumarol due to CYP2C9 and CYP1A2 induction, which result in subtherapeutic INR levels.[48]The effect of its interactions with warfarin can be observed only after several days of starting Lopinavir-Ritonavir and also the effect may persist for several days to weeks even after withdrawal of the inducer drug. These factors must be considered

for monitoring International Normalized Ratio (INR) levels and subsequent dose modifications of warfarin.[49]

There are several case reports in which concomitant use of azithromycin and warfarin has led to elevated anticoagulant effect of warfarin, but the mechanism behind this interaction is not clearly elucidated.[50] In a study with geriatric patients receiving warfarin therapy, a significant increase in the value of International Normalized Ratio (INR) was observed after administration of azithromycin, though it was not associated with any adverse effects such as bleeding.[51]Despite inconclusive and contradicting information on this drug interaction, the possibility cannot be ruled out until further definitive evidence becomes available. Hence, it mandates the need of INR monitoring when azithromycin is prescribed for treatment of COVID-19 in patients who are already on warfarin therapy, particularly in the elderly.[52,53]

Lopinavir-Ritonavir also affects the pharmacokinetics of direct oral anticoagulants(DOACs)such as apixaban, rivaroxaban, edoxaban and dabigatran to varying extent. Metabolism and excretion of rivaroxaban is dependent on several enzymes including hepatic CYP3A4 and renal P-glycoprotein efflux transporter. Thus use of rivaroxaban is contraindicated with ritonavir which is a potent inhibitor of both CYP3A4 and P-gpdue to risk of increased exposure to rivaroxaban.[54] Similarly, the elimination of apixaban also involves CYP3A4 and P-gp, hence affected by ritonavir.[55]It is recommended to avoid coadministration of ritonavir and apixaban in patients requiring 2.5 mg of apixaban and a 50% dose reduction of apixaban is recommended in those requiring apixaban 5 mg or 10 mg twice daily.[56]Dabigatran is not metabolised by CYP450 enzymes and it is renally excreted. It is available as prodrug, dabigatron etexilate which is a substrate of intestinal P-gp. There is a theoretical concern that ritonavir may increase systemic exposure to dabigatran by inhibition of intestinal P-gp.[57]But there are evidences postulating that exposure to dabigatran is not much influenced by Lopinavir-Ritonavir and it can be safely used without any dose modification unless the patient have an impaired renal function.[58]

Thus, for concomitant use with Lopinavir-Ritonavir, dabigatran is found to be the safest among the direct oral anticoagulants(DOACs).

5. PERIPHERAL VASCULAR DISEASE

Peripheral vascular disease may predispose patients to life-threatening complications such as myocardial infarction, stroke or even cardiovascular death.[59]Pharmacotherapy of peripheral

vascular disease includes drugs such as antiplatelets, anticoagulants, antihypertensives, statin and possible interactions related to these drugs are discussed in the previous sections.

Cilostazol is used for the treatment of intermittent claudication resulting from peripheral arterial disease. In vitro and in vivo studies found that cilostazol is metabolised by CYP3A and so caution should be taken when administering cilostazol with CYP3A inhibitors like ritonavir.[60]

Exposure to cilostazol is further increased when a CYP2C19 inhibitor such as fluconazole or omeprazole is also given.[61] In the summary of product characteristics (SmPc) European recommendation, it is stated that cilostazol is contraindicated in patients receiving CYP3A and CYP2C19 inhibitors, whereas US FDA recommends a lower dose of 50mg twice daily.

6. PULMONARY ARTERY HYPERTENSION:

Cardiac dysfunction can lead to complications such as pulmonary artery hypertension(PAH) which is categorised as WHO group 2 PAH. The antiviral drug, Lopinavir-Ritonavir have clinically significant interactions with the drugs used for treatment of PAH such as bosentan and sildenafil. Bosentan, an endothelin receptor antagonists is used for the treatment of pulmonary arterial hypertension (PAH). The transporter OATP1B1 and enzymeCYP3A4 are involved in the uptake and metabolism of bosentan in liver. In a study conducted with 12 healthy participants where they received treatment with Lopinavir/Ritonavir(400 mg/100 mg) and bosentan (125 mg twice daily), bosentan concentration increased up to 48-fold during the first 4 days. This could be primarily due to inhibition of OATP1B1 by ritonavir which blocked bosentan uptake into hepatocytes. Ritonavir is a strong CYP3A4 inhibitor, whereas bosentan and lopinavir are CYP3A4 inducers. Unlike enzyme inhibition, enzyme induction is a slower process and it may take several days to weeks. At steady state of Lopinavir-Ritonavir on day 10, the increase in bosentan exposure was comparitively low (5 fold). This may be due to a combined effect of CYP3A4 inhibition by ritonavir, and CYP3A4induction mediated by both bosentan and lopinavir.[62,63]In the prescribing information of bosentan, it is suggested that bosentan should be discontinued at least 36 hours prior to initiation of ritonavir and after 10 days, it can be reinitiated at lower dose. It is also recommended to avoid concurrent use of multiple drugs such as ritonavir and voriconazole or fluconazole with bosentan at the same time. This is because, inhibition of both CYP3A4and CYP2C9by

ritonavir and voriconazole respectively, would substantially increase the exposure to bosentan.

Sildenafil, a phosphodiesterase (PDE) inhibitor used for the treatment of pulmonary arterial hypertension is primarily metabolised by enzyme CYP3A4. Hence drugs that inhibit CYP3A4 isoenzyme may lead to risk of increased exposure to sildenafil and subsequent toxicity.[64]

It is well known that ritonavir is a strong CYP3A4 inhibitor. Despite lack of clinical evidence of hypotension or any other adverse effects of sildenafil, it is recommended to avoid combined use of sildenafil with ritonavir, particularly when it is used for treatment of pulmonary artery hypotension.[65]

COVID-19 AND DIABETES

Diabetes may have an adverse impact on the prognosis of COVID-19. Likewise, the drugs proposed for treating COVID-19 and the infection itself have varying effects on the glycaemic control of patients with diabetes.[66]This emphasizes the need of intense blood glucose monitoring in diabetic patients acquiring COVID-19.

Hydroxychloroquine (HCQ) is found to have clinically significant antidiabetic properties and it is approved in India as add-on therapy for Type 2 diabetes mellitus. Though, studies reported that the risk of adverse hypoglycemic events with HCQ is only mild and clinically non-significant,[67]in the product monograph of HCQ, caution against hypoglycemia is recommended both for patients with or without diabetes. Further studies are needed regarding the influence of HCQ in blood glucose level when used for treatment of COVID-19.

Saxagliptin, an antidiabetic drug of the class dipeptidyl peptidase-4 (DPP-4) inhibitor, is metabolised by CY3A4 isoenzyme. Strong CYP3A4 inhibitors like ritonavir may increase the serum concentration of saxagliptin.[68] In the prescribtion information for saxagliptin, it is suggested to limit saxagliptin dose to 2.5 mg daily when combined with strong CYP3A4 inhibitors. It is also recommended to avoid concomitant use of strong CYP3A4 inhibitors with saxagliptin combination products such as (saxagliptin/dapagliflozin combination or saxagliptin/dapagliflozin/metformin combination). Evidence on interaction of Lopinovir-Ritonavir with other gliptins is unclear.

Corticosteroids are not recommended in patients with COVID-19 except for any compelling indications. Also, it is noteworthy that corticosteroid may lead to poor glycemic control in diabetic patients.[69]

DISCUSSION:

Many drugs are being proposed or studied for the treatment of COVID-19 and the possible drug-drug interactions related to them with the drugs for common co-morbid conditions such as cardiovascular disease and diabetes have been reviewed in this article. As with drugs such as Lopinavir-Ritonavir, chloroquine and hydroxychloroquine, evidence on drug-drug interactions (DDIs) and safety is mostly based on their long term use in conditions like HIV and autoimmune diseases respectively. Information on DDIs and safety profile specific to use in patient with COVID-19 is still lacking.

Drug interactions and their adverse outcomes may be time-dependent, dose-dependent and specific to certain risk factors related to individual patient or patient groups. Analyzing the clinical relevance of theoretical risks and previously documented drug interactions is needed for decision-making in routine clinical practice.

Chloroquine and hydroxychloroquine are known to cause adverse cardiac events such as restrictive cardiomyopathy, conduction disorders, myocardial thickening and heart failure. But these effects are observed only with long term use.[14]Likewise, long term use of Lopinavir-Ritonavir is known to cause, lipodystrophy, premature atherosclerosis, dyslipidemia, hyperglycemia and even diabetes.[22,70]

In the management of COVID-19, these drugs are used for a short duration of 10 to 14 days. In general, mechanism of a drug interaction can either be pharmacodynamic or pharmacokinetic such as enzyme induction and inhibition. Studies have shown that, unlike enzyme inhibition, enzyme induction is a slower process and it may take several days to weeks for the effects to be observed.[49]Hence it becomes necessary to analyze the clinical relevance of drug-drug interaction and drug related adverse outcomes specific to COVID 19 management.

The clinically significant drug-drug interactions and adverse cardiovascular outcomes even with short-term exposure of drugs proposed for COVID-19 management are summarized in

Table 3. The available evidence on prevention or handling of such interactions is also discussed.

It is now evident that close monitoring for any possible DDIs in patients under treatment for COVID-19 is an absolute necessity. Knowledge on preventable drug interactions help in avoiding drug related harm to patients. Further prospective studies are needed to analyze the drug safety aspects, specific to COVID-19 treatment.

Table No. 3: Summary of potential Drug-Drug interaction in patient with COVID-19 and co-morbid cardiovascular disease

Adverse Outcome Related To Interaction	Risk Factors	Interacting Drug Combination	Mechanism of drug-drug interaction	Effect of drug-drug Interaction	Available Evidence On Prevention/ Management of Interaction
Cardiac Conduction abnormalities	**QT Prolongation**				
	Advanced age, Hypokalemia, Hypomagnesemia, Hypocalcemia, Use of diuretics, AV Block, Bradycardia, Congenital long QT syndrome Myocardial Infarction, Heart failure or any other structural heart disease, Renal or hepatic impairment	Lopinavir-ritonavir + Amiodarone/ quinidine	CYP3A4 inhibition by lopinavir-ritonavir leads to elevated plasma concentrations of Amiodarone (same effect is seen with quinidine)	Risk of torsade de pointes (TdP) due to Amiodarone is substantially increased (same effect is seen with quinidine)	Avoid this combination (especially if pretreatment QTc is >450 ms or left ventricular ejection fraction <20%) (or) monitor closely- discontinue if QTc interval >500 ms posttreatment (or) increase in QTc interval is >60 ms compared
		Chloroquine/ Hydroxychloroquine + Amiodarone/ quinidine	Combined use of drugs with risk of TdP	QT prolongation and TdP due to Amiodarone is potentiated (same effect is seen with quinidine)	
		Azithromycin + Amiodarone/ quinidine	Combined use of drugs with risk of TdP	QT prolongation and TdP due to Amiodarone is potentiated (same effect is seen with	

				quinidine)	with pretreatment value.
Drug Toxicity	**Digoxin toxicity**				
	Low body weight, advanced age, impaired renal function, hypokalemia, hypercalcemia, hypomagnesemia.	Lopinavir-ritonavir +Digoxin	p-glycoprotein inhibition by lopinavir-ritonavir leads to elevated digoxin (AUC) level.	Digoxin toxicity	Monitor serum digoxin level and adjust dose. Also, check renal function and serum electrolytes.
		Hydroxychloroquine +Digoxin	inhibition of p-glycoprotein	increased serum digoxin levels	Monitor serum digoxin level
		Azithromycin +Digoxin	Possibly by inhibition of P-gp (weak inhibitor)	Possible risk of digoxin toxicity (lower risk)	May consider monitoring for signs of digoxin toxicity.
	Ivabradine toxicity				
	Use of drugs known to cause bradycardia can further intensify the adverse outcomes of this interaction	Lopinavir-ritonavir +Ivabradine	CYP3A4 inhibition-decreased metabolism of ivabradine	Risk of ivabradine toxicity(exacerbation of bradycardia and conduction disturbances)	Avoid this combination
	Statin Toxicity				
	advanced age (notably >80 years), patients with existing myopathies, Diabetes mellitus (particularly combined with advanced age and chronic renal	Lopinavir-ritonavir +Statins	Inhibition of CYP3A4 mediated metabolism of statins	Risk of toxicity (myopathy, rhabdomyolysis)	Avoid - Simvastatin and lovastatin ▪ Atorvastatin-10 mg/day ▪ Rosuvastatin-10 mg/day ▪ Pravastatin, pitavastatin-dose

	failure), hepatic impairment, Untreated hypothyroidism				adjustment not required ▪ Fluvastatin- no data available
Altered therapeutic effect	**Altered anticoagulant effect**				
	-	Lopinavir-ritonavir +Warfarin	CYP2C9 and CYP1A2 induction- increased metabolism of warfarin	Decreased INR (delayed effect), also persists for several days to weeks	Monitor INR and adjust warfarin dose accordingly
		Lopinavir-ritonavir +Acenocoumarol	increased metabolism of acenocoumarol due to enzyme induction	May lead to subtherapeutic INR	Monitor INR and adjust dose accordingly
	geriatric patients	Azithromycin +Warfarin	Unknown	Possible increase in INR	Monitor INR levels
		Lopinavir-ritonavir + Direct oral anticoagulants(DOACs)	Inhibition of both CYP3A4 and P-glycoprotein	Increased exposure to rivaroxaban and apixaban	▪ Rivaroxaban- Avoid ▪ For patients requiring Apixaban 2.5 mg- avoid use ▪ For patients requiring apixaban 5 mg or 10 mg- reduce dose to half ▪ Dabigatran- safe (except in patients with renal impairment)
	Altered antiplatelet effect				
	-	Lopinavir-ritonavir +Clopidogrel	Bioactivation of clopidogrel(prodrug) is inhibited	Decreased antiplatelet effect	Prasugrel is the preferred alternative to clopidogrel
	-	Lopinavir-	Inhibition of	Increased	

		ritonavir +Ticagrelor	ticagrelor metabolism	exposure to ticagrelor. Risk of bleeding	and ticagrelor for patients who are on ritonavir. (Ticagrelor use with strong CPY3A4 inhibitor is contraindicated
	Others				
	Exposure to cilostazol is further increased when a CYP2C19 inhibitor is also given	Lopinavir-ritonavir +cilostazol	Inhibition of CYP3A4 mediated metabolism of cilostazol	Possible increased exposure to cilostazol. Clinical effect unknown	Restrict cilostazol dose to 50 mg twice daily
	-	Lopinavir-ritonavir +sildenafil	Inhibition of CYP3A4 mediated metabolism of sildenafil	Increased exposure to sildenafil- may lead to hypotension or syncope	Contraindicated (if used for pulmonary artery hypertension)
	Addition use of drugs inhibiting CYP2C9 will further worsen the effects of this interaction	Lopinavir-ritonavir +bosentan	CYP3A4 inhibition and also Inhibition of OATP1B1mediated uptake of bosentan into hepatocytes.	Increased exposure to Bosentan	Bosentan should be discontinued at least 36 hours prior to initiation of ritonavir

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