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REVIEW

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Pharmacotherapeutic agents for the management of COVID-19 patients with preexisting cardiovascular disease

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic is the largest public health challenge of the twenty-first century. While COVID-19 primarily affects the respiratory system, manifesting as interstitial pneumonitis and severe acute respiratory distress syndrome (ARDS), it also has implications for the cardiovascular system. Moreover, those admitted to hospital with severe COVID-19 are more likely to have cardiovascular comorbidities such as hypertension and diabetes mellitus. The underlying pathophysiology of why COVID-19 onset can further decline cardiac pathologies as well as trigger acute onset of new cardiac complications is not yet well understood.

Areas covered: In this review, the authors extensively review literature focused on the current understanding and approaches of managing patients who have underlying cardiovascular diseases and concomitant COVID-19 infection. Furthermore, the authors explore the possible cardiovascular implications of the suggested COVID-19 therapeutic agents that are used to treat this lethal disease.

Expert opinion: Current evidence is evolving around the many trialed pharmacotherapeutic considerations for the management of coronavirus disease 2019 (COVID-19) in patients with cardiovascular disease. While we await such data, clinicians should advocate for careful consideration of all concomitant medications for those presenting with COVID-19 on a patient-by-patient basis.

1. Introduction

The coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on 11 March 2020, and as of February 2021, most of the world still remains affected [1]. The outbreak started in Wuhan, China, where the first official case was reported in December 2019 [2], after which the disease spread globally, bringing unprecedented change in the public health sector and the delivery of healthcare. The virus was identified as genus *betacoronavirus*, making it the third coronavirus of the twenty-first century to result in a global health crisis, after severe acute respiratory syndrome (SARS) in 2002 [3], and Middle East respiratory syndrome (MERS) in 2012 [4]. The new coronavirus was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Currently, over 100 million people [1] are infected with the virus worldwide, making it more transmissible than previous coronaviruses [5]. The infection that it causes can range from asymptomatic, to life-threatening disease [6], as is evident by the total number of global deaths surpassing 2.2 million [1]. At present, vaccination programs in several countries are underway, but the world is still a long way off from eradicating the threat of SARS-CoV-2.

While varying respiratory symptoms are the common clinical manifestations of disease, cardiovascular events, including myocarditis, arrhythmias, heart failure, and ischemic stroke, have been reported in multiple studies [6,7]. Similar to other respiratory infections, those with established cardiovascular disease (CVD) or its risk factors are at a higher risk for developing severe COVID-19, where disease onset can cause a further decline of cardiac pathologies as well as trigger acute onset of new cardiac complications [8]. A meta-analysis [9] of 159,698 COVID-19 patients showed a high prevalence of CVDs that were significantly associated with higher intensive care unit admission, mechanical ventilation, and mortality. Acute cardiac injury (52%) was the most prevalent CVD among COVID-19 patients, followed by hypertension (51%), arrhythmia (37%), heart failure (27%), coronary heart disease (23%), and other CVDs (23%). Among patients that are hospitalized with COVID-19, the CVD risk factors of hypertension and diabetes mellitus are the most prevalent comorbidities [7,10]. Similarly, in a cohort of 5,700 hospitalized COVID-19 patients, Richardson et al. [8] found that 56.6% had hypertension, 41.7% were obese, and 33.8% suffered from diabetes.

2. COVID-19 and Cardiovascular disease

SARS-CoV-2 infection is caused by the binding of viral cell surface spike (S) protein to the human angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the heart, kidneys, lungs, and small intestine [5,11]. ACE2 may be an important factor in counteracting the negative impact of the renin-angiotensin system (RAS), and its expression in the heart might be key to understanding the acute-onset of cardiac pathologies in severe COVID-19 [12]. It is also reported that soluble angiotensin II (Ang II), the peptide hormone substrate of ACE2, has a higher plasma concentration in COVID-19 patients than in healthy controls, and is positively correlated with SARS-CoV-2 viral loads [13]. The wide range of CVDs mentioned above have been shown to interact with the renin-angiotensin system (RAS), and the way in which these pathologies and RAS inhibitors can alter ACE2 expression is discussed below. The *de novo* cardiovascular complications associated with COVID-19 may also be a result of a heightened inflammatory response, which is described as a cytokine storm. Excessive cytokine release has been correlated with worse disease outcomes in COVID-19, particularly in acute myocardial injury [14]. Studies have suggested that targeted therapy to disrupt the signaling of cytokines such as interleukin-6 may reduce disease severity, as it was shown to be markedly elevated in COVID-19 patients [15,16]. Hypercoagulability is yet another mechanism attributed to severe disease and it has been noted in severely ill COVID-19 patients where it likely contributes to mortality. In a study of 1,026 COVID-19 patients, 40% of the patients were considered at high risk of venous thromboembolism [17]. Consideration of thromboprophylaxis in higher risk COVID-19 patients may therefore improve clinical outcomes.

Patients with underlying CVD presented with a higher proportion of COVID-19 related cardiac injury, which consequently related to higher mortality rates [18]. As with many other diseases, CVD comorbidity significantly increases the risk of mortality and complications arise due to a diminished circulatory reserve to meet the excessive demands on the cardiovascular system [19]. Hence, it is of great importance to understand the relationship between CVD and COVID-19. As proposed, COVID-19 disease may be worsened due to the higher inflammatory burden, and the increased risk of thromboembolic events, as well as the changes in ACE2 levels seen in CVD patients. In terms of pediatric COVID-19 patients, those with CHD (cyanotic defects, depressed myocardial contractility, pulmonary hypertension, immunodeficiencies) are more likely to require ICU admission and artificial respiratory support [20]. Targeted therapies have been developed against some of the pathophysiological mechanisms found in adult patients and we will discuss evidence on the implications that these therapies have in clinical practice.

3. Targeting COVID-19 therapy

3.1. Cardiovascular Agents

3.1.1. ACEi/ARBs/RAAS agents

Research on SARS-CoV-2 has brought forward evidence that the ACE2 receptor on lung alveolar epithelial cells is a central point for the cell entry of SARS-CoV-2 [21]. Therefore, many have been reluctant to use renin angiotensin system (RAS) agents for CVD patients who contract the virus, in fear that it would increase the viral load through upregulation of the ACE2 receptors found mainly in the airway epithelial cells [22,23]. ACE2 is an endogenous counter-regulator of RAS as its role is degrading Ang II to angiotensin 1–7; Ang II is a vasoconstrictor and is produced within RAS – the angiotensin converting enzyme (ACE) converts angiotensin I (Ang I) to Ang II [24]. SARS-CoV-2 infection relies on the binding of its Spike protein to ACE2 receptors in the host's cells. A recent study showed that S protein can directly damage vascular endothelial cells by downregulating ACE2, which results in poor mitochondrial function but enhanced glycolysis, implying that endothelial damage outweighs virus infectivity [25]. This suggests that a vaccine-induced antibody against S protein not only protects the host cells from SARS-CoV-2 infection but also against endothelial harm caused by S protein [25].

Although, the predicted upregulation of ACE2 due to RAS agents has not been a conclusive finding in many studies, including both rodent and human subjects [26,27]. However, one study found the ARB olmesartan to be associated with an increased renal expression and urinary secretion of ACE2 [25]. Another clinical study indicates that compared to other ARBs, olmesartan's unique effects lie in reducing proteinuria and upregulating urinary ACE2, potentially yielding renal protection by several cumulative effects [28]. Moreover, a recent study on COVID-19 patients has discovered infections of cells that lack the ACE2 receptor expression such as in immune cells, as well as a lack of infected cells where there is high ACE2 expression (e.g smooth muscle cells), thereby indicating

additional mechanisms and receptors for SARS-CoV-2 cell entry [29]. Evidence suggesting tissue renin-angiotensin system (tRAS) is involved in the course of numerous human disease development has grown in recent years [30]. Although the role of tRAS in the evolution of COVID-19 disease is unclear, multiple investigations have reported elevated ACE2 receptor levels in patients, which could be of substantial clinical significance in the future [31]. A review by Saveri et al. proposes that changes in tissue and systemic RAS activity during infection and disease could be attributable to a counterregulatory rise in ACE2 gene expression due to the early ACE2 shedding, so while tissue RAS is the first target, there will be effects on the entire RAS system [31,32].

Although RAS inhibitors have not been associated with mortality or a severe onset of COVID-19, there are concerns that patient may face further adverse outcomes if they manage their underlying CVD by taking RAS inhibitors. However, the causal relationship between RAS inhibitors and ACE2 in the context of SARS-CoV proves beneficial (Figure 1), especially as there is emerging evidence of Ang II being directly associated with pulmonary vascular permeability, and inflammation [26]. Moreover, a clinical study noticed an increase of Ang II in hospitalized COVID-19 patients as compared to the healthy control group, which further credits the use of RAS inhibitors in this cohort of patients [33]. By limiting the availability of Ang II (in the case of ACEIs) or limiting activation of MAPK pathways-driven decline of AT1-R, ACEI/ARBs may provide a protective effect by suppressing ACE2-mediated viral uptake, resulting in less serious viral pathogenesis [34,35]. Many MAPK pathways are already overexpressed in CVD, and the steady progression of CVDs, may signal that elevated

MAPK signaling cascades and SARS-CoV-2 pathogenesis lead to higher infection severity and consequences in individuals with preexisting CVD [36]. While the specific mechanisms underlying the pathophysiology of SARS-CoV-2 infection are yet unknown, presented research might be interpreted to indicate that RAAS and MAPK pathway imbalances are involved in the reported association between COVID-19 and CVD [35].

There is a range of evidence supporting metformin, a drug typically used to treat diabetes mellitus, playing a beneficial role in CVD treatment regardless of a patient's diabetic status [36]. This may suggest potential for regrouping metformin in CVD treatment, however findings from prospective studies that examine the effect of metformin in CVD patients without diabetes mellitus are widely neutral [37,38,39]. Metformin is also associated with a reduced risk of mortality/morbidity from COVID-19 infections, as it increases ACE2 expression and inhibits inflammatory response via activation of AMP-activated protein kinase [40,41,42]. This, combined with metformin's potential benefit in treating CVD, might make the drug an effective resource for COVID-19 patients with underlying CVD. There is a need for randomized clinical trials to prove these speculations.

As highlighted in Figure 1, the RAS agents' upregulation of ACE2 can be beneficial in treating COVID-19 patients. Monteil et al. [43] showed that ACE2 can significantly block early spread of SARS-CoV-2, but also inhibit the direct infection of SARS-CoV-2 on human blood vessel organoids and human kidney organoids. Moreover, there are several studies which indicate that ACEI/ARBs have a positive effect on patients with acute respiratory distress syndrome (ARDS), including
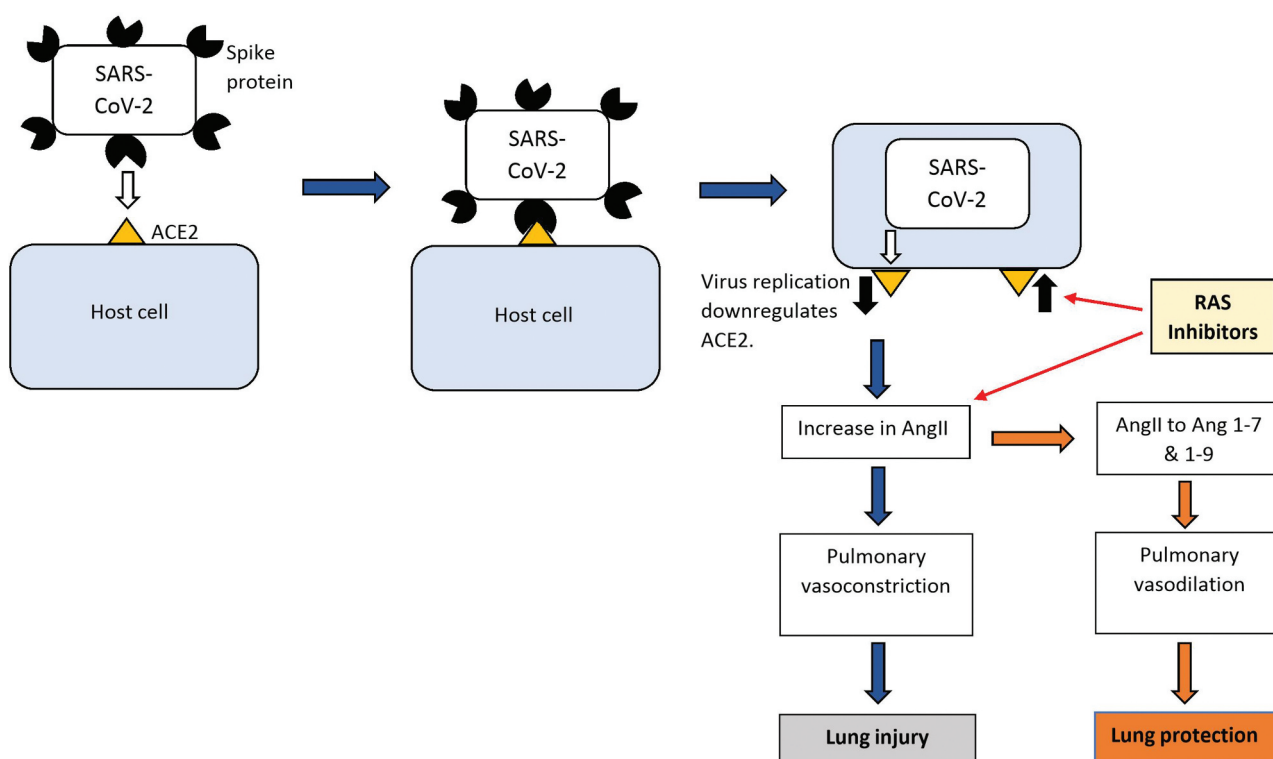

Figure 1. Mechanism of SARS-CoV-2 contributing to pulmonary pathogenesis via ACE2 pathway and RAS attenuating fund injury.

pneumonia. Recent studies have demonstrated that ACEI/ARB treatment in COVID-19 patients is associated with a reduced mortality risk, with a meta-analysis demonstrating a reduction in all-cause mortality [44,45]. Zhang et al. [46] showed no significant difference in the outcome and length of hospital stay in hypertensive COVID-19 patients who continued to take RAS inhibitors compared to the control group [46]. Another study indicated that the peak viral load for patients taking ACEI/ARBs was significantly lower than the control group (p = 0.03), even though the baseline viral load remained the same for both groups [38]. Conversely, Mancia et al. [47] noticed that a large proportion of COVID-19 patients who took ACEI/ARB faced adverse outcomes compared to patients with more moderate infections. There are several confounding factors in all these clinical studies that are difficult to control, especially as there is a very high likelihood hypertensive patients with other CVD are more likely to be obese; a combination of these comorbidities increases the risk of an aggressive course of COVID-19 [48]. A large observational study showed reduced COVID-19 risk in hypertensive patients treated for a long time with ACEi or ARBs, compared to CCBs. ACEi and ARBs were presented with a lower risk of COVID-19 hospitalization and death compared to CCBs (hazard ratios of 0.74 and 0.84, respectively), with ACEi having a greater decrease in risk than ARBs [49]. Though the observational aim of the study hinders from establishing firm conclusions regarding the association, it adds to the current information that ACEi or ARBs may have a protective role in hypertensive patients from COVID-19 disease [49].

The majority of professional medical bodies recommend continuing patient medication for underlying CVD after being infected by SARS-CoV-2. It has been suggested that discontinuing medications when hospitalized may often result in clinical inertia, hence significantly increasing the risk of long-term complications [47,48,50]. A systematic review has gathered growing research from multiple cohorts of patients that could not confirm negative effects of RAAS inhibitors in COVID-19 disease despite the concerns [51]. Discontinuation of ACEIs/ARBs in hospitalized hypertensive COVID-19 patients resulted in a prolonged hospital stay, particularly in patients with a moderate case of infection [52]. Although, it is recommended to continue CVD medication in patients who are infected by SARS-CoV-2, it is important to note that the effect of a drug can vary between individual patients, therefore daily review is a necessity to assess the optimization of using these medications based on the clinical course of the disease [50,53]. Where patients suffer severe adverse outcomes whilst using the medications, such as hyperkalemia, it is imperative to reconsider the continuation of RAS inhibitors [52].

3.1.2. Beta-blockers

Beta-adrenergic receptor blockers are traditionally used for the management of myocardial infarctions, coronary artery disease, and stable/unstable angina [54]. However, there is emerging evidence that beta-blockers have beneficial effects in patients with respiratory illnesses [55]. As is the case with SARS-CoV-2, multiple recent studies and hypotheses-generating papers have indicated various mechanisms via which beta-blockers can induce protective effects in COVID-19 patients [56,57]. Many studies suggest an association between COVID-19 infections with hyperinflammation, as well as an increased activation of the Th17 response [58,59]. Some indicate that nonselective beta-blockers, such as propranolol, reduce inflammatory cytokine release and Th17 response, can therefore slow down the worsening of SARS-CoV-2 infection [60]. Severe infections result in hypoxia and hyperinflammation, activating the sympathetic nerve pathway where use of beta-blockers may possibly inhibit this response [60]. Moreover, beta2-adrenergic blockers reduce the RAS activities by downregulating renin release, which can decrease ACE2 receptor levels in alveolar epithelial cells, therefore reducing viral entry [61]. Additionally, propranolol negatively regulates cluster of differentiation 147 (CD147) – another spike protein recently found to be involved in SARS-CoV-2 entry into the host cell [62].

There are some limitations to the role of beta-blockers; therefore it is necessary to weigh up their benefits and adverse effects carefully, especially as many heart failure patients have a negative response, leading to reactive airways disease and bradycardia from malfunctioning of conduction system [55]. Further investigations are needed on the protective properties and limitations of beta-blockers on COVID-19 patients. There is also a need for clarity as to which sub-type of beta-blockers is the most effective for COVID-19 patients.

Recent findings indicate that beta-adrenergic blockers may be more effective against septic shock in COVID-19 patients, as compared to norepinephrine, which is primarily used to treat septic shock [63,64]. There are rising concerns that the use of norepinephrine in septic shock may worsen the patient's condition by increasing catecholamine levels, hence increasing ACE2 expression and easing SARS-CoV-2 cell entry [65,66]. However, the use of beta-blockers in septic patients may still present risks, as some findings report an exacerbated sepsis-stimulated response with use of beta-blocker propranolol [67].

3.1.3. Calcium channel blockers

Calcium channel blockers (CCBs) are typically prescribed to treat hypertension. CCBs act through the relaxation of vascular smooth muscle cells, which results in vasodilation and thereby reduces blood pressure. Hypertension is a comorbidity often seen in severe COVID-19 disease and is linked to poor clinical outcomes in elderly populations [7,8,10]. The research discussed suggests there may be some benefit from the use of dihydropyridine CCB in the prevention of severe COVID-19 disease. In-vitro studies looking into the effect of CCB on SARS-CoV-2 illustrated that dihydropyridines were effective in inhibiting post-entry viral replication [68]. Furthermore, this study looked into the effects of amlodipine besylate on 225 COVID-19 patients in Tongji Hospital in Hubei province, China, where 42% of these patients were found to have hypertension as their only comorbidity. The case fatality rate was 0% in the group receiving amlodipine besylate (n = 19), compared to 19.5% in the non-amlodipine besylate treated group (n = 77) [58]. Another study [69] explored the effect of FDA-approved CCB drugs on SARS-CoV-2 in Vero E6 cells isolated from epithelial kidney cells and epithelial lung cells. In the epithelial lung cells, amlodipine and nifedipine were the most effective CCB at inhibiting SARS-CoV-2 entry and replication [69].

Further evidence of the efficacy of CCBs in treating COVID-19 was found in a study [70] following 65 patients in Brooklyn, New York. In the group treated with a CCB (n = 24), 50% patients survived compared to 14.6% survival in the non-CCB group (n = 41) (P < 0.01; p = 0.0036). The study found that amlodipine and nifedipine were associated with significantly better patient outcomes, including a lower risk of intubation and mechanical ventilation [70]. These findings are promising, and support the safety and efficacy of dihydropyridine use in hypertensive COVID-19 patients. However, larger cohort studies and meta-analyses must be carried out to further explore whether CCBs may actually reduce the incidence of severe COVID-19, as some research has found negative implications of CCB use in COVID-19.

One study [71] theorizes that CCB use can lead to worsening respiratory failure in COVID-19 patients. Dihydropyridines have been associated with inhibition of hypoxic pulmonary vasoconstriction, and as a consequence can cause severe hypoxemia. The study retrospectively analyzed data from 245 hypertensive COVID-19 patients, and concluded that treatment with dihydropyridines may lead to a substantial increase in the risk of intubation and mortality compared to the non-dihydropyridines group [71]. A limitation of this study is the bias arising from unmeasured confounding variables that likely contribute to the mortality in these patients. A review [72] of 2,573 COVID-19 patients with hypertension found a marginal increase (4.4%, 95% CI0.5–8.2) of severe COVID-19 disease in patient groups using a CCB, however this increase was not considered of significance in the clinical setting [72]. The evidence on the use of CCB suggests that it is safe to continue usage in COVID-19 patients with a history of hypertension. However, if there are contraindications, such as severe hypotension and heart failure, these drugs should be avoided.

3.1.4. Anti-arrhythmics

Antiarrhythmic drugs (AADs) are predominantly categorized using the Vaughan-Williams classification [73], with four main classes as shown in Table 1. This classification is of no clinical significance, and instead separates the drugs based on their electrophysiological effect on myocardial cells. Some antiarrhythmics are known for causing cardiovascular toxicity, such as class Ia sodium channel blocker quinidine, which may induce prolongation of QT interval with an increased risk of progressing to a pleomorphic tachyarrhythmia Torsades-de-Pointes in 1% to 3% of patients [74]. However, quinidine is rarely used for arrhythmias and has been replaced with better therapeutics, mainly procainamide (class Ia) and amiodarone

(class III) [75]. Procainamide is administered intravenously for conversion to sinus rhythm in atrial fibrillation (AF) patients, including Wolff-Parkinson-White Syndrome presenting with pre-excited AF, and those with wide-complex or ventricular tachycardia [76]. As it is partially metabolized by CYP2D6, its plasma concentration can be decreased by CYP2D6 inducers, such as tocilizumab and sarilumab [77]. Additionally, as quinidine and procainamide have IKr blocking effect, they cannot be used concomitantly with COVID-19 therapies, such as hydroxychloroquine (HCQ) and azithromycin (AZ), due to risk of potentiating QT prolongation [77]. Though, tocilizumab and sarilumab have both been considered as potential therapies for COVID-19, which is discussed in later sections.

Class III amiodarone is both a multi-channel blocker (including INa, IKr, calcium channel, acetylcholine-dependent potassium channel, and α and β receptors), as well as the most common AAD used in AF [78]. It has the least proarrhythmic effect, and although it prolongs QT, it rarely causes Torsades-de-Pointes (<0.5%) [79]. Amiodarone is used for AF and ventricular arrhythmia prophylaxis, and is the preferred drug for AF rate and rhythm control in critically ill COVID-19 patients, with significant congestive heart failure or borderline blood pressure; and it should be noted that surveillance for liver, lung, and thyroid toxicity is recommended [80]. Although little is known about the interactions between amiodarone and COVID-19 pharmacotherapy, there are reports of serious pulmonary toxicity attributed to amiodarone use [81]. Similar to class Ia agents, caution should be exercised in amiodarone use with QT prolongation suggested COVID treatments, such as lopinavir/ritonavir and/or HCQ/AZM [82].

3.1.5. Diuretics

As many hospitalized COVID-19 patients are elderly, the use of diuretics to treat congestion in hypertension and heart failure is common among this cohort. Some clinicians have hypothesized [83] that [84] the use of diuretics could lead to a worse prognosis following mechanical ventilation in COVID-19 patients with pre-existing hypertension. Heart-lung interactions play a major role in mechanical ventilation [74], and are exacerbated in hypovolemic patients [83]. COVID-19 patients that develop respiratory failure prior to ventilation are hypovolemic as a result of fever and compromised fluid intake secondary to respiratory distress [6,7,10]. The hypothesis suggests that these heart-lung interactions may be more pronounced in hypertensive patients on diuretics, therefore contributing to some of the fatal outcomes seen [83]. However, it is important to highlight this is only

Table 1. Vaughan Williams classification of antiarrhythmic drugs and known interactions with COVID-19 pharmacotherapies.

Classification	Drugs	Interaction with COVID drugs
Class I: Sodium channel blockers (Ia, Ib, Ic)	Ia: quinidine, procainamide, disopyramide Ib: lidocaine, mexiletine Ic: flecainide, propafenone	Ia drugs are the most pro-arrhythmic and prolong QTc interval. Practice caution and close monitoring when administering with hydroxychloroquine and azithromycin therapy.
Class II: Beta-blockers	β-adrenoreceptor blockers	Nonselective beta-blocker propranolol downregulates CD147 (a spike protein used in SARS-CoV-2 host cell entry)
Class III: Potassium channel blockers	amiodarone, dronedarone dofetilide, sotalol, Ibutilide	For Amiodarone, practice caution and close monitoring when administering with hydroxychloroquine and azithromycin therapy. Contraindicated use with lopinavir/ritonavir.
Class IV: Calcium channel blockers	diltiazem, verapamil amlodipine, nifedipine	Discontinue CCB if contraindications such as heart failure and severe hypotension.

relevant in the context of mechanically ventilated patients, and lacks evidence to guide treatment.

Other studies focus on the interaction between current COVID-19 therapies and diuretics. In cases where COVID-19 is being treated using lopinavir/ritonavir [85,86], loop diuretics can continue being administered as there is no evidence that suggests a direct interaction between these two drug classes [87]. The same applies to the administration of thiazides along with lopinavir/ritonavir. However, caution must be taken if indapamide is being administered alongside lopinavir/ritonavir, as it requires dose adjustment.

Potassium and magnesium levels should be regularly monitored in patients being treated for COVID-19 using chloroquine/hydroxychloroquine, as the electrolyte disturbances can further increase the risk of QT prolongation [87]. Vital signs, creatinine, and serum electrolytes of patients with COVID-19 need to be monitored regularly, as they have an increased rate of acute kidney injury (AKI) and Torsades-de-Pointes [87].

Kotfis et al. [88] showed potential therapeutic benefits of spironolactone use in COVID-19, where animal models administered with the mineralocorticoid receptor antagonist were protected against pulmonary fibrosis, a complication seen in COVID-19 [78,88]. However, the potassium-sparing effects of mineralocorticoid receptor antagonists (MRA) may cause fatal hyperkalemia in at-risk patients, hence caution is advised if used in COVID-19 infection where there is propensity for multi-system failure (i.e. AKI, HF) [89].

At present, there is still limited evidence on the use of diuretics in COVID-19 patients with cardiovascular complications; hence high-quality data is needed to determine the drug-drug interactions of diuretics with COVID-19 medications.

3.1.6. Lipid-Lowering Therapies
3.1.6.1. Statins. Statins are the first-line treatment in the management of hypercholesterolemia and can help prevent the development of CVD. Evidence suggests that statins can improve endothelial function through the upregulation of nitric oxide synthase, as well as reduce inflammatory markers and decrease oxidative stress [90].

Hence, their beneficial use in counteracting the associated hyperinflammatory states and endothelial dysfunction seen in severe COVID-19 disease has been widely hypothesized. As discussed earlier, ACE2 mediates the entry of SARS-CoV-2 into the host cell. There is some concern with the use of statins in COVID-19, as they were shown to increase the expression of ACE2 in animal studies [91]. On the contrary, it is thought ACE2 can subside the hyperinflammatory reaction and tissue damage seen in severe forms of COVID-19 disease, protecting against lung injury [92]. Statins may also exert immunomodulatory effects, in particular on T-cell proliferation and differentiation. This has been demonstrated in studies where statin use was beneficial in reducing influenza mortality [93]. Moreover, overexpression of the myeloid differentiation primary response protein (MyD) 88 pathway is associated with overwhelming inflammation and poorer prognosis in previous coronaviruses, but has not been shown in SARS-Cov-2 as of yet. Statins stabilize MyD88 levels and therefore can protect against the inflammatory response seen in the pathway; thus,

as a result, could be considered in the treatment of severe illness from COVID-19 [94].

Furthermore, a meta-analysis [95] of 8,990 COVID-19 patients provided support for the use of statins in COVID-19 disease. The study found that statins could reduce the severity of illness from COVID-19 by 30% (pooled HR = 0.70; 95% CI0.53–0.94) [95]. The largest study of this meta-analysis showed that in 4,305 patients in the Hubei Province, China, the mortality rate in the patients was 5.2% and 9.4% in the matched statin and non-statin groups, respectively (with an adjusted hazard ratio of 0.58) [96].

However, conflicting evidence from a meta-analysis of 3,449 patients concluded that there was no improvement in patient outcomes with statin use [97]. Similarly, in a nationwide cohort study in Denmark of 4,842 patients with COVID-19, the standardized mortality risk at 30 days was 9.8% and 9.5% in the statin and non-statin groups, respectively. There was no statistical difference between the two groups, suggesting no indication that statin use reduces mortality in COVID-19 [98]. Also, as statin use is linked to hepatotoxicity, it is recommended to hold treatment in COVID-19 patients that have developed severe rhabdomyolysis and/or liver injury, as indicated by increased liver enzymes [83,99].

In conclusion, there is not enough clear evidence to suggest using statins as a treatment of severe COVID-19 disease, especially not in those with liver injury complications. Although they are associated with improved prognosis in influenza [93] and pneumonia [94,95,96] caused by other coronaviruses, this does not necessarily indicate beneficial use in COVID-19. We anticipate further data from cohort studies in 2021 that will shed more light on the efficacy of statins as an independent treatment. The current recommendations are to continue statin use in the management of CVD following COVID-19 infection, unless contraindicated due to liver function.

3.1.6.2. Ezetimibe and PCSK9 inhibitors. Ezetimibe and PCSK9 inhibitors can also be commenced in the treatment of hyperlipidemia, typically when there is an inadequate response to statin therapy, or if statins cannot be tolerated. Familial hypercholesterolemia (FH) is a genetic condition that can cause sustained elevations in low-density lipoprotein cholesterol (LDL-C) from a young age. As a result, these patients are at high risk of CVD and can suffer deleterious effects from COVID-19 disease. FH patients with poorly controlled LDL-C levels can benefit greatly from lipid lowering therapies; these can be a fixed combination therapy of statins with ezetimibe or PCSK9 inhibitors [100].

Studies have shown that PCSK9 inhibitors are effective at controlling LDL-C levels, and when added to statin therapy, there is a further reduction of levels by 60% [101]. This highlights that lipid lowering therapies can greatly reduce the risk of CVD disease, and may provide favorable outcomes in FH COVID-19 patients. It has also been hypothesized that PCSK9 inhibitors can exhibit anti-inflammatory effects through down-regulation of LDL receptors [101]. As discussed, reducing the hyperinflammatory state seen in COVID-19 disease can lower the disease burden. Gain-of-function mutations that cause upregulation of PCSK9 have been recognized in certain FH

patients, and this is thought to suppress the patients' antiviral response. For these reasons, PCSK9 inhibitors are thought to enhance the efficacy of type 1 interferons in the prevention of severe COVID-19 disease and a single initial dose administered in high-risk patients may provide some benefit [102].

Ezetimibe and PCSK9 inhibitors do not appear to have many side effects, and there are no recognized drug interactions with current antiviral therapies [103]. However, there have been concerns over the use of combination therapies involving statins and ezetimibe, with a study in hypercholesterolemic patients showing there is an increased risk of upper respiratory tract infections while on this treatment regimen [104]. Further clinical studies can help address whether this particular combination therapy can exacerbate the severity of COVID-19 disease. PCSK9 inhibitors should be continued in the treatment of poorly controlled hyperlipidemia. Additional data is required from COVID-19 patients receiving this treatment; this will help to better understand the relationship between PCSK9 inhibitors and interferons, and the role they may play in stopping the progression of severe COVID-19 illness.

3.1.6.3. Lomitapide.
Lomitapide is a drug that has been developed for the treatment of FH. Lomitapide is metabolized through the enzyme CYP3A4 and the metabolites lead to the inhibition of microsomal triglyceride transfer protein (MTP). This reduces the secretion of very low-density lipoproteins (VLDL) and thereby can reduce LDL-C levels. This process was seen in a large cohort trial carried out by the Lomitapide Observational Worldwide Evaluation Registry (LOWER) where Lomitapide treatment achieved a 33% mean reduction in LDL-C levels [105]. Lomitapide can therefore provide some benefit in the control of hyperlipidemia in COVID-19 patients. Lomitapide was also found to be an inhibitor of CYP3A4 and so concomitant administration of a strong CYP3A4 inhibitor with Lomitapide is contraindicated [106]. The COVID-19 medications lopinavir and ritonavir can cause increased exposure to Lomitapide systemically and therefore treatment with Lomitapide should be stopped in patients on this treatment regime [107].

3.1.6.4. Fibrates.
Fibrates are PPAR-alpha agonists that can be used in the treatment of hyperlipidemia. They were shown to reduce mortality in mice infected with influenza virus (91), hence, theorized to be able to reduce the inflammatory burden seen in COVID-19 disease. However, there is a lack of human studies displaying the effectiveness of fibrates in the treatment of viral pneumonias. It is recommended that fibrates are continued in COVID-19 patients unless not tolerated by patients or contraindicated with certain COVID-19 treatments. There are drug-drug interactions with fibrates and the Covid-19 medications interferon-beta-1-alpha and tocilizumab, therefore fibrates should be stopped in COVID-19 patients taking these therapies [107]. Fibrates should also be stopped if there is evidence of myopathy, AKI, or transaminitis developing in the COVID-19 patient [108].

3.1.6.5. Nicotinic acid (Niacin).
Niacin is known to reduce the levels of LDL-C and increase HDL-C but there has not been any significant evidence to suggest it can reduce the risk of

cardiovascular events [109]. It may exert anti-inflammatory effects; this is seen in animal models where there was reduced lung damage from hyperinflammatory cascades [110]. However, it is unknown whether these findings would translate into human studies and there are limited data on the effectiveness of niacin in the treatment of COVID-19 CVD patients. There are very little concerns over the safety of niacin use and it may be continued in COVID-19 patients.

3.1.6.6. Omega-3-Fatty acids.
There have been several large-scale studies investigating the impact of the omega-3-fatty acids: docosahexaenoic acid (DHA) eicosapentaenoic acid (EPA), on the prevention of cardiovascular events in high-risk CVD patients. A combination of both DHA and EPA was given to 3851 patients who had experienced an acute myocardial infarction in the OMEGA trial and no further reduction in sudden cardiac death was seen [111]. Another large-scale meta-analysis, REDUCE-IT, found that in CVD patients that were given icosapent ethyl (an ethyl ester of EPA), there was a significant reduction in the risk of cardiovascular events [112]. EPA has been found to exert anti-inflammatory effects through lowering concentrations of C-reactive protein (CRP) and by regulating the effects of pro-inflammatory cytokines (*5). EPA may consequently play a role in controlling the disease severity in COVID-19 patients. Omega-3-fatty acids are thought to be safe to continue in COVID-19 patients.

3.1.6.7. Other therapies.
At present, there is a lack of data that reports any significant outcomes in the use of bile acid sequestrants and nutraceuticals in CVD patients. Further studies are required to understand the potential role they may play in the treatment of CVD in COVID-19 patients.

3.1.7. Anticoagulation and antiplatelets
Many patients infected with SARS-CoV-2 have a severe proinflammatory state linked with characteristic coagulopathy and endotheliopathy [113], with the SARS-CoV-2 endothelial status made distinct by platelet activation, as well as increased levels of Von Willebrand factor and factor VIII [114,115]. Coagulopathy, due to blockage of blood vessels following thrombus formation, is seen in severe SARS-CoV-2 infections as a result of platelet hyperactivity and aggregation [113]. In this context, the protective antiplatelet aggregation role of resveratrol, a polyphenol, can be utilized in the management of SARS-CoV-2 infection, via its various mechanisms of action. One such mechanism involves nitric oxide (NO), a gasotransmitter, which prevents platelet aggregation [116]. By increasing the activity and expression of endothelial nitric oxide synthase, an NO isoform that controls the generation of NO in the endothelium, resveratrol seems to promote NO production, thereby inhibiting platelet hyperactivity and aggregation [117].

As discussed earlier, COVID-19 is associated with a hyperinflammatory and prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers [12,14,15,16,17], as well as proinflammatory cytokines including IL-1, IL-6, and tumor necrosis factor-α

[113]; therefore, the administration of anticoagulation therapy in COVID-19 positive CVD patients must be carefully monitored. Additionally, as indications of drug treatment include prophylaxis against stroke and embolism [5,14,19], it is crucial for patients to be able to continue treatment safely if infected with SARS-CoV-2.

Older oral anticoagulants, such as warfarin, have a propensity for various drug-drug interactions; hence newer direct oral anticoagulants (DOACs) are the preferred therapy [118]. Previous research [119,120] shows that patients on warfarin had a decreased international normalized ratio (INR) after commencement of treatment with lopinavir-ritonavir, the antivirals used in COVID-19. This resulted in a substantial dose adjustment of warfarin (from 5.5 mg/d to 13 mg/d) to maintain an INR between 2 and 3. Although the interaction between the two is not well understood, it appears to be mediated through the alteration of warfarin's CYP2C9 metabolism [121]. Therefore, close INR monitoring is recommended for any CVD patients receiving concomitant anticoagulation and COVID-19 antiviral therapies.

Other interactions include the DOAC anticoagulant drugs apixaban and rivaroxaban, which should not be used alongside the antiviral lopinavir-ritonavir, as it inhibits CYP3A4 which in turn metabolizes apixaban and rivaroxaban, and can increase the risk of bleeding [118,122]. An increased risk of bleeding is also present if dabigatran and edoxaban are used in combination with lopinavir/ritonavir, through P-glycoprotein inhibition by the antivirals [87].

As hospitalized COVID-19 patients are at an increased risk of venous thromboembolism (VTE) [85,123], prophylactic anticoagulation with heparin or enoxaparin has been recommended as it reduces the risk of VTE. The European Society of Cardiology [99] proposed an anticoagulation algorithm for patients with high thrombotic risk – defined as those with dyspnea, oxygen saturation < 90%, respiratory rate > 24, elevated C reactive protein, rising D-dimer levels, and elevated fibrinogen levels; anticoagulation strategies should be considered. Heparin has been shown to bind COVID-19 spike proteins as well as down-regulate IL-6 [85], which is elevated in COVID-19 patients, making it a good choice for prophylactic anticoagulation. However, as there is an increased risk of bleeding associated with the use of these anticoagulants, doses need to be carefully monitored and adjusted according to the patient's condition [113].

Patients that are affected by acute or chronic coronary syndromes, including ST-elevation/non-ST elevation myocardial infarctions, unstable angina, ischemic heart disease, or any other relevant syndrome, will be on antiplatelet therapy to reduce their risk of further CVD events [86]. Certain anti-platelets have interactions with antivirals commonly used in COVID-19. The anti-platelet drug, clopidogrel, can be used as a P2Y12 inhibitor in patients with coagulopathy, provided the patient is not being actively treated for COVID-19 [87]. While lopinavir/ritonavir is being administered, prasugrel is the recommended treatment provided the patient does not have a bleeding risk and is without coagulopathy [86]. Caution should be exercised if either clopidogrel, prasugrel, or ticagrelor are combined with ritonavir, as ritonavir leads to the decrease in antiplatelet activity of clopidogrel and prasugrel by preventing their bioactivation [124], and increases the risk of bleeding if used in combination with ticagrelor [118,125] through the strong inhibition of the CYP3A4 pathway [87]. In cases where these anti-platelet drugs are combined with ritonavir, P2Y12 platelet function assays are recommended to ensure sufficient antiplatelet activity [118], following which the dosage of clopidogrel can be adjusted accordingly [87]. High-quality research is needed to determine whether there are significant drug-drug interactions with other COVID-19 medications such as remdesivir.

3.2. Non-Cardiovascular agents

3.2.1. Corticosteroids

Following the COVID-19 pandemic, corticosteroids have been used as an anti-inflammatory treatment in order to curb lung inflammation in severe cases, with dosage depending on disease severity [106]. Recommendations on the use of corticosteroids for COVID-19 are largely based on data from the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, which is a large, multicenter, randomized, open-label trial performed in the United Kingdom. The trial compared the use of dexamethasone in 2104 hospitalized COVID-19 patients with 4321 patients receiving usual care. They found that use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support [126,127]. Other studies have reported a similar lower mortality rate when critically ill COVID-19 patients with respiratory complications are treated using corticosteroids [128,129,130], but there is limited literature on the effects of using corticosteroid therapy in COVID-19 patients with cardiovascular disease. Also, prior to the RECOVERY data, there was conflicting evidence for the use of corticosteroids in previous coronavirus infections, where use in MERS and SARS was associated with delayed virus clearance [3,4].

In cases where ischemia is the primary condition, the use of corticosteroids to treat heart failure should be avoided as they could increase the risk of mechanical infarction difficulties [87]. If NSAIDs have been contraindicated in a patient with heart failure, corticosteroids at low doses can be used as an anti-inflammatory treatment when combined with colchicine [131]. For severe COVID-19 patients with pericarditis, 0.2–0.5 mg/kg/day of prednisone is administered for up to 1 month [132]. However, in cases of viral myocarditis, more research is required to establish whether myocardial inflammatory response can be lessened following the administration of corticosteroids.

A meta-analysis performed by Tufan et al. [133] mentions improvement following the administration of IV glucocorticoids and immunoglobulin therapy in some patients with acute fulminant myocarditis induced by COVID-19, as they could be effective in reducing inflammation caused by an amplified inflammatory response [134], which could prevent further myocardial injury.

3.2.2. Anti-virals

As the clinical manifestations of COVID-19 are caused by SAR-CoV-2 viral replication, an efficient approach to finding a treatment is to test existing antiviral drugs for their effectiveness against it. These drugs exert their effect by inhibiting viral entry via the ACE2 receptor [135], thereby reducing the viral replication in the earlier stages of the illness, and preventing the hyperinflammation state that categorizes the later stages of disease, including critical illness. For this reason, several drugs [127] previously used in SARS and MERS were tested for their effect on SARS-CoV-2, but so far, only one is approved within the UK and USA – Remdesivir (GS-5734) [136].

Remdesivir is an adenosine analog that introduces itself into viral RNA, acting as an RNA polymerase inhibitor, thereby leading to premature chain termination and viral replication inhibition. It demonstrated successful *in vitro* activity against SARS-CoV-2 [137]. Moreover, in a rhesus macaque model of SARS-CoV-2 infection, the drug-treated animals had lower virus levels in the lungs and less lung damage in comparison to control animals [138]. A study by the US National Institutes of Health [139], with a cohort of 541 COVID-19 patients that received remdesivir, found they recovered faster on average compared to the placebo group; 10 days compared to 15 days. However, the Solidarity trial by WHO [140], including 2,750 patients, found that treatment with remdesivir did not reduce mortality among hospitalized COVID-19 patients. As remdesivir is a relatively new drug, its cardiac toxicity is somewhat unknown and as of yet, clinical drug-drug interaction studies have not been conducted. Current guidelines [141] state that the drug may cause an increase in prothrombin time and lists hypotension as a side-effect, therefore caution must be practiced in those patients on anticoagulant and hypertension medication.

Chloroquine phosphate, and its less toxic derivative hydroxychloroquine, have been used for many years in the treatment of malaria and chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus [142]. They have broad-spectrum antiviral activity, which is achieved through increasing lysosomal pH, therefore inhibiting viral endocytotic cell entry, along with changing the glycosylation process of ACE2 receptors, and thus, preventing viral fusion with host cells [143]. Many *in vitro* studies [137] demonstrated the effectiveness of HCQ in inhibiting SARS-CoV-2, and some early clinical trials backed this up. Chen et al. [144] conducted a randomized control trial with 62 patients where they found 80.6% of those in the drug treatment group showed improvement in pneumonia, compared to only 54.8% of patients in the control group.

However, HCQ has since fallen out of favor with regards to treatment of COVID-19, as it failed to produce any clinically relevant results. In the UK, the RECOVERY trial [145], an ongoing randomized control trial, administered HCQ to 1,561 COVID-19 patients with comorbidities of diabetes mellitus (27%), and heart disease (26%), the results showed that HCQ did not decrease mortality when compared to normal care. Additionally, it resulted in a longer hospital stay, and in patients not already on mechanical ventilation – HCQ treatment made them more likely to require intubation during hospitalization. A separate cohort study did not find any significant reduction in intensive care admission or in development of pneumonia [146]. The SOLIDARITY trial [140] conducted by WHO (954 patients on HCQ with 25% with diabetes) also found no real clinical benefit with use of HCQ in COVID-19. Moreover, HCQ use can have serious implications for cardiovascular patients [147,148], including fatal arrhythmias. Furthermore, the popular combination of administering HCQ with azithromycin for COVID-19 treatment raised questions of safety, as both drugs are known to prolong the QTc interval, thereby increasing the risk of Torsade-de-Pointes.

3.2.3. Other Immunomodulators

3.2.3.1. Interleukin-6 Inhibitors.
As the pro-inflammatory cytokine IL-6 has been implicated to have a dose-dependent relationship with severity of SARS-CoV-2 infection [149], several clinical trials have explored the use of tocilizumab, an anti-IL-6 receptor monoclonal antibody, as a therapy for severe COVID-19 disease [150,151,152,153,154,155]. Tocilizumab is currently an approved drug for use in rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis [156,157]. It has been noted that patients with severe COVID-19 – in particular those within intensive care units – have increased plasma concentrations of inflammatory cytokines (TNF-α, IL-2, 6, 7, and 10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and interferon-γ-inducible protein 10) that are suggestive of a cytokine storm. Cytokine storm syndrome (CSS) is an umbrella term for several disorders of immune dysregulation, characterized by constitutional symptoms, an excessive systemic inflammatory response, and multi-organ failure if untreated [158]. It was hypothesized that IL-6 receptor blockade could reduce the incidence of CSS, and hence the disease severity accredited to it. A meta-analysis of nine studies showed that tocilizumab treatment is associated with reduction of C-reactive protein [155]. Another meta-analysis of 38 studies, including 13,412 COVID-19 patients, showed that tocilizumab treatment is associated with reduction of mortality rate from COVID-19 [154]. However, Roche's Phase III COVACTA trial [159] showed no improvement in clinical status, which was measured as the need for intensive care and/or ventilator use and the requirement for supplemental oxygen over a 4-week period, when compared to the placebo. There was no statistical difference found in mortality rates between tocilizumab and placebo groups (19.7% vs. 19.4%; difference of 0.3%; 95% CI, −7.6% to 8.2%; $P = 0.94$). Even so, a recent systematic review and meta-analysis [158] of 24 studies (5 RCTs and 19 cohorts), which included the COVACTA trial in its analysis, found that tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients. Hence, the evidence for the benefit of tocilizumab in COVID-19 is conflicting, and as of yet no large-scale RCTs have been carried out to ascertain its effectiveness in reducing disease severity.

3.2.3.2. Janus Kinase Inhibitors.
Baricitinib, an anti-inflammatory drug used in rheumatoid arthritis, is the latest drug to be investigated as a possible treatment for COVID-19. The drug is a selective inhibitor of Janus kinase (JAK) 1 and 2, which prevent phosphorylation of key proteins involved in the intracellular signaling pathway leading to activation of proinflammatory cytokines such as IL-6. Additionally, baricitinib has

a theoretical direct antiviral effect where it may block SARS-CoV-2 entry into lung cells [160,161].

There is some clinical trial evidence that supports this theory; the Adaptive Covid-19 Treatment Trial (ACTT-2) [138], an RCT of 1,033 patients with moderate to severe COVID-19, tested baricitinib with remdesivir, against remdesivir with a placebo. The results showed that Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, notably among those receiving high-flow oxygen or noninvasive ventilation. Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a recovery time of 10 days with combination treatment, and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group, and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09) [162].

Although the survival rate was numerically better in the baricitinib treated group, the use of glucocorticoids was avoided in the trial, and it was not large enough to detect differences in mortality, hence further randomized evidence is needed to establish the value of baricitinib in current clinical practice. Thus, the RECOVERY group [163] have announced the addition of baricitinib to their trial, and anticipate at least 2,500 patients to be recruited. The RECOVERY trial aims to research the effect of baricitinib, in addition to corticosteroids (steroids), which are now standard of care for severe COVID-19 worldwide.

3.2.4. Ivermectin (Anti-parasitic)

Ivermectin is a cheaply available broad-spectrum anti-parasitic agent that is a topic of widespread contention. In humans, Ivermectin is currently prescribed in tablet form to treat certain roundworm infections and the inflammatory skin condition rosacea. In 2020, Caly et al. [164] found that Ivermectin is an inhibitor of SARS-CoV-2 in-vitro and though the mechanism is unknown, it is hypothesized to work by disinhibiting the virus's evasion tactics from the host immune cells and thus abrogate sufficient viral replication and allow the host to clear it. Another suggested mechanism is the suppression of the production of Interleukin-6 (IL-6) and Tumor Necrosis Factor alpha (TNFα), two major components of the detrimental cytokine storm induced by SARS-CoV-2 [165].

The results from Caly et al. [164], combined with other in silico and in vitro studies that suggested the same, led to a considerable amount of protocols in Latin America that recommended use of Ivermectin as a COVID-19 treatment. However, as these results were not peer shared, their dissemination caused confusion and the spread of misinformation online claiming it is a COVID-19 cure [166]. Many countries heavily contest the benefit of the drug and some have described its use as being politicized. Both the Food and Drug Administration (FDA) of the United States and European Medicines Agency (EMA) have advised against its use, stating insufficient evidence for any benefit [166]. It has been highlighted that the required concentration of 5 μM to reach the anti-SARS-CoV-2 action of Ivermectin observed in vitro is fifty-fold higher than the current FDA-approved dosage (200 μg/kg) [165,166]. Hence, this may explain why it was not included in large-scale clinical trials such as the

Solidarity trial [166]. It was included in a few smaller trials that have been summarized by Wehbe at al [165]. where they found that the clinical data lacks uniformity and the optimal antiviral dose has not been established. They have also highlighted that Ivermectin on its own did not result in significantly improved outcomes for COVID-19 patients and nor should it be particularly encouraged as a monotherapy. However, some success has been found in these smaller trials. A recently published study by Samaha et al. [145] found a single dose of ivermectin (150 μg/kg) in 50 patients resulted in fewer clinical symptoms, lower viral loads, and reduced hospital admission, in comparison to the 50 patients in the control group. Another meta-analysis [167] of 19 studies with 2768 patients showed that ivermectin was associated with reduced severity of COVID-19 (RR 0.43 [95% CI 0.23–0.81], p = 0.008), with reduction of mortality, higher negative RT-PCR test results rate, higher symptoms alleviation, and shorter time to discharge. Although, it must be noted that the trials included in this meta-analysis have small treatment groups (31–400 patients) and most are open-label randomized control trials. Hence, there is conflicting information about this drug but it should not be ruled out as a potential treatment, as researchers have shown it does have some benefit, but currently lacks large-scale clinical trials to support it. It will be interesting to note the ivermectin clinical trials in the upcoming year and how they pan out.

3.3. Clinical Trials

Currently, there are over 5,000 trials registered on Clinicaltrial.gov that are researching the therapeutic benefits of preexisting drugs in the treatment of COVID-19. Some of the largest trials are highlighted in Table 2 and Table 2b, including the RECOVERY trial (ClinicalTrials.gov Identifier: NCT04381936), World Health Organization (WHO) COVID-19 Solidarity Trial for COVID-19 Treatments (ClinicalTrials.gov Identifier: NCT04647669), and the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial (ClinicalTrials.gov Identifier: NCT02735707). The early drugs of interest in 2020 were the anti-virals lopinavir/ritonavir, hydroxychloroquine, and remdesivir. However, data from the RECOVERY [168] and SOLIDARITY [140] trial showed that treatment with these drugs had little or no effect on hospitalized COVID-19 patients, as indicated by overall mortality, initiation of ventilation, and the duration of hospital stay. The newer drugs of interest are the ones discussed earlier: IL-6 inhibitors and JK-inhibitors, such as tocilizumab and baricitinib respectively. As of February 2021, tocilizumab showed promising results in the RECOVERY trial [168], as well as in [169] the REMAP-CAP [170] trials. Both have reported better patient outcomes in terms of mortality (Table 2b).

As discussed in the anti-coagulation section, hospitalized COVID-19 patients are at an increased risk of life-threatening VTE [171]. It has been hypothesized that full-dose anticoagulation in these patients could have some therapeutic benefits in reducing overall clots and associated mortality. Therefore, an unprecedented collaboration between three clinical trial platforms has formed to carry out a multiple platform RCT to explore this. The three platforms include: REMAP-CAP trial,

Table 2. Summary of large clinical trials studying repurposed drugs for use in COVID-19

Clinical Trials	Trial Details	Primary Outcome	Secondary Outcome	Lopinavir/ritonavir Intervention	Lopinavir/ritonavir Results	Corticosteroids* Intervention	Corticosteroids* Results	Chloroquine and hydroxychloroquine Intervention	Chloroquine and hydroxychloroquine Results
RECOVERY Trial (Registered at ISRCTN50189673 Clinical Trials.gov: NCT04381936 [105,141,142]	Participants: 39,636 Sites: 181 Study Type: Interventional (Clinical Trial) Start: 19 March 2020 Primary Completion: December 2021 (estimated) Study Completion: December 2031 (estimated)	All-cause mortality [Time Frame: Within 28 days after randomisation]	(1) Duration of hospital stay (2) Composite endpoint of death or need for mechanical ventilation or ECMO [Time Frame: Within 28 days and up to 6 months after the main ran-domisation]	Dose: Lopinavir 400mg-Ritonavir 100mg every 12 hours for 10 days. Route: Oral (or nasogastric tube) Drug group: 1596 patients Standard care: 3376 patients	There was no significant difference in the primary endpoint of 28-day mortality. No evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay [141]	Dose: Dexamethasone 6mg once daily for 10 days Route: Oral (liquid or tablets) or intravenous Drug group: 2104 patients Standard care: 4312 patients	Dexamethasone reduced deaths by one-third in ventilated patients and by one fifth in other patients receiving oxygen only. There was no benefit among those patients who did not require respiratory support [105]	Dose: HCQ 400mg every 12 hours (not including loading dose of 800mg) for total of 9 days or until discharge Route: Oral Drug group: 1561 patients Standard care: 3155 patients	There was no significant difference in the primary endpoint of 28-day mortality. No evidence of beneficial effects on hospital stay duration or other outcomes [141].
SOLIDARITY Trial (Registered at ISRCTN83971151 Clinical Trials.gov NCT04315948 [118]	Participants: 11,266 Sites: 405 Study Type: Interventional (Clinical Trial) Start: 22 March 2020 Primary/Study Completion: 25 March 2021	All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study [Time Frame: Day 15]	Measured using patient (1) Duration of hospital stay (hours) (2) Time to first receiving ventilation (or intensive care) (hours)	Dose: Lopinavir 200mg-Ritonavir 50mg every 12 hours for 14 days Route: Oral Drug group: 1411 patients Standard care: 4088 patients					

(Continued)

Table 2. (Continued).

Clinical Trials	Trial Details	Primary Outcome	Secondary Outcome	Lopinavir/ritonavir		Corticosteroids*		Chloroquine and hydroxychloroquine	
				Intervention	Results	Intervention	Results	Intervention	Results
Lopinavir appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay [118].			Dose: 200mg HCQ tablets. Hour 0, four tablets; Hour 6, four tablets; Hour 12, begin two tablets twice daily for 10 days. Route: Oral Drug group: 954 patients Standard care: 4088 patients	HCQ appeared to have little or no effect on	hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay [118].				
REMAP-CAP Trial (ClinicalTrials.gov Identifier: NCT02735707) [143]	**Participants:** 12,631 **Sites:** 310 **Study Type:** Interventional (Clinical Trial) **Start:** 11 April 2016 (Originally a trial for CAP) **Primary Completion:** December 2021 **Study Completion:** December 2023	All-cause mortality [Time Frame: Day 90] Days alive and not receiving organ support in ICU [Time Frame: Day 21] Superiority was defined as the posterior probability of an OD >1 (threshold for trial Frame: Day 28 conclusion of superiority >99%)	(1) ICU Mortality [Time Frame: Day 90] (2) ICU length of stay [Time Frame: Day 90] (3) Hospital length of stay [Time Frame: Day 90] (4) Ventilator free days [Time Frame: Day 28] (5) Organ failure free days [Time Frame: Day 28] (6) All-cause mortality [Time Frame: 6 months]	Protocol found on Clinicaltrials.gov but no results published		Dose: Fixed-dose group - IV hydrocortisone 50mg every 6 hours for 7 days (n=137) Shock- dependent group -IV hydrocortisone, 50 mg, every 6 hours while in shock for up to 28 days (n=146) Route: Intravenous Drug group: 283 patients Standard care: 101 patients	Hydrocortisone treatment (fixed-dose and shock-dependent) compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support–free days within 21 days. The trial was stopped early due to dexamethasone results of RECOVERY trial [143].	Protocol found on Clinicaltrials.gov but no results published.	

Abbreviations: COVID-19, Coronavirus Disease 2019; HCQ, Hydroxychloroquine; ECMO, extracorporeal membrane oxygenation; IV, intravenous; CAP, Community Acquired Pneumonia; LD, Loading dose; ICU, Intensive Care Unit; OR, Odds Ratio.
*Dexamethasone and hydrocortisone

Table 2b. Summary of large clinical trials studying repurposed drugs for use in COVID-19

Clinical Trials	Trial Details	Primary Outcome	Secondary Outcome	Tocilizumab		Baricitinib		Remdesivir	
				Intervention	Results	Intervention	Results	Intervention	Results
RECOVERY Trial (Registered at ISRCTN50189673, Clinical Trials. gov: NCT04381936) [105,141,142]	**Participants:** 39,636 **Sites:** 181 **Study Type:** Interventional (Clinical Trial) **Start:** 19 March 2020 **Primary Completion:** December 2021 (estimated) **Study Completion:** December 2031 (estimated)	All-cause mortality [Time Frame: Within 28 days after randomisation]	(1) Duration of hospital stay (2) Composite endpoint of death or need for mechanical ventilation or ECMO [Time Frame: Within 28 days and up to 6 months after the main randomisation]	Dose: determined by body weight Route: Intravenous infusion Drug group: 2022 patients Standard care: 2094 patients	Treatment significantly reduced deaths: 596 (29%) of the patients in the tocilizumab group died within 28 days compared with 694 (33%) patients in the usual care group, an absolute difference of 4% [142].	Dose: 4mg once daily for 10 days Route: Oral or		nasogastric tub Drug group: 2500 (target) Standard care: 2500 (target)	Currently being tested no preliminary results yet
SOLIDARITY Trial (Registered at ISRCTN8397151, Clinical Trials.gov NCT04315948) [118]	**Participants:** 11,266 **Sites:** 405 **Study Type:** Interventional (Clinical Trial) **Start:** 22 March 2020 **Primary/Study Completion:** 25 March 2021	All-cause mortality,subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study [Time Frame: Day 15]	Measured using patient records: **1.** Duration of hospital stay (hours) **2.** Time to first receiving ventilation (or intensive care (hours)					Dose: Day 0, 200mg; days 1-9, 100mg. Route: Intravenous Drug group: 2750 patients Standard care: 4088 patients	Remdesivir appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay [118].

(Continued)

Table 2b. (Continued).

Clinical Trials	Trial Details	Primary Outcome	Secondary Outcome	Tocilizumab Intervention	Tocilizumab Results	Baricitinib Intervention	Baricitinib Results	Remdesivir Intervention	Remdesivir Results
REMAP-CAP Trial (ClinicalTrials.gov Identifier: NCT02735707) [143]	**Participants:** 12,631 **Sites:** 310 **Study Type:** Interventional (Clinical Trial) **Start:** 11 April 2016 (Originally a trial for CAP) **Primary Completion:** December 2021 **Study Completion:** December 2023	All-cause mortality [Time Frame: Day 90] Days alive and not receiving organ support in ICU [Time Frame: Day 21] Superiority was defined as the posterior probability of an OD >1 (threshold for trial conclusion of superiority >99%)	(1) ICU Mortality [Time Frame: Day 90] (2) ICU length of stay [Time Frame: Day 90] (3) Hospital length of stay [Time Frame: Day 90] (4) Ventilator free days [Time Frame: Day 28] Organ failure free days [Time Frame: Day 28] (5) All-cause mortality [Time Frame: 6 months]	Dose: Tocilizumab 8mg per kg of actual body weight (max 800mg) Route: Intravenous infusion Drug group: 353 patients Standard care: 402 patients	Median adjusted cumulative OR was 1.64 (95% CI, 1.25 to 2.14) for tocilizumab, resulting in >99.9% probabilities of superiority to control. In critically ill COVID-19 patients receiving organ support in ICUs,drug treatment improved outcomes, including survival [143].				Protocol found on Clinicaltrials.gov but no results published.

Abbreviations: COVID-19, Coronavirus Disease 2019; HCQ, Hydroxychloroquine; ECMO, extracorporeal membrane oxygenation; IV, intravenous; CAP, Community Acquired Pneumonia; LD, Loading dose; ICU, Intensive Care Unit; OR, Odds Ratio.

Antithrombotic Therapy to Ameliorate Complications of COVID-19 trial (ATTACC; ClinicalTrials.gov Identifier: NCT04372589), and Antithrombotics for Adults Hospitalized With COVID-19 (ACTIV IV-4a; ClinicalTrials.gov Identifier: NCT04505774). The multicentre RCT intervention [172,173] includes the administration of therapeutic low molecular weight heparin (LMWH) or unfractionated heparin (UFH) to hospitalized COVID-19 patients of varying disease severity and comparing this to the usual pharmacologic VTE prophylaxis in the control group. Some preliminary results showed favorable outcomes, but as the data is not yet peer reviewed or published, it is too early to base clinical decisions on it.

Another more recent method to identify therapeutic drug targets for clinical trials is via Mendelian randomization (MR) analyses, as done so by Gaziano et al. [173]. Through investigating more than 1,000 potential targets using several of the largest currently available human genetic datasets, they provided evidence for drug targets of type I IFNs (IFNAR2) and ACE2 modulators (ACE2) as priority candidates for evaluation in randomized trials of early management in COVID-19. We are yet to see whether such analysis will prove beneficial in finding a treatment for COVID-19 but it does demonstrate a focused approach to choose drugs for future COVID-19 clinical trials.

4. Conclusion

Research is ever growing in understanding the correlation between cardiovascular diseases in patients with COVID-19, and the use of pharmacological interventions with these patients. Many recent studies indicate a slight benefit of using RAS inhibitors in COVID-19 patients, potentially due to the pulmonary vasodilation leading to increased lung protection. However, the mechanisms by which RAS inhibitors provide protection against the virus is not fully understood. Moreover, several classes of beta-blockers have been found to downregulate the impact of coronavirus via different mechanisms, and are thus recommended to be continued, unless the patient experiences differentiative side effects. There is a need for larger studies to compare the outcomes between different categories of pharmaceutical interventions in patients with COVID-19 who have underlying cardiovascular diseases.

5. Expert opinion

Current evidence is evolving around the many trialed pharmacotherapeutic considerations for the management of coronavirus infection 2019 (COVID-19) in patients with cardiovascular diseases. The key findings of the preliminary research to date suggest consideration of RAS inhibitors as an adjuvant treatment to those patients who have tested positive for SARS-CoV-2 infection as a potential protectant due to increased pulmonary vasodilation. While some evidence suggests they may lead to worse patient outcomes and a more severe disease, hypothetically their effect of increasing the soluble form of ACE2 in the circulation could serve as a decoy receptor that binds to SARS-CoV-2 virus and deactivate it within the peripheral circulation, thus helping clear the virus. As a result, current recommendations from specialist medical associations are consistent in advocating no changes in the treatment guidance with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists for cardiac patients infected with SARS-CoV-2 virus.

In addition, there is also promising evidence that some beta-blockers may also provide a beneficial effect to COVID-19 patients. Patients with COVID-19 can suffer from many clinical changes, including inflammation, due to the SARS-CoV-2 virus' disruption to the body's immune system. Beta-2 receptor antagonists could potentially reduce this inflammation and help rebalance the immune system. Moving forward, the beta-2-adrenergic pathway may be further investigated as a possible target to reduce the inflammatory symptoms related to COVID-19. This is thought to be a potential area of interest due to the mechanism of action of beta blockers, which causes a temporary blockade of noradrenaline, diminishing the body's innate 'fight or flight' response. This reduces the stress and therefore workload of the areas in which there are active receptors, such as the vasculature and heart.

Both the hypotheses of using ACEi/ARBs and beta blockers require further study to fully understand the mechanisms of action in the pathophysiology of the SARS-CoV-2 virus.

Drug-induced cardiac myocyte death occurring during SARS-CoV-2 treatment is also a concern. In particular, the use of antiviral drugs should be closely examined. Many antiviral drugs can cause cardiac insufficiency, arrhythmia, and other cardiovascular disorders. The risk of cardiac toxicity must be monitored when antivirals are used.

A further area of research may include the effect of media reports from the beginning of the pandemic, which stated taking certain blood pressure drugs could modify levels of receptors on the surface of our body's cells, thereby making it easier for someone to contract the SARS-CoV-2 virus. Interestingly, these antihypertensives include ACE inhibitors and ARBs. These reports were based on speculation, and there is no evidence to support them. Likewise, there was media speculation that suggested taking ibuprofen, an NSAID, could be associated with a greater risk of a more complex SARS-CoV-2 viral infection. Once again, the evidence base was unfounded and no such association has been established between taking ibuprofen and contracting the SARS-CoV-2 virus, or the resulting development of more severe symptoms. In fact, more recently researchers have been trialing the potentially advantageous anti-inflammatory effects of ibuprofen, which may bring about a benefit in treating those with the SARS-CoV-2 virus by reducing injury. At the time of publication, the evidence base for the use of this treatment is extremely limited.

The potential implications of this research may ultimately allow for the better treatment and outcome of mortality of those patients who contract SARS-CoV-2 with underlying cardiovascular disease. The obvious weaknesses of the research are that we are still retrospectively and prospectively analyzing the data of those affected by the SARS-CoV-2 virus pandemic, and conducting clinical trials based on the theoretical potential benefit these novel therapy options may bring to those affected by SARS-CoV-2.

The ultimate goal of any further research in this field must be to ensure the continued safety and efficacy of treatment of

patients with cardiovascular disease with understanding of the potential implications this may have as and when members of this cohort become unwell with SARS-CoV-2 virus.

We are particularly intrigued by the potential beneficial roles that ACE inhibitors, ARBs, and beta blockers may have in the future treatment of the SARS-CoV-2 virus, due to the high percentage of cardiovascular patients receiving one or more of these drugs. Clinical trials exploring the alternative therapies that may be beneficial in treating the SARS-CoV-2 virus must now be performed. We envisage the research to develop further in the coming months, and for the resultant outcome to include evidence-based trials focusing on ACEi, ARBS, beta blocking agents, and NSAIDs; medications which have been, and continue to be, used for many years with a wealth of evidence base in their currently licensed indications.

While we await further data to inform our practice, clinicians should advocate careful consideration of all concomitant medications and comorbidities for those presenting with SARS-CoV-2 on a patient-by-patient basis.

Declaration of interest

Reviewer disclosures

Abbreviations

COVID-19, Coronavirus Disease 2019; HCQ, Hydroxychloroquine; ECMO, extracorporeal membrane oxygenation; IV, intravenous; CAP, Community Acquired Pneumonia; LD, Loading dose; ICU, Intensive Care Unit; OR, Odds Ratio.

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