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REVIEW ARTICLE

A Double-Edged Sword—Cardiovascular Concerns of Potential Anti-COVID-19 Drugs

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Abstract
Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 significantly affects multiple systems including the cardiovascular system. Most importantly, in addition to the direct injury from the virus per se, the subsequent cytokine storm, an overproduction of immune cells and their activating compounds, causes devastating damage. To date, emerging anti-SARS-CoV-2 treatments are warranted to control epidemics. Several candidate drugs have been screened and are currently under investigation. These primarily include antiviral regimens and immunomodulatory regimens. However, beyond the anti-SARS-CoV-2 effects, these drugs may also have risks to the cardiovascular system, especially altering cardiac conduction. Herein, we review the cardiovascular risks of potential anti-COVID-19 drugs.

Keywords COVID-19 · SARS-CoV-2 · Potential cardiotoxicity · Complications

Introduction

Although there are lacking drugs evident for treating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), scientists remain attempting to identify those with therapeutic potential [1]. Among the worldwide emerging clinical trials, Solidarity is an international clinical trial searching for an effective Coronavirus disease 2019 (COVID-19) treatment launched by the World Health Organization and its partners [2, 3]. The trial intends to rapidly evaluate the potential efficacy of thousands of existing antiviral and anti-inflammatory agents that are not yet approved for treating COVID-19, a process called "repurposing" or "repositioning" [2]. Notably, in case reports, hydroxychloroquine (HCQ) has been regarded as an effective regimen reducing the copy number of SARS-CoV-2 [4, 5], but HCQ is also known for its cardiotoxicity [6–8]. In this article, we summarize the updated drugs that are currently regarded as potential anti-SARS-CoV-2 regimens and the documented cardiovascular risks.

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Antiviral Drugs

Remdesivir

Mechanisms By reducing viral replication and binding to the active site on RNA polymerase of SARS-CoV-2, remdesivir has been viewed as one of the most potentially effective regimens [9]. It has been approved for the treatment of Ebola, respiratory syncytial virus (RSV), Junin virus, Lassa fever virus, Nipah virus, Hendra virus, and the coronaviruses (including MERS and SARS viruses) [9, 10]. According to a case report in the New England Journal of Medicine (NEJM), a patient recovered post remdesivir [11]. However, it may be much more potent if given early in infection.

Currently, Gilead Sciences is launching several clinical trials to evaluate its effect in patients with moderate or severe COVID-19 compared with those treated with standard care. On April 10, 2020, the company announced it was expanding the enrolled number and changing the end points and subsequently released the preliminary report in the *NEJM* [12]. Of 53 patients who received at least one dose of remdesivir, 36 (68%) had improved oxygen support, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated during a median follow-up of 18 days. A total of 25 patients (47%) were discharged, and 7 (13%) died. Overall, the mortality was 18% (6 of 34) among patients who received invasive ventilation and 5% (1 of 19) among those who did not. Although 68% of the patients demonstrated clinical improvements, the major weakness of this study was a lack of placebo and the non-randomized study design. Further investigation is urgently required.

Drug Interactions As a prodrug, remdesivir is predominantly metabolized by hydrolase activity [10]. It is also a substrate of CYP2C8, CYP2D6, and CYP3A4 in vitro but given its rapid distribution, metabolism, and clearance, coadministration with inhibitors of these CYP isoforms is unlikely to increase remdesivir levels.

Cardiovascular Risks While extensive cardiovascular toxicities and drug interactions have not yet been reported, prior evaluations of this drug during the Ebola outbreak noted that one patient developed hypotension and subsequent cardiac arrest. [13] However, the current evidence indicates that high doses of the drug might be administered without documented cardiotoxicities.

Atazanavir

Mechanisms Using a deep learning-based drug-target interaction model called molecular transformer-drug target interaction (MT-DTI), atazanavir, an analog of the peptide chain substrate approved for the treatment of HIV, has the potential to prevent the pro-form of SARS-CoV-2 proteins cleaving into the working form. In recent in vitro experiments, atazanavir inhibited SARS-CoV-2 replication and pro-inflammatory cytokines [14]. Clinical trials have been launched to evaluate its anti-SARS-CoV-2 effect [15].

Drug Interactions As an inhibitor of CYP3A4 and UGT1A1 and a strong inhibitor of OATP1B1, atazanavir may increase the plasma concentrations of other drugs such as proton-pump inhibitors, antacids, and H2-receptor antagonists. Statins such as simvastatin and atorvastatin are also known as *CYP3A4* isoenzyme substrates [16].

Cardiovascular Risks Dose-related asymptomatic prolongation in the PR interval with atazanavir has been observed in clinical studies [17, 18]. It should be used with caution as prescribed with medicinal products that have the potential to increase the QT interval and/or in patients with preexisting risk factors (bradycardia, long congenital QT, and electrolyte imbalances) [19].

Ritonavir/Lopinavir

Mechanisms Ritonavir/lopinavir, a combination drug also called Kaletra, was approved in USA in 2000 to treat HIV infection [20]. With the capability to inhibit the protease of HIV, an important enzyme that cleaves a long protein chain into peptides during the assembly of new viruses, ritonavir/lopinavir may also be able to bind SARS-CoV-2 3C-like proteinase (3CLpro) and consequently suppress its replication [21]. Although ritonavir/lopinavir has been tested in patients diagnosed with SARS or MERS, the results were indeterminate [22, 23]. In the first randomized and open-label trial conducted in China among 199 COVID-19 patients treated with ritonavir/lopinavir, no differences were reported compared with the standard care regarding clinical improvements and mortality at 28 days [24]. The percentages of patients with detectable viral RNA at various time points were similar. However, the authors indicated that the overall mortality in this trial (22.1%) was substantially higher than the 11 to 14.5% mortality reported in initial descriptive studies of hospitalized patients infected with SARS-CoV-2 [24]. This implied that the enrolled patents had severe illness or the initiation of ritonavir/lopinavir therapy was too late to reverse the situation. Several ongoing trials continue to investigate the therapeutic effects of ritonavir/lopinavir on SARS-CoV-2 [15, 24, 25].

Drug Interactions Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by CYP3A [20, 26]. It also inhibits drug transporters such as P-gp, BCRP, and OATP1B1 [20]. Thus, ritonavir/lopinavir is prone to increase plasma concentrations of medications primarily metabolized by CYP3A or substrates of these drug transporters. Ritonavir/lopinavir may require dose reductions or avoidance of CYP3A-mediated drugs such as rivaroxaban and apixaban. Ritonavir/lopinavir can also influence the activity of P2Y12 inhibitors through CYP3A4 inhibition, which results in decreased serum concentrations of the active metabolites of clopidogrel and prasugrel and increased serum concentrations of ticagrelor. The VerifyNow P2Y12 assay may be used to monitor the effect of antiplatelet agents [27]. Other agents metabolized by CYP3A are statins. Among them, rosuvastatin undergoes minimal metabolism by CYP450, so no CYP450-based interaction with lopinavir/ritonavir is expected. Otherwise, atorvastatin, pravastatin, and pitavastatin can also be considered at a low starting dose.

Cardiovascular Risks Ritonavir/lopinavir has been shown to cause QT and PR interval prolongation in some healthy adults [28, 29]. There were rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and preexisting conduction system abnormalities [30].

Favipiravir

Mechanisms Due to its competitive inhibition of the RNA-dependent RNA polymerase, favipiravir was approved to treat influenza [31]. Although one report showed shorter viral clearance durations and improved chest imaging in patients diagnosed with COVID-19 compared to controls [32], less preclinical support has been established. To date, patients have been recruited to evaluate the efficacy of favipiravir plus interferon-α in China (ChiCTR2000029600) [33]. Based on the anticipated synergistic effect of viral inhibition and immune enhancement, a randomized control trial (THDMS-COVID-19) combining various regimens including protease inhibitors, oseltamivir, favipiravir, and hydroxychloroquine was initiated to test whether the cocktail formula is effective for treating COVID-19 [34].

Drug Interactions Favipiravir is primarily metabolized by aldehyde oxidase and is not involved in CYP isoenzymes [35]. Thus, drug interactions are minimal.

Cardiovascular Risks The QT interval prolongation risk of favipiravir is considered to be low [36].

Ribavirin

Mechanisms Similar to remdesivir, ribavirin functions as an RNA-dependent RNA polymerase inhibitor and is approved for the treatment of RSV and HCV [37]. Although ribavirin was recommended for COVID-19 treatment according to Chinese guidelines, it lacks solid evidence [38]. Currently, an open-label randomized controlled trial on lopinavir/ritonavir, ribavirin, and interferon-β1b combination vs lopinavir/ritonavir alone is ongoing to evaluate the therapeutic effects on COVID-19 [25].

Drug Interactions Ribavirin is metabolized by a reversible phosphorylation pathway or a degradative pathway involving de-ribosylation and amide hydrolysis [39]. It does not inhibit cytochrome P450 enzymes. Therefore, there is minimal potential for P450 enzyme-based interactions. However, case reports showed that ribavirin has variable effects on warfarin dosing [40]. The detailed mechanism has yet to be elucidated.

Cardiovascular Risks No effect on the QT interval was observed in patients receiving ribavirin.

Ivermectin

Mechanisms Ivermectin causes an influx of Cl ions through the cell membrane that results in hyperpolarization of ion channels, leading to muscle paralysis [41]. It is approved for the treatment of head lice, scabies, strongyloidiasis, trichuriasis, ascariasis, and lymphatic filariasis [42, 43]. Beyond its anti-parasite effects, ivermectin has also been identified as an inhibitor of interactions between the human HIV integrase protein and the importin α/β 1 heterodimer [44, 45]. Notably, studies on SARS-CoV proteins have revealed a potential role of importin α/β 1 during infection [45]. Nuclear transport of viral proteins is essential for the replication cycle and inhibition of the host's antiviral response [45]. An in vitro study showed that a single ivermectin treatment reduced SARS-CoV-2 by 5000-fold at 48 h in cell culture [45]. However, there is a lack of clinical evidence.

Drug Interactions Ivermectin should be considered an inducer of several cytochrome P450 isoenzymes, including CYP1A, 2B, and 3A subfamilies [46].

Cardiovascular Risks Tachycardia, orthostatic hypotension, and PR interval prolongation have been documented in case reports [47, 48].

Immune-Modulating Drugs

Hydroxychloroquine (HCQ; Plaquenil)

Mechanisms Hydroxychloroquine has actions, pharmacokinetics, and metabolism similar to those of chloroquine [49]. As an anti-malarial and anti-autoimmune agent, by sequestering protons in lysosomes, HCQ increases the intracellular pH in antigen-presenting cells, which is required for virus/cell fusion [50]. It was also shown to suppress the replication of SARS-CoV by interfering with the glycosylation of its cellular receptor ACE2 [51]. Recent in vitro testing revealed its ability to effectively reduce the viral copy number of SARS-CoV-2 [52]. Several small-scale clinical trials demonstrated various degrees of therapeutic effects of HCQ for treating COVID-19-associated pneumonia [53, 54]. A small open-label non-randomized clinical trial in France demonstrated a positive effect of HCQ in combination with azithromycin [5]. Upon this finding, although the US FDA issued an Emergency Use Authorization for hydroxychloroquine in treating COVID-19, the trial design has been questioned. Most importantly, a high dose of HCQ could cause serious toxicities including cardiomyopathy and fatal arrhythmia [7, 8].

Drug Interactions Chloroquine and HCQ undergo CYP-mediated metabolism by CYPs 2C8, 3A4, and 2D6 [50].

Caution may be required when coadministering co-medications metabolized or transported by these pathways such as beta-blockers [55].

Cardiovascular Risks HCQ has an inhibitory effect on the funny current channels (I_f), a hyperpolarization-activated current ion channel, along with delayed rectifier potassium currents (I_{Kr}) and L-type calcium ion currents (I_{CaL}) [55]. By blocking these channels, HCQ causes QT prolongation and should be avoided with concomitant QT-prolonging medications such as azithromycin, metabolic derangements, and renal failure [55]. Of note, hydroxychloroquine has a long half-life of 40 days [56]. ECG monitoring is recommended during this therapy. HCQ also has the potential for intermediate to delayed myocardial toxicity [8]. Prolonged exposure (> 3 months) or a higher weight-based dose of HCQ may cause restrictive or dilated cardiomyopathy, especially in patients with preexisting cardiac disease or renal failure [8]. On April 11, 2020, the *Wall Street Journal* reported that since March 27, the Pharmacovigilance Center in Nice, France, received up to 54 cases developing cardiovascular complications post-hydroxychloroquine use for the treatment of COVID-19 [57].

Tocilizumab

Mechanisms The rapid development of ARDS in patients diagnosed with COVID-19 may not be primarily due to SARS-CoV-2 per se but the cytokine storm [58]. Interleukin (IL)-6 is one of the most important pro-inflammatory cytokines [58]. Hence, specific blockade of the IL-6-regulated signaling pathways represents a promising approach to attenuate inflammation-associated damage [59]. Tocilizumab is an antihuman interleukin 6 (IL-6) receptor monoclonal antibody approved for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis [60, 61]. In a recently published study of 15 patients with COVID-19, tocilizumab combined with methylprednisolone ameliorated increased CRP and IL-6, but the result was insufficient to support its therapeutic effects [62]. Upon the recently launched randomized, double-blind, placebo-controlled phase III clinical trial called COVACTA, the safety and efficacy of intravenous tocilizumab in hospitalized adult patients with severe COVID-19 pneumonia will be compared with placebo in addition to the standard of care [63].

Drug Interactions Tocilizumab has no inhibitory effects on cytochromes. However, tocilizumab reverses IL-6 induced suppression of cytochromes and the elevation of IL-6 during inflammation has been shown to inhibit CYP3A4, CYP2C19, CYP2C9, and CYP1A2 expression, resulting in higher exposure of substrate drugs [64].

Cardiovascular Risks No clinically significant effect on QT prolongation was observed in healthy subjects at therapeutic doses. Some patients taking tocilizumab experienced rapid increases in blood pressure and low-density lipoprotein cholesterol [65]. However, according to the findings of the ENTRACTE study that compared the cardiovascular safety in patients with rheumatoid arthritis receiving either tocilizumab or etanercept [66], there were no significant increases in stroke, heart attack, heart failure hospitalization, or cardiac death.

Interferon-β

Mechanisms Type 1 interferons (IFN-I) play a major role in antiviral immunity [67]. Because of their immunomodulatory properties, IFN-β is used to treat many diseases, including multiple sclerosis [68]. When used alone or in combination with other drugs, IFN-I exerts a broad-spectrum antiviral effect against HCV, RSV [69]. This study showed that IFN-I can be used as a prophylaxis against SARS-CoV-2, which was confirmed by the in vitro efficacy of interferon pretreatment against the virus [70], while the replication of MERS-CoV [71] and SARS [72] was reported to be indifferent to IFN-I prophylaxis. Trials are now focusing on the safety and efficacy for treating COVID-19 pneumonia [73]. SOLIDARITY will also have an arm that combines the two antivirals with interferon-beta, a molecule involved in regulating inflammation in the body that has also shown an effect in marmosets infected with MERS [3].

Drug Interactions It reduces the activity of hepatic cytochrome P450-dependent enzymes [74].

Cardiovascular Risks No clinically significant effects on QTc prolongation have been observed. Only rare case reports showed premature ventricular captures and atrioventricular *block* [75].

Fingolimod (FTY-720)

Mechanisms Fingolimod is an oral immunomodulating agent that is primarily used to treat refractory multiple sclerosis [76]. By structurally resembling the lipid sphingosine-1-phosphate (S1P), fingolimod can act as a highly potent functional antagonist of S1P1 receptors in the lymph node T cells [76]. Similar to the immunomodulatory properties of IFN-I, fingolimod is regarded as a method of treating the SARS-CoV-2 triggered overactivation of immune responses [77]. A non-randomized and open-label study is preparing to evaluate the efficacy of fingolimod for treating COVID-19 [78].

Drug Interactions Fingolimod is primarily metabolized by CYP4F2 [79]. Since few drugs are metabolized by CYP4F2,

Table 1 The cardiovascular risks of potential anti-COVID-19 drugs

Drugs	Pharmacologic mechanism	Evidences of anti-COVID-19	FDA approved Indications	Clinical trials for COVID-19#	CV drug interactions	Cardiovascular risks	Other organ toxicity	Ref.
Anti-viral drugs								
Remdesivir	A nucleotide prodrug, transforming to adenosine analogue, causing RNA pre-mature termination and inhibiting viral replication	• Reducing viral copy numbers in SARS-CoV-2 and binding to the active site on RNA polymerase of SARS-CoV-2	RSV, Junin virus, Nipah virus, Hendra virus, and research on Ebola virus	NCT04302766 NCT04280705 • NCT04292730; NCT04292899*	A substrate of CYP2C8, CYP2D6, CYP3A4, and transporters OATP1B1 and P-gp but due to rapid distribution, metabolism and clearance, drug interaction is minimal.	CV toxicity has yet to be reported	Liver toxicity (rare)	14, 15, 17, 73
Atazanavir	An analog of the peptide chain substrate binding to the active site HIV protease and preventing the pro-form of viral proteins cleaving into the working form.	Binding to SARS-CoV-2 3C-like proteinase (3CLpro); Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine in vitro experiments	HIV	Not yet lunched	An inhibitor of CYP3A4, UGT1A1, CYP2C8, and OATP1B1	Dose-dependent PR and QTc prolongations	Liver toxicity	21–24
Ritonavir/lopinavir	A nucleoside analogue *and* protease inhibitor of HIV; SARS, MERS?	Binding to SARS-CoV-23C-like proteinase (3CLpro); Though no significant benefits in clinical improvement and mortality in a randomized clinical trial (ChiCTR2000029308)	HPV; HIV	NCT04252885 NCT04275388 NCT04276688 NCT04286503 NCT02845843 NCT04307693 NCT04261907 NCT04295551 NCT00578825	Inhibitors of CYP3A and drug transporters such as P-gp, BCRP, and OATP1B1	PR/QTc prolongation; rare reports of 2nd or 3rd degree AVB; lopinavir/ritonavir; decreased serum concentrations of clopidogrel and prasugrel but increase statins, ticagrelor, rivaroxaban, and apixaban	Liver toxicity, pancreatitis, GI upset, neurotoxicity	22, 26, 28, 29, 33, 42, 73
Favipiravir	A selective inhibition of viral RNA-dependent RNA polymerase	Suppressing viral RNA-dependent RNA polymerase of SARS-CoV-2; in vitro?	Influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus	NCT04303299 (THDMS-COVID-19); NCT04310228; ChiCTR2000029600 (plus IFN-α)	Only a weak inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4	Minimal clinically significant drug interactions	Not reported	34–38
Ribavirin	A nucleoside inhibitor, stopping viral RNA synthesis and mRNA capping	Binding to the active site on RNA polymerase on SARS-CoV-2; in vitro?	HCV, RSV and some viral hemorrhagic fevers	NCT04276688	No report of cytochrome P450 enzyme mediated metabolism of ribavirin.	Ribavirin has no characterized direct CV toxicity; ribavirin has variable effects on warfarin dosing	Liver toxicity, hematologic disorder	40, 43, 44
Ivermectin	An influx of Cl− ions through the cell membrane of invertebrates by activation of specific ivermectin-sensitive ion channels.	Inhibiting the nuclear transport activity of SARS-CoV-2; currently on in vitro study	Head lice, scabies, strongyloidiasis, trichuriasis, ascariasis, and lymphatic filariasis	Not yet lunched	An inducer of several cytochrome P450 isoenzymes, including CYP1A, 2B, and 3A	Tachycardia, orthostatic hypotension, PR interval prolongation	Dermatitis, GI upset	4, 45–51
Immune-modulating drugs								
Chloroquine/hydroxy-chloroquine (HCQ)	Sequestering protons in lysosomes to increase the intracellular pH; interfering with the glycosylation of its cellular receptor, ACE2; reduce the viral copy number of SARS-CoV-2.	Reducing viral copy numbers in SARS-CoV-2; Under debates between China and France?	Anti-malaria. Treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda	NCT04286503 NCT04303507 NCT04307693 NCT04261517 NCT04303299 NCT04334512 More than 50 ongoing trials combined with Zithromax, vitamin, zinc	Metabolism by CYPs 2C8, 3A4 and 2D6 (increased concentration beta-blockers)	Intermediate-to-delayed cardiotoxicity 1. Direct: restrictive or dilated cardiomyopathy 2. Altered conduction: AV block, bundle branch block, torsade de pointes, ventricular tachycardia/fibrillation	Neutropenia, seizure, blurred vision, GI upset	10, 12, 13, 37, 53, 55–59

Table 1 (continued)

Drugs	Pharmacologic mechanism	Evidences of anti-COVID-19	FDA approved Indications	Clinical trials for COVID-19#	CV drug interactions	Cardiovascular risks	Other organ toxicity	Ref.
Tocilizumab	Anti-IL-6 receptor monoclonal antibody	Anti-cytokine storm? In vitro?	Rheumatoid arthritis, juvenile idiopathic arthritis.	NCT04306705 (TACOS); NCT04320615 (COVACTA)	Reversal of IL-6 inducing suppression of CYP3A4, CYP2C19, CYP2C9, and CYP1A2, resulting in higher drug exposure of substrate drugs	Hypertension, increased serum cholesterol; no known effect on QTc interval	Allergic reaction, susceptible to infection	62–68
Interferon-β1	A cytokine produced by innate immune cells, including macrophages, dendritic cells, and non-immune cells	Recognizing viral components by pattern recognition receptors (PRR) (Liu, 2005)	Multiple sclerosis	NCT04293887	Reduce the activity of hepatic cytochrome P450-dependent enzymes	No clinically significant effects on QTc prolongation have been observed. PVC and AVB case report	Flu-like symptoms	69–72, 74, 86
Fingolimod	An oral immune-modulating agent with high potent of functional antagonist on the lipid sphingosine-1-phosphate (S1P) receptors in the lymph node T cells	As an effective immunology modulator, fingolimod with potentials of anti-SARS-CoV-2	Multiple sclerosis, refractory	NCT04280588	Metabolism by CYP4F2. Us in caution when combined with class Ia and III anti-arrhythmic agents and beta-blockers	Pros: Arthero-protection, anti-hypertrophy Cons: Bradycardia, AVB, hypertension	Liver toxicity, headache, GI upset, flu-like symptoms	80–84

The FDA-approved CV drugs involved with COVID-19

CV cardiovascular, *GI* gastrointestinal, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *RNA* ribonucleic acid, *RSV* respiratory syncytial virus, *HIV* human immunodeficiency virus, *HPV* human papillomavirus, *AVB* atrioventricular *block*

Clinical trials summarized here till April 13, 2020

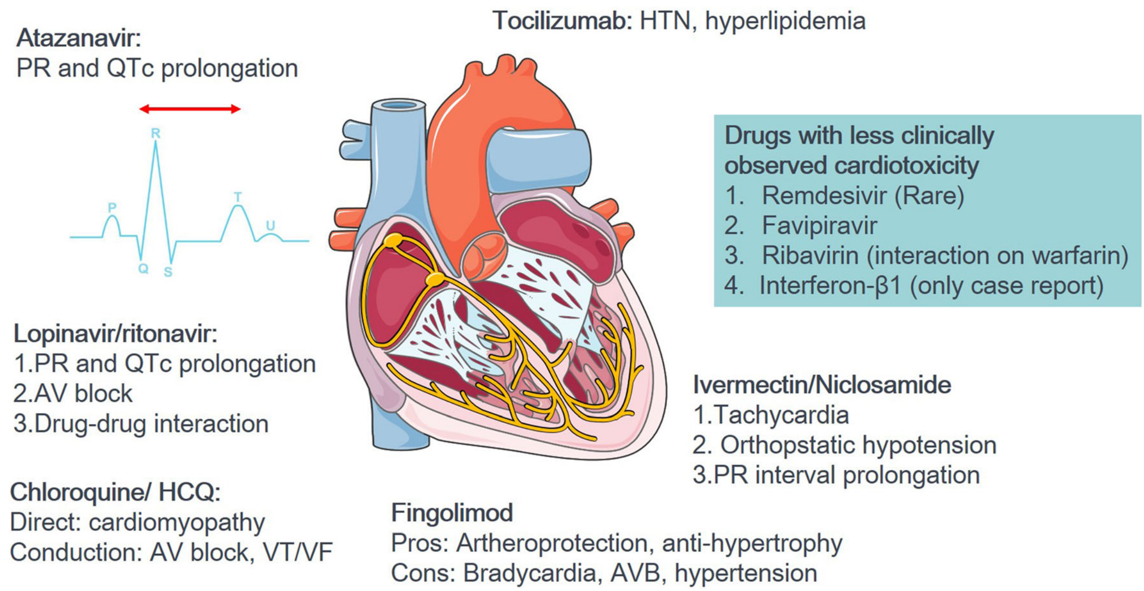

Fig. 1 The illustration of cardiovascular concerns of potential anti-COVID-19 drugs

fingolimod is expected to have a relatively low potential for drug-drug interactions. However, it should be used with caution when combined with class Ia and III anti-arrhythmic agents and beta-blockers [80]. CYP4F2 genotypes were observed contributing to both warfarin clearance and sensitivity differences [79].

Cardiovascular Risks Given that S1P is crucially involved in vascular barrier function, coagulation, vascular homeostasis, angiogenesis, and atherosclerosis, Fingolimod has been reported to induce bradyarrhythmia, atrioventricular block, and blood pressure through increasing the vascular tone [81, 82]. Regarding fingolimod-induced intracellular calcium release and its consequent contractile effects on smooth muscle cells, it may cause retinal arterial vasospasm and retinal vein occlusion [76, 81]. Conversely, upon its atheroprotective effects, fingolimod diminishes atherosclerosis plaque volume and macrophage and collagen content in vivo [83]. In another perspective, through S1P cascade to p-21 activated kinase (Pak1), a pivotal regulator of channel activity and contractility, fingolimod resists load stress-induced murine hypertrophic remodeling without deterioration of cardiac function [83].

Conclusions

Collectively, in this review we summarized the current state of knowledge on FDA-approved drugs with potentials for treating SARS-CoV-2 and the COVID-19 pandemic. Most importantly, given that patients affected by this disease commonly have cardiovascular comorbidities, a careful evaluation of the possible cardiovascular complications of these drugs is crucial. Table 1 summarizes the updated drugs with anti-SARS-CoV-2 potential, pharmacologic mechanisms, preliminary results of studies, ongoing clinical trials, drug metabolism, and the possible cardiovascular complications. Most of the drugs are based on repurposing therapeutic agents previously designed for other applications. These agents can be divided into two categories, including those with antiviral or immune-modulating effects. We reviewed several drugs with updated information until the middle April 2020. Figure 1 shows that among the aforementioned drugs, remdesivir, favipiravir, ribavirin, and interferon-β1 have been less reported with cardiovascular complications. We believe that this review provides additional cardiovascular concerns along with the aggressive exploration of candidate drugs with anti-SARS-CoV-2 potential.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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