

# Cardiovascular disease and COVID-19: les liaisons dangereuses

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## Abstract

Patients with cardiovascular risk factors or established cardiovascular disease have an increased risk of developing coronavirus disease 19 and have a worse outcome when infected, but translating this notion into effective action is challenging. At present it is unclear whether cardiovascular therapies may reduce the likelihood of infection, or improve the survival of infected patients. Given the crucial importance of this issue for clinical cardiologists and all specialists dealing with coronavirus disease 19, we tried to recapitulate the current evidence and provide some practical recommendations.

## Keywords

Coronavirus, cardiovascular, comorbidities, risk factors, COVID-19, SARS-CoV-2

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As of 12 April 2020, over 1.7 million cases of infection by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and almost 109,000 deaths have been reported, and coronavirus disease 19 (COVID-19) is the leading cause of daily deaths in the United States, before heart disease and cancer.<sup>1,2</sup> Although the clinical picture of COVID-19 is usually dominated by respiratory symptoms, these patients may also develop cardiovascular disorders, which may even become the ultimate cause of death. The following cardiovascular complications have been reported: myocarditis, acute coronary syndrome (ACS), decompensated heart failure (HF), pulmonary embolism (PE), cardiogenic shock and infection of a heart transplant recipient.<sup>3</sup> COVID-19-related myocarditis may be caused by coronavirus-induced cardiomyocyte damage or an excessive immune response to cardiomyocyte infection; it is characterised by chest pain, prominent electrocardiographic changes, such as diffuse ST-segment elevation, and troponin elevation, which may be accompanied by fever and respiratory symptoms or be isolated manifestations.<sup>3–5</sup> This condition must be differentiated from ACSs. In patients with

severe disease, the cytokine storm, high catecholamine levels and profound hypoxia may contribute to cardiomyocyte damage and acutely reduce cardiac function (myocardial stunning).<sup>5</sup> These mechanisms may explain HF decompensation or the occurrence of cardiogenic shock, which can require extracorporeal membrane oxygenation.<sup>3</sup> Atrial fibrillation or other tachyarrhythmias triggered by systemic inflammation are other possible precipitants of HF decompensation.<sup>5</sup> Furthermore, a generalised activation of coagulation mechanisms may elicit acute venous thromboembolism,<sup>6</sup> or lead to disseminated intravascular coagulation (DIC),<sup>7,8</sup> which is often fatal.

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A high proportion of patients with COVID-19 have cardiovascular risk factors or an established cardiovascular disease, which are even more prevalent than respiratory disorders,<sup>9,10</sup> and are associated with a reduced survival.<sup>10</sup> At present, it is unclear whether cardiovascular therapies may reduce the likelihood of infection, or improve the outcome of infected patients. Given the uttermost importance of this issue for clinical cardiologists and all specialists dealing with COVID-19, we tried to recapitulate the current evidence and provide some practical recommendations.

### Prevalence and prognostic impact of cardiovascular disease in COVID-19

The presence of underlying cardiovascular disease and/or risk factors was common in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In SARS, cardiovascular disease or diabetes mellitus were reported in about 8% and 11% of cases, respectively,<sup>11</sup> and the presence of either of the two was associated with a 12-fold higher risk of mortality.<sup>12</sup> In MERS, about 30% of patients presented with a cardiovascular disease, and the prevalence of cardiovascular comorbidities was even higher (50% had hypertension, 50% diabetes mellitus and 16% obesity).<sup>13</sup> Similarly, several small cross-sectional studies from China have supported the notion that patients with underlying cardiovascular disease and/or cardiovascular risk factors are at higher risk of developing COVID-19, especially its most severe manifestations. However, an accurate estimation of the prevalence and prognostic impact of cardiovascular disease and risk factors is limited by the lack of standardisation in COVID-19 testing and data collection between different countries as well as the inhomogeneous definitions of cardiovascular disease and the retrospective enrolment with different inclusion criteria in the epidemiological studies published so far. In a recent meta-analysis on 10 cross-sectional studies inclusive of 3403 hospitalised COVID-19 patients from China, the pooled prevalence of cardiovascular disease, smoking history, hypertension and diabetes was 12.11%, 7.63%, 16.37% and 7.87%, respectively.<sup>14</sup> Similarly, a systematic review on 3470 COVID-19 patients from 72 studies (including case reports, case series, case-control and cross-sectional studies) from different countries (mostly China) reported a pooled prevalence of cardiovascular disease, hypertension and diabetes of 8.3%, 13.3%, and 7.3%, respectively.<sup>15</sup> A recent study on 476 COVID-19 patients from three Chinese hospitals underscored that the incidence of cardiovascular comorbidities was higher in those with either severe or critical manifestations compared to those with a

moderate clinical presentation.<sup>16</sup> Analogously, a meta-analysis on 1527 COVID-19 patients reported higher incidences of cardiovascular disease (three-fold), hypertension (two-fold) and diabetes (two-fold) among those who required intensive care unit (ICU) admission compared to non-ICU counterparts.<sup>17</sup>

In fact, various reports have demonstrated that cardiovascular disorders, hypertension and diabetes are among the most relevant negative prognostic factors for COVID-19, together with advanced age, male gender, chronic respiratory diseases and cancer.<sup>18–20</sup> Indeed, in a series of 44,672 confirmed COVID-19 cases from Wuhan, China, the overall case fatality rate was 2.3%, but it was significantly higher in patients with an underlying cardiovascular disease (10.5%), hypertension (6.0%) and diabetes (7.3%); notably, patients with cardiovascular diseases were only 4.2% of total cases, yet constituted 22.7% of all fatal cases.<sup>21</sup> More recently, data from European cases have become available. In Italy, the first western country to be struck by COVID-19, the fatality rate was particularly high (13% as of April 9).<sup>22</sup> The fatality rate rises steeply with age and is higher in men (67% of cases). Overall, 96.7% of deceased patients had at least one comorbidity: 14.4% had one, 20.5% had two and 61.9% had three or more comorbidities; hypertension was present in 70%, diabetes in 32%, ischaemic heart disease in 28%, atrial fibrillation in 23%, chronic renal failure in 23%, chronic lung disease in 18%, HF in 16% and stroke in 11% of patients.

As highlighted previously, SARS-CoV-2 infection can cause a cardiac injury of variable degree in a substantial proportion of patients, and the presence of underlying cardiovascular comorbidities can contribute to the occurrence of this complication. In a study on 113 COVID-19 deceased patients, common complications included acute cardiac injury (77%), HF (49%), acute kidney injury (25%) and hypoxic encephalopathy (20%); patients with cardiovascular comorbidity were more likely to develop cardiac complications.<sup>23</sup> Guo et al.<sup>24</sup> investigated the association between cardiovascular disease/risk factors and myocardial injury with fatal outcomes in 187 hospitalised patients with COVID-19 (43 died; 144 discharged). In that study, 35% had an underlying cardiovascular comorbidity (hypertension, coronary heart disease, or cardiomyopathy), and 28% showed evidence of acute myocardial injury (defined as troponin T (TnT) >99th percentile upper limit). Patients with high TnT levels were older, more likely to be men and had more comorbidities including hypertension, coronary heart disease, cardiomyopathy and chronic kidney disease. Patients with a high TnT level showed a higher incidence of complications such as acute respiratory distress syndrome (ARDS), malignant arrhythmias, acute renal injury

and acute coagulopathy. The mortality during hospitalisation was 7.62% (eight of 105) for patients without underlying cardiovascular disease and normal TnT levels, 13.33% for those with underlying cardiovascular disease and normal TnT, 37.50% for those without underlying cardiovascular disease but elevated TnT and 69.44% for those with underlying cardiovascular disease and elevated TnT.<sup>24</sup>

### Cardiovascular drugs and risk of infection

It has been hypothesised that patients with cardiovascular risk factors or cardiovascular disease are disproportionately affected by COVID-19 because widely used medications such as angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) increase the susceptibility to infection by SARS-CoV-2 and viral replication. This point has been discussed extensively in a dedicated review.<sup>25</sup> Briefly, angiotensin-converting enzyme 2 (ACE2) is a key counter-regulatory enzyme that degrades angiotensin II to angiotensin 1–7 thereby attenuating its effects on vasoconstriction, sodium retention and fibrosis.<sup>25</sup> SARS-CoV-2 appears not only to gain initial entry through ACE2 but also subsequently to down-regulate ACE2 expression such that the enzyme is unable to exert protective effects in organs. Down-regulation of ACE2 activity in the lungs facilitates the initial neutrophil infiltration in response to bacterial endotoxin and may result in unopposed angiotensin II accumulation and local renin–angiotensin–aldosterone system (RAAS) activation.<sup>25–28</sup> In a small study, patients with COVID-19 appeared to have elevated levels of plasma angiotensin II, which were in turn correlated with total viral load and the degree of lung injury.<sup>27</sup> Dysregulated ACE2 may theoretically also attenuate cardiac protection in the setting of myocardial involvement and abnormal pulmonary haemodynamics in COVID-19.<sup>29,30</sup> ACEis and ARBs are known to induce ACE2 expression: on the one hand they would promote SARS-CoV-2 infection, on the other hand they would activate the ACE2/angiotensin 1–7/Mas receptor axis, which exerts beneficial antihypertrophic, antifibrotic, antioxidant and vasodilating effects in different tissues.<sup>25</sup> Previous studies, performed before the SARS-CoV-2 pandemic outbreak, demonstrated that ACEis and ARBs have significant immunomodulatory effects and protect against acute lung injury by blocking the classic ACE pathway.<sup>31–33</sup> Currently it is still uncertain if effects on ACE2 expression are uniform across different drug classes acting on the RAAS (for example, ACEis or ARBs), and even in response to different drugs from the same class.<sup>25,34</sup> Moreover, there are currently no experimental or clinical data demonstrating beneficial or adverse outcomes with the background use of ACEis, ARBs or other RAAS antagonists in COVID-

19 patients.<sup>25</sup> For this reason, the European Society of Cardiology (ESC), Heart Failure Society of America, American College of Cardiology and American Heart Association have recommended to continue RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as HF, hypertension, or ischaemic heart disease. In the event that patients with cardiovascular disease are diagnosed with COVID-19, individualised treatment decisions should be made according to each patient's haemodynamic status and clinical presentation.<sup>35,36</sup>

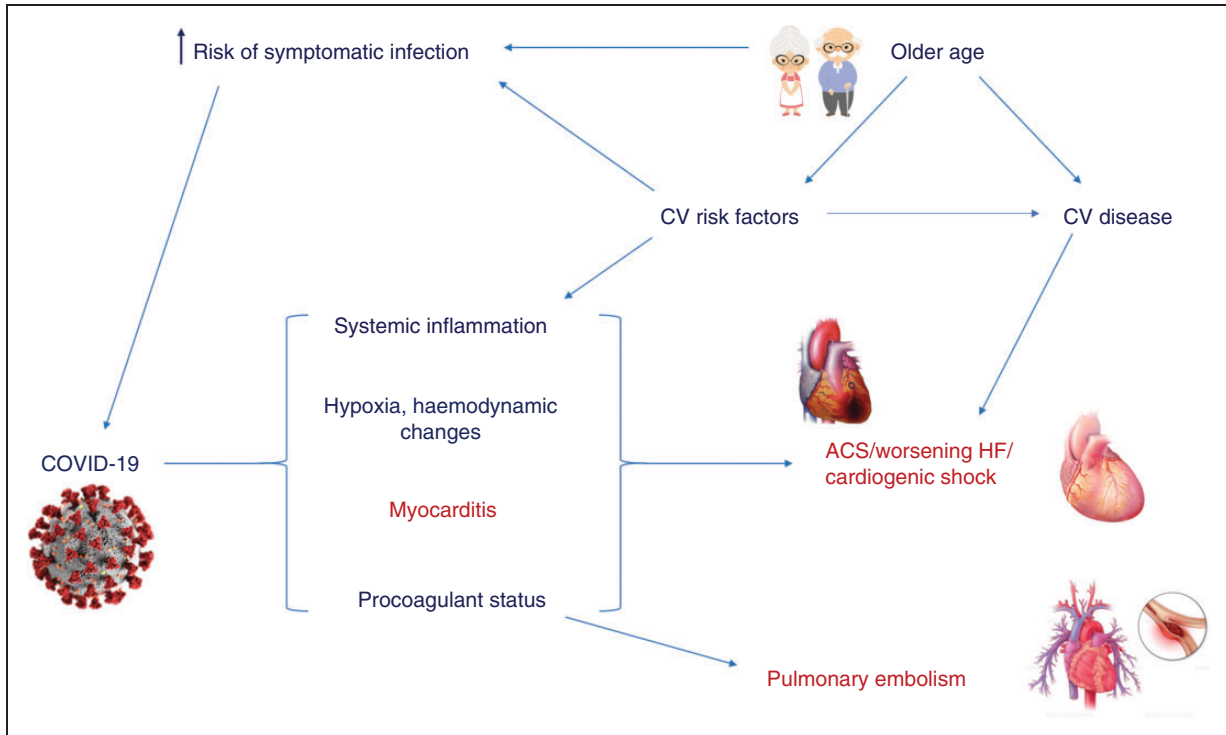
Other commonly prescribed drugs are statins, which are believed to have anti-inflammatory properties. In some observational studies on patients with influenza virus or bacterial pneumonia, statin therapy was associated with a reduction in various cardiovascular outcomes and even mortality.<sup>37–42</sup> Randomised controlled trials (RCTs) investigating the effects of the oral administration of statins in patients with ventilator associated pneumonia have provided mixed results,<sup>43,44</sup> but there are currently no other large-scale observational or randomised studies about the effects of statins on coronavirus infection. On the other hand, caution should be given to the potential interaction of statins and some antiviral agents such as ritonavir and cobicistat, which could increase the risk of statin-related adverse effects such as myopathy and liver injury.

The human dipeptidyl peptidase 4 (DPP-4) acts as a functional receptor for the spike protein of the MERS coronavirus,<sup>45</sup> and a dysregulated immune response mediated by DPP-4 seems to play a role in infection development.<sup>46</sup> Based on these premises, the intriguing hypothesis that DPP-4 inhibitors might reduce the risk of infection or modulate the immune response in patients with COVID-19 has been formulated.<sup>47</sup>

Colchicine is a widely available, safe anti-inflammatory drug representing the mainstay of therapy for pericarditis and a possible option for myocardial infarction. Colchicine shows pleiotropic immunomodulatory activities including the non-selective inhibition of NLRP3 inflammasome, which is a major pathophysiological component in the development of ARDS. Based on this evidence, it has been proposed that colchicine may improve the clinical course and prevent complications in patients with COVID-19.<sup>48</sup>

### Cardiovascular disease and COVID-19

Several mechanisms may account for the greater propensity of patients with cardiovascular disease or cardiovascular risk factors to COVID-19, and the worse outcome of this condition (Figure 1):



**Figure 1.** Interplay between cardiovascular (CV) disease or risk factors and coronavirus disease 19 (COVID-19). Arrows indicate association or cause–effect relationship. ACS: acute coronary syndrome; HF: heart failure.

- These patients are usually older and have a greater burden of comorbidities, including chronic obstructive pulmonary disease.<sup>49</sup> Smoking is another major risk factor for both cardiovascular and pulmonary diseases, including COVID-19.
- Cardiovascular risk factors are associated with systemic inflammatory activation,<sup>50</sup> which combines with the virus-induced immune response and increases the global inflammatory burden.
- The cardiovascular effects of the viral infection are potentially more dangerous in patients with underlying cardiovascular disease, in which SARS-CoV-2 cytotoxic damage superimposes on an already impaired myocardial or vascular function.
- Increased heart rate, hypoxia and hypotension may precipitate an ischaemia–supply imbalance in patients with coronary atherosclerosis, but also potentially in those with cardiac hypertrophy and microvascular dysfunction.
- Systemic inflammation (often leading to a cytokine storm) and adrenergic activation can trigger pre-existent plaque disruption, resulting in an ACS event.<sup>51</sup>
- A procoagulant state in COVID-19 has been consistently reported,<sup>5,52</sup> including endothelial, smooth muscle cell and macrophage activation, tissue factor expression in atheromatous plaque

and platelet activation; it may increase further the risk of ACS.

- An impaired blood pressure regulation may occur in critically ill patients, manifesting with either profound hypotension<sup>53</sup> or hypertension;<sup>19</sup> whether this is a reaction to the illness or is due to the potential derangements in ACE2 expression is still unknown.

### Can we reduce the risk of infection and mortality in patients with cardiovascular disease?

Aggressive compliance with basic hygiene skills, social distancing, widespread use of personal protective equipment such as gloves and face masks are key to preventing COVID-19 and should be strongly implemented, particularly in patients with cardiovascular disease and in people who care for them. In selected cases, such as HF outpatients, self-isolation should be recommended. Moreover, healthy lifestyle habits, healthy diet and a regular self-monitoring (blood pressure, heart rate, weight) should be encouraged in all patients with cardiovascular disease; periodical phone calls or email contacts with their general practitioner might be helpful to check adherence to medical therapy and to detect early signs of cardiac or non-cardiac diseases. The ESC has also released specific



recommendations on how to provide cardiac rehabilitation activities despite limitations imposed by the pandemic.<sup>54</sup> On the other hand, patients should be instructed to contact the emergency services in case of new symptoms, in order not to delay life-saving therapies for fear of SARS-CoV-2 infection.

In case of COVID-19 infection, patients with cardiovascular disease are at increased risk of complications and death, particularly those with increased troponin levels.<sup>24</sup> Myocardial biomarkers should be evaluated in patients with COVID-19 for risk stratification and possible early and more aggressive intervention, particularly in patients with underlying cardiovascular disease; biomarkers may also reduce the need for cardiac imaging, which requires strict isolation and increases the risk to the medical staff. Sometimes the differential diagnosis between COVID-19 and more common cardiac diseases, such as ACS, PE and HF decompensation, is not straightforward, and patient management should target all possible concomitant diseases.<sup>3</sup> Because of the risks incurred by transporting infected patients and subjecting them to percutaneous intervention, some centres are reconsidering thrombolytic therapy for ACS,<sup>55</sup> although this may not be the case in areas where regional ST-segment elevation myocardial infarction (STEMI) networks are smoothly set up.

Besides supportive care, several anti-inflammatory and antiviral drugs are being used to treat COVID-19,<sup>56</sup> and special care should be taken to avoid potentially dangerous cardiovascular side effects, particularly in patients with underlying cardiovascular disease. First, many antiviral, anti-inflammatory and cardiovascular drugs (such as anticoagulants, antiplatelets, anti-arrhythmics and statins) are inhibitors of the P-glycoprotein transporter and/or the cytochrome P450: their co-administration may significantly increase drug concentrations and cause potentially serious adverse effects (bleeding, arrhythmias). Second, the use of corticosteroids, convalescent plasma or intravenous immunoglobulin in COVID-19 patients may precipitate HF decompensations because of the haemodynamic effects of sodium/water retention. Third, many antiviral, antibiotics and anti-inflammatory agents may induce conduction abnormalities and QTc prolongation, necessitating careful electrocardiographic monitoring, particularly in patients affected by structural heart disease or treated with anti-arrhythmic drugs: this is the case with chloroquine, hydroxychloroquine and azithromycin. Table 1 summarises pharmacological interactions between the main cardiovascular drugs and those currently used (often empirically) to treat COVID-19, and provides some indications about the use of cardiovascular drugs in this setting.<sup>57</sup>

As of 12 April there are 458 clinical trials on COVID-19.<sup>58</sup> Pharmacological research is mainly focused on antiviral and anti-inflammatory drugs, but there are some trials focusing on cardiovascular drugs. Several potential therapeutic targets against SARS-CoV-2 infection involve the ACE2 axis.<sup>59</sup> Systemic delivery of recombinant ACE2 (NCT04287686 and NCT04335136) is expected to sequester viral SARS-CoV-2 particles in the circulation preventing their interaction and subsequent internalisation through endogenous ACE2 receptors, acting as a bait to neutralise the Spike protein. Moreover, recombinant ACE2 protein may be beneficial in restoring the ACE2/angiotensin 1–7/Mas receptor axis to relieve lung injuries and to prevent angiotensin II-induced hypertension, myocardial hypertrophy, injury and fibrosis.

As outlined previously, ACEis and ARBs may influence mortality and morbidity in patients with COVID-19: some observational studies are undergoing to investigate how epidemiological and outcome measures in COVID-19 patients are related to concomitant ACEi or ARB therapy (NCT04318301, NCT04318418). An open label, phase 1 clinical trial aims to evaluate the safety of losartan 50 mg in respiratory failure due to COVID-19 (NCT04335123). Paired double-blinded, phase 2 trials of losartan as a treatment for COVID-19 are being conducted among patients who have not previously received treatment with ACEis or ARBs and are either hospitalised (NCT04312009) or not hospitalised (NCT04311177).

As stated above, colchicine immunomodulatory properties may prove effective in patients with COVID-19; this hypothesis is currently being tested by four RCTs (COLCORONA, NCT04322682; GRECCO-19, NCT04326790; COLCOVID, NCT04328480; NCT04322565).

SARS-CoV-2 infection increases the risk of DIC and venous thromboembolism, and anticoagulant therapy (mainly low molecular weight heparin) lowers 28-day mortality in selected patients, such as those with a sepsis-induced coagulopathy score of 4 or greater (40.0% vs. 64.2%,  $P=0.029$ ) or D-dimer more than six-fold of the upper limit of normal (32.8% vs. 52.4%,  $P=0.017$ ).<sup>60</sup> Similar results were found in another study, in which heparin improved 28-day mortality in COVID-19 patients with D-dimer greater than 3.0 µg/mL (32.8% in heparin-treated patients vs. 52.4% in controls,  $P=0.017$ ).<sup>61</sup> Given the high incidence of acute cardiac injury in COVID-19 patients and the impossibility to perform routine cardiological tests for a definite aetiological diagnosis, another trial (NCT04333407) will randomly allocate patients to a cardioprotective medical therapy (aspirin 75 mg,

**Table 1.** Cardiovascular drugs and coronavirus disease 19 (COVID-19): drug interactions and recommendations for use.

	ATV	LPV/r*	RDV	FAVI	CLQ*/HCLQ*	RBV	TCZ	IFN-β	Clinical recommendations
<b>Anti-hypertensive and vasodilator drugs</b>									
ACEis	Enalapril	↔	↔	↔	↔	↔	↔	↔	Generally safe, continue administration in COVID-19 patients. May be beneficial through ACE2 upregulation.
	Lisinopril	↔	↔	↔	↔	↔	↔	↔	
	Perindopril	↔	↔	↔	↔	↔	↔	↔	
	Ramipril	↔	↔	↔	↔	↔	↔	↔	
ARBs	Candesartan	↔	↔	↔	↔	↔	↔	↔	Generally safe, continue administration in COVID-19 patients. May be beneficial through ACE2 upregulation.
	Irbesartan	↔	↓	↔	↔	↔	↔	↔	
	Losartan	↔	↓	↔	↔	↔	↔	↔	
	Valsartan	↑	↑	↔	↔	↔	↔	↔	
ARNI	Sacubitril/valsartan	↑	↑	↔	↔	↔	↔	↔	
MRA	Eplerenone	↑	↑	↔	↔	↔	↔	↔	
	Spirolactone	↔	↔	↔	↔	↔	↔	↔	
CCBs	Amlodipine	↑	↑	↔	↔	↔	↔	↔	
	Diltiazem	↑	↑	↔	↔	↔	↔	↔	
	Nifedipine	↑	↑	↔	↔	↔	↔	↔	
	Verapamil	↑	↑	↔	↔	↔	↔	↔	
	Isosorbide dinitrate	↑	↑	↔	↔	↔	↔	↔	
	Hydralazine	↔	↔	↔	↔	↔	↔	↔	
<b>Diuretics</b>									
Thiazides	Hydrochlorothiazide	↔	↔	↔	↔	↔	↔	↔	
Loop	Furosemide	↔	↔	↔	↔	↔	↔	↔	
	Torsemide	↔	↓	↔	↔	↔	↔	↔	
<b>Beta-blockers</b>									
	Atenolol	↔	↔	↔	↔	↔	↔	↔	
	Bisoprolol	↑	↑	↔	↔	↔	↔	↔	
	Carvedilol	↑	↓	↔	↔	↔	↔	↔	
	Metoprolol	↔	↑	↔	↔	↔	↔	↔	
	Nebivolol	↔	↑	↔	↔	↔	↔	↔	
<b>Antiarrhythmics</b>									
Class IA	Disopyramide*	↑	↑*	↔	↔	↔*	↔	↔	Coadministration of most antiarrhythmics with LPV/r or CLQ/HCLQ generally contraindicated due to increased risk of QT prolongation.
Class IB	Lidocaine	↑	↑	↔	↔	↔	↔	↔	
	Mexiletine	↔	↑	↔	↔	↔	↔	↔	
Class IC	Flecainide*	↑	↑*	↔	↔	↔*	↔	↔	
	Propafenone	↑	↑	↔	↔	↔	↔	↔	
Class III	Amiodarone*	↑	↑*	↔	↔	↑*	↔	↓	
<b>Inotropes and vasopressors</b>									
Amines	Dopamine	↔	↔	↔	↔	↔	↔	↔	
	Epinephrine	↔	↔	↔	↔	↔	↔	↔	
	Norepinephrine	↔	↔	↔	↔	↔	↔	↔	
<b>Lipid lowering drugs</b>									
Statins	Atorvastatin	↑	↑	↔	↔	↔	↔	↔	Use lowest dose possible of atorvastatin and rosuvastatin with ATV and LPV/r. Statins may be beneficial for COVID-19 through modulation of immune response.
	Rosuvastatin	↑	↑	↔	↔	↔	↔	↔	
	Simvastatin	↑	↑	↔	↔	↔	↔	↔	
	Ezetimibe	↑	↔	↔	↔	↔	↔	↔	
	Evolocumab	↔	↔	↔	↔	↔	↔	↔	Evolocumab enhances TCZ immunosuppressive effects
	Fenofibrate	↔	↔	↔	↔	↔	↔	↔	
	Gemfibrozil	↔	↓	↔	↔	↔	↔	↔	
<b>Anti-diabetics</b>									
SGLT2i	Canagliflozin	↔	↓	↔	↔	↔	↔	↔	Possible risk of ketoacidosis
	Dapagliflozin	↔	↔	↔	↔	↔	↔	↔	
	Empagliflozin	↔	↔	↔	↔	↔	↔	↔	
DPP4 inhibitors	Linagliptin	↔	↑	↔	↔	↔	↔	↔	May be beneficial for COVID-19 through inhibition of infection and modulation of immune response.
	Sitagliptin	↑	↑	↔	↔	↔	↔	↔	
	Insulin	↔	↔	↔	↔	↔	↔	↔	
	Metformin	↔	↔	↔	↔	↔	↔	↔	
	Repaglinide	↑	↑	↔	↔	↔	↔	↔	
<b>Anti-platelets, Anti-coagulants, Fibrinolytics</b>									
	ASA	↔	↔	↔	↔	↔	↔	↔	
P2Y12 inhibitors	Clopidogrel	↓	↓	↔	↔	↔	↓	↔	Prasugrel should be preferred in case of ATV or LPV/r coadministration
	Ticagrelor	↑	↑	↔	↔	↔	↓	↔	
	Prasugrel	↔	↔	↔	↔	↔	↓	↔	
Heparins	Enoxaparin	↔	↔	↔	↔	↔	↔	↔	May reduce thromboembolic risk in COVID-19 patients.
	Fondaparinux	↔	↔	↔	↔	↔	↔	↔	
	Warfarin	↑	↓	↔	↔	↔	↓	↓	Close monitoring of INR with ATV or LPV/r
NOACs	Dabigatran	↑	↑	↔	↔	↑	↔	↔	Dose reduction should be considered in case of coadministration with ATV or LPV/r
	Apixaban	↑	↑	↔	↔	↑	↓	↔	
	Edoxaban	↑	↑	↔	↔	↑	↔	↔	
	Rivaroxaban	↑	↑	↔	↔	↑	↓	↔	
	Streptokinase	↔	↔	↔	↔	↔	↔	↔	
<b>Others</b>									
	Digoxin	↑	↑	↔	↔	↑	↔	↔	
	Ivabradin	↑	↑	↔	↔	↔	↔	↔	
	Ranolazine	↑	↑	↔	↔	↔	↔	↔	

↔	Coadministration must be avoided	↑	Potential increased exposure of the CV drug
↑	Potential interaction possibly requiring close monitoring or dose adjustment	↓	Potential decreased exposure of the CV drug
↓	Potential weak interaction rarely requiring close monitoring or dose adjustment	↔	Potential increased exposure of the COVID-19 drug
↔	No significant interaction expected	↔	No significant interaction
		*	Possible risk of QT prolongation and/or Torsades des Points

Drug interaction data are modified from Liverpool Drug Interaction Group.<sup>57</sup> ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ATV, atazanavir; CCB, calcium channel blocker; CLQ, cloroquine; FAVI, favipiravir; HCLQ, hydroxychloroquine; IFN-β, interferon beta; LPV/r, lopinavir/ritonavir; MRA, mineralocorticoid receptor antagonist; NOAC, non-vitamin K oral anticoagulant; RBV, ribavirin; RDV, remdesivir; SGLT2i, sodium-glucose co-transporter-2 inhibitor; TCZ, tocilizumab.

Drug interaction data are modified from Liverpool Drug Interaction Group.<sup>57</sup>

ACEi: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; ATV: atazanavir; CCB: calcium channel blocker; CLQ: cloroquine; FAVI: favipiravir; HCLQ: hydroxychloroquine; IFN-β: interferon beta; LPV/r: lopinavir/ritonavir; MRA: mineralocorticoid receptor antagonist; NOAC: non-vitamin K oral anticoagulant; RBV: ribavirin; RDV: remdesivir; SGLT2i: sodium-glucose co-transporter-2 inhibitor; TCZ: tocilizumab.

clopidogrel 75, rivaroxaban 2.5 mg, atorvastatin 40 mg and omeprazole 20 mg) or control.

## Conclusions

The pathogenesis of COVID-19 presents a tight link with the cardiovascular system. Patients with cardiovascular risk factors or established cardiovascular disease have an increased risk of infection and a worse outcome when infected, but translating this notion into effective action is currently challenging.

SARS-CoV-2 receptor is represented by ACE2, a key enzyme in inflammatory and cardiovascular homeostasis: besides direct cytotoxic damage, SARS-CoV-2 induces a potent inflammatory and cardiovascular reaction, possibly resulting in a fatal outcome even in previously healthy people. Patients with underlying cardiovascular disease are at increased risk of complications and death, and deserve careful monitoring and enhanced therapeutic effort. Patient management should be redefined based on the risk of viral transmission to the medical staff, the overlap clinical presentation between COVID-19 and more common acute cardiac diseases, as well as the pharmacological interactions between antiviral, anti-inflammatory and cardiovascular drugs. The rapidly growing number of clinical trials is expected to find definitive therapies, including some drugs with cardiovascular effects.

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