

# COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease

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Patients with cardiovascular disease and, namely, heart failure are more susceptible to coronavirus disease 2019 (COVID-19) and have a more severe clinical course once infected. Heart failure and myocardial damage, shown by increased troponin plasma levels, occur in at least 10% of patients hospitalized for COVID-19 with higher percentages, 25% to 35% or more, when patients critically ill or with concomitant cardiac disease are considered. Myocardial injury may be elicited by multiple mechanisms, including those occurring with all severe infections, such as fever, tachycardia, adrenergic stimulation, as well as those caused by an exaggerated inflammatory response, endotheliitis and, in some cases, myocarditis that have been shown in patients with COVID-19. A key role may be that of the renin–angiotensin–aldosterone system. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects human cells binding to angiotensin-converting enzyme 2 (ACE2), an enzyme responsible for the cleavage of angiotensin II into angiotensin 1–7, which has vasodilating and anti-inflammatory effects. Virus-mediated down-regulation of ACE2 may increase angiotensin II stimulation and contribute to the deleterious hyper-inflammatory reaction of COVID-19. On the other hand, ACE2 may be up-regulated in patients with cardiac disease and treated with ACE inhibitors or angiotensin receptor blockers. ACE2 up-regulation may increase the susceptibility to COVID-19 but may be also protective vs. angiotensin II-mediated vasoconstriction and inflammatory activation. Recent data show the lack of untoward effects of ACE inhibitors or angiotensin receptor blockers for COVID-19 infection and severity. Prospective trials are needed to ascertain whether these drugs may have protective effects.

**Keywords** COVID-19 • Heart failure • Angiotensin II

## Introduction

In late December 2019, an outbreak of viral pneumonia was reported in Wuhan, Hubei, China and rapidly affected several countries becoming a pandemic disorder. The pathogen is a novel enveloped, positive stranded RNA betacoronavirus, provisionally named 2019 novel coronavirus (2019-nCoV) and subsequently officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup> SARS-CoV-2 is one of the few pathogenic coronaviruses to humans, along with severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). SARS-CoV was first isolated in China in 2002, while MERS-CoV was detected in Saudi Arabia in 2012.<sup>2,3</sup> They both

caused respiratory syndromes in humans and were responsible for several victims worldwide. SARS-CoV-2 is the cause of coronavirus disease 2019 (COVID-19), the most recent, lethal and widespread pandemic of current times.

Although COVID-19 has been initially associated with respiratory symptoms, it has become rapidly clear that it may affect multiple organs including the heart.<sup>4–8</sup> This is shown by the high prevalence of comorbidities involving the cardiovascular system as well as by their dramatic impact on patients' outcomes in COVID-19.<sup>9–16</sup> More recent studies have shown the prominent role of heart failure (HF) both as a risk factor for a more severe clinical course and for increased mortality and as a possible consequence of COVID-19 related myocardial damage.<sup>5,17</sup>

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**Table 1** Prevalence of cardiovascular and respiratory comorbidities in COVID-19 patients

Study	Patients, n	Males, %	Age, years <sup>a</sup>	HBP, %	Diabetes, %	CV disease, %	HF, %	Respiratory disorder, %
Huang et al. <sup>21</sup>	41	73	49 [41–58]	15.0	20.0	15.0	–	2.0
Liu et al. <sup>14</sup>	137	45	57 [20–83]	9.5	10.2	7.3	–	1.5
Wang et al. <sup>12</sup>	138	54	56 [42–68]	31.2	10.1	14.5	–	2.9
Zhang et al. <sup>15</sup>	140	51	57 [25–87]	30.0	12.1	5.0	–	1.4
Guan et al. <sup>18</sup>	1099	58	47 [35–58]	15.0	7.4	2.5	–	1.1
Arentz et al. <sup>11</sup>	21	52	70 [43–92]	–	33.3	42.9	42.9	33.3
Zhou et al. <sup>20</sup>	191	62	56 [46–67]	30.4	18.8	7.9	–	3.1
Mo et al. <sup>16</sup>	155	55	54 [42–66]	23.9	9.7	9.7	–	3.2
Yang et al. <sup>19</sup>	52	67	60 ± 13	–	17.3	9.6	–	7.7
Shi et al. <sup>24</sup>	416	49	64 [21–95]	30.5	14.4	10.6	4.1	2.9
Guo et al. <sup>25</sup>	187	49	58 ± 14	32.6	15.0	15.5	–	2.1
Chen et al. <sup>26</sup>	274	62	62 [44–70]	34.0	17.1	8.4	0.4	6.6
Mancia et al. <sup>27</sup>	6272	63	68 ± 13	–	13.7	30.1	5.1	10.4

CV, cardiovascular; HBP, high blood pressure; HF, heart failure.

<sup>a</sup>Median [interquartile range] or mean ± standard deviation.

The aim of this review is to describe the role of cardiac injury and HF in COVID-19, its pathogenetic mechanisms and potential implications for treatment, including the use of drugs affecting the renin–angiotensin–aldosterone system: angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs).

## COVID-19 and cardiovascular comorbidity

The clinical presentation of COVID-19 is extremely variable. It may be asymptomatic or cause mild symptoms such as fever, dry cough and fatigue. Other patients develop severe pneumonia, which can eventually cause acute respiratory distress syndrome (ARDS) and death. First reports already showed a high prevalence of comorbidities and their association with severity of COVID-19 and increased mortality.<sup>10,12,14–16,18–22</sup> The role of cardiovascular disease seemed more important, among different comorbidities. In a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, the overall case-fatality rate of COVID-19 was 2.3% (1023 deaths among 44 672 confirmed cases), but it rose up to 10.5% for those with pre-existing cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease and 6.0% for hypertension.<sup>23</sup> No more than a generic definition of cardiovascular comorbidities was, however, used in most of these reports and the contribution of each condition, including HF, was unsettled.<sup>10,13,18,20</sup> Current data are summarized in Table 1.<sup>11,12,14–16,18–21,24–27</sup>

## Acute myocardial injury during COVID-19

As in the case of many other acute conditions, myocardial injury during COVID-19 may be asymptomatic and can be detected

only by laboratory markers. Observational studies of hospitalized patients with COVID-19 have detected myocardial injury through troponin levels and defined it as their increase above the 99th percentile upper reference limit. Cardiac troponin levels were increased in 8% to 12% of unselected COVID-19 cases<sup>12,20,21,24,25,28</sup> and their percentage rose up to 23% to 33% in critically ill patients with a further rise when those with concomitant cardiac disease are considered (Table 2).<sup>12,17,19,20</sup> Most studies and one meta-analysis showed their independent prognostic role for in-hospital mortality.<sup>17,24,25,29</sup> Few studies evaluated also N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels and found them higher in patients with myocardial injury, although not independently related with outcomes (Table 2).<sup>24,25,28</sup>

In other cases, cardiac involvement may be clinically evident. In addition to chest pain, suggestive of myocardial ischaemia or myocarditis, and palpitations, patients may present with acute HF. After ARDS and sepsis, HF was the most frequent cause of death in a series of 113 patients who died with COVID-19.<sup>26</sup> Similar, in the series by Zhou et al.,<sup>20</sup> HF was the fourth most frequent complication of COVID-19, after sepsis, ARDS and respiratory failure, and developed in 23% of patients, 52% in non-survivors vs. 12% of survivors. Severe acute HF or end-stage HF has been described as the main clinical manifestation of COVID-19 in other smaller series of patients or case reports.<sup>30–33</sup>

Cardiac complications, including hypotension, HF and cardiomegaly, were already reported in SARS-CoV infections.<sup>34</sup> Rabbit models of dilated cardiomyopathy were also described after coronavirus infection. They presented increased heart weight, biventricular dilatation, myocyte hypertrophy, myocardial fibrosis and myocarditis with histopathological signs of interstitial and replacement fibrosis.<sup>35</sup> In COVID-19, HF or worsening of cardiac dysfunction may develop as a consequence of myocardial damage or as acute myocarditis. This last diagnosis is, however, controversial and often difficult.

**Table 2** Prevalence of heart failure and laboratory signs of cardiac injury or dysfunction and risk of in-hospital death in COVID-19 patients

Study	Patients, n	Males, %	Age, years <sup>a</sup>	HF, %	Deaths, HF vs. non-HF, %	Elevated troponin, %	Deaths, high vs. low troponin, %	Elevated NPs, %	Deaths, high vs. low NPs, %
Huang <i>et al.</i> <sup>21</sup>	41	73	49 [41–58]	–	–	12.2	80.0 vs 25.0 <sup>b</sup>	–	–
Shi <i>et al.</i> <sup>24</sup>	416	49	64 [21–95]	4.1	–	19.7	51.2 vs. 4.5	–	–
Guo <i>et al.</i> <sup>25</sup>	187	49	58 ± 14	–	–	27.8	59.6 vs. 8.9	–	–
Zhou <i>et al.</i> <sup>20</sup>	191	62	56 [46–67]	–	–	17.2	95.8 vs. 22.3	–	–
Chen <i>et al.</i> <sup>26</sup>	274	62	62 [44–70]	0.4	–	40.8	81.9 vs. 21.7	49.1	80.0 vs. 13.6
Wei <i>et al.</i> <sup>28</sup>	101	54	49 [34–62]	–	–	15.8	18.8 vs. 0	–	–
Inciardi <i>et al.</i> <sup>17</sup>	99	81	67 ± 12	21.2	57.1 vs. 17.9	–	–	–	–

Deaths are in-hospital deaths. Numbers are percentage of patients died.

HF, heart failure; NP, natriuretic peptide.

<sup>a</sup>Median [interquartile range] or mean ± standard deviation.

<sup>b</sup>Data are for patients who required intensive care unit care.

So far, few cases of COVID-19 related acute myocarditis have been described in the literature.<sup>31–33,36–38</sup> Although rare, their presentation might be severe with hypotension and low cardiac output requiring inotropic therapy. Cardiac magnetic resonance may show diffuse ventricular wall thickening and oedema. However, endomyocardial biopsy may show different degrees of myocardial inflammation and limited or absent myocardial necrosis.<sup>31,32,36–38</sup> Among two patients who underwent endomyocardial biopsy, the criteria for acute myocarditis were met in only one case.<sup>37</sup> In the other case, SARS-CoV-2 was shown although within macrophages, but not in cardiomyocytes, and biopsy showed only low-grade interstitial myocardial inflammation and aspecific changes of cardiac myocytes with myofibrillar lysis and lipid droplets.<sup>32</sup> These data show that the virus can reside within the heart but do not prove that it has a direct pathogenetic role.<sup>6,39</sup> Thus, although a few cases of direct virus-related myocarditis may exist, several mechanisms other than viral infection alone are responsible for myocardial injury in most patients.<sup>5,6,39–41</sup>

As for SARS-CoV, a viraemic response may occur with SARS-CoV-2 shedding and migration from the lungs to other organs, possible via the vascular route. This is also consistent with the large expression of angiotensin-converting enzyme 2 (ACE2), the tissue receptor of SARS-CoV-2 (see below), in the vascular system<sup>42</sup> as well as with the finding of acute endotheliitis in patients with COVID-19.<sup>41,43,44</sup>

## Mechanisms of myocardial damage in COVID-19

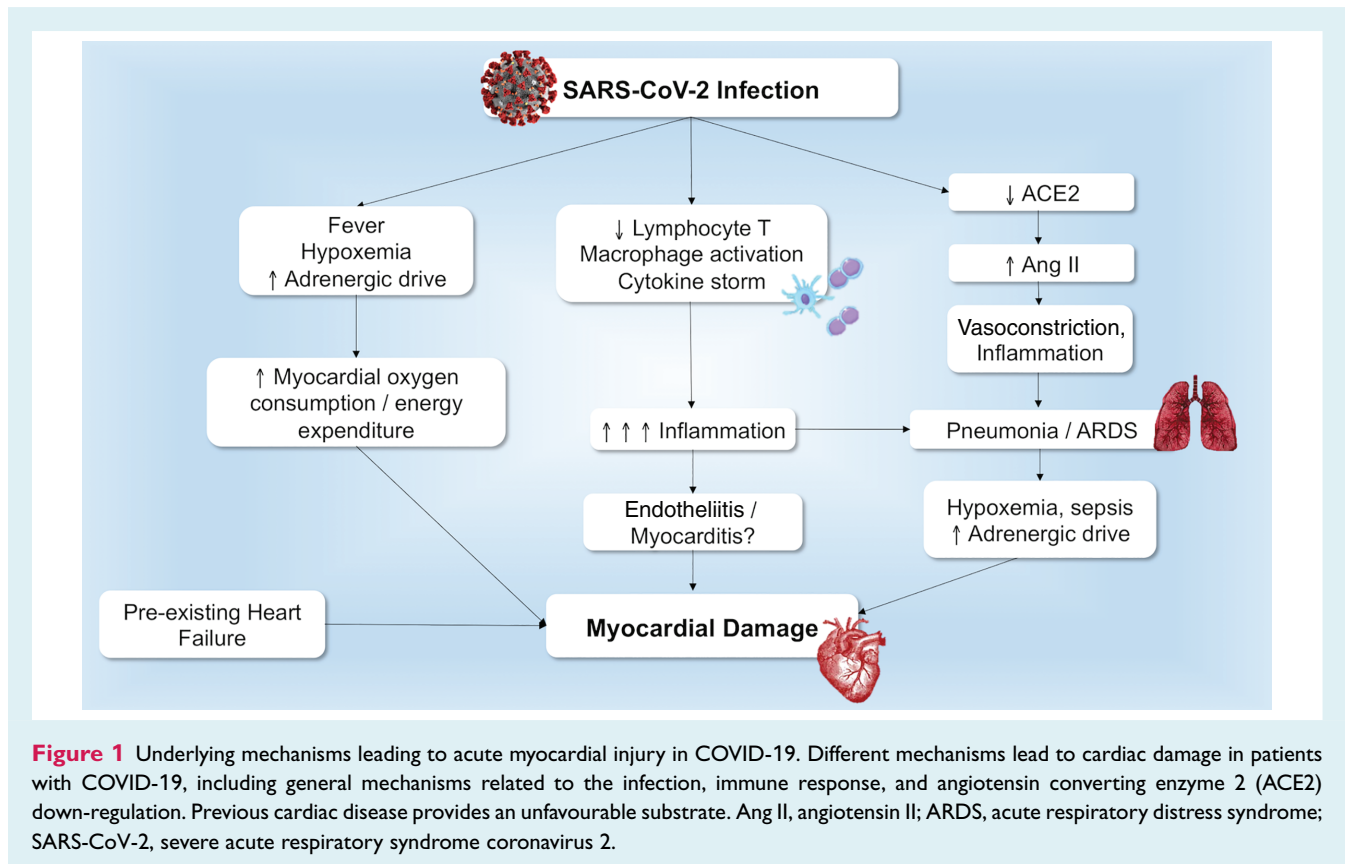
COVID-19 may cause myocardial damage through different mechanisms, all independent of direct effects of viral infection. These are summarized in *Figure 1* and *Table 3*.<sup>12,20,24,25,34,38,43,45–52</sup> First, there are aspecific mechanisms shared by COVID-19 with other severe infections (*Table 3*).<sup>45–50</sup> COVID-19 has general deleterious effects such as those caused by fever, sympathetic activation and tachycardia with increased myocardial oxygen consumption and energy

expenditure.<sup>47</sup> Prolonged bed rest, another general consequence of severe infection, predisposes to thromboembolic events, a major complication of COVID-19.<sup>52</sup> Hypoxaemia, another hallmark of COVID-19, is associated with enhanced oxidative stress with reactive oxygen species production, intracellular acidosis, mitochondrial damage and cell death.<sup>12,29,47,51</sup>

A second series of mechanisms are those related with the peculiar abnormal inflammatory response that COVID-19 may elicit. Approximately 7 to 10 days after COVID-19 onset, a hyper-inflammatory response with massive cytokine release (cytokine storm) may occur. Such a response is likely the main cause of COVID-19 pneumonia and ARDS and may be the cause of acute HF as well as other complications such as thromboembolic events, renal failure, shock and multiorgan failure.<sup>20,21,24,25,53</sup> The increased mortality of COVID-19 patients with HF might also be explained by this mechanism as inflammatory activation and oxidative stress are present in these patients and may predispose them to a more severe clinical course once infected.<sup>54,55</sup>

COVID-19 is associated with a depletion of CD4+ and CD8+ T lymphocytes caused by an immune reaction and/or by direct viral infection, with a predominance of neutrophils and innate immune macrophages. Ineffective activation of cytotoxic CD8+ T lymphocytes and natural killer T lymphocytes favours virus persistence with further aspecific macrophage activation and massive cytokine release. This condition is similar to that described in oncology with immune targeted chimeric antigen receptor T-cell therapies and in haemophagocytic lymphohistiocytosis syndromes.<sup>7,41,53,56</sup> Inflammation may take place in the endothelium. Biopsies and post-mortem histological findings showed lymphocytic endotheliitis with apoptotic bodies and viral inclusion structures in multiple organs, including the lungs, heart, kidneys, gut.<sup>38,43</sup> Marked inflammation with endotheliitis can also lead to disseminated intravascular coagulation with small or large vessel thrombosis and infarction.<sup>57</sup>

Consistent with this inflammatory hypothesis of COVID-19, a persistent increase in inflammatory markers, such as C-reactive



protein, D-dimer, ferritin, interleukin-6, is associated with major complications and increased mortality.<sup>20,21,24</sup> A positive correlation was also noted between the increase in inflammatory markers and myocardial damage, consistent with the role of hyperinflammation as a cause of cardiac dysfunction.<sup>24,25</sup> Lastly, anti-inflammatory therapies are currently studied for COVID-19.<sup>41,56,58</sup> However, also drugs active on endothelial function, such as statins and ACEi or ARBs may be beneficial.<sup>43</sup>

## The role of angiotensin-converting enzyme 2

SARS-CoV attaches human cells after binding with its spikes to ACE2, a peptide highly expressed on the surface of lung alveolar epithelial cells, arterial and venous endothelial cells, arterial smooth muscle cells and enterocytes of the small intestine.<sup>4,59–62</sup> The spike glycoprotein S on the virion surface is cleaved into S1 and S2, forming a receptor domain capable of binding to ACE2 in the S1 subunit.<sup>59</sup> SARS-CoV has a prominent cardiotropism. Autopsy reports of patients died from SARS showed viral RNA in the cardiac muscle in 35% of cases. The presence of SARS-CoV in the heart was associated with marked reduction in ACE2 protein expression.<sup>63</sup>

The binding domains of SARS-CoV and SARS-CoV-2 are almost identical. However, the SARS-CoV-2 binding site is more compact and stable with enhanced affinity for ACE2 and has a furin cleavage site that can further increase its ability to infect cells.<sup>7,64</sup>

Once binding is complete, the virus attaches ACE2 throughout membrane fusion and invagination, causing a down-regulation in ACE2 activity<sup>59</sup> (Figure 2). The down-regulation of ACE2 may be the result of ADAM-17/TACE activation by SARS spike protein, which is known to cleave and release ACE2, and/or to the endocytosis of the ligand/receptor complex and subsequent intracellular degradation.<sup>65,66</sup>

ACE2 is an enzyme involved in the renin–angiotensin–aldosterone system pathway. It has a catalytic domain 42% identical to ACE.<sup>67</sup> Despite this similarity, ACE2 cannot convert angiotensin I into angiotensin II and its catalytic efficiency is much higher towards angiotensin II. ACE2 cleaves angiotensin II, converting it into the heptapeptide angiotensin 1–7, which binds to Mas receptors that, opposite to angiotensin type 1 receptors, have vasodilatory, anti-fibrotic and anti-hypertrophic effects.<sup>68</sup> Of note, angiotensin 1–7 can also be synthesized by alternative pathways. ACE2 also has a weaker affinity for angiotensin I and can convert it into the nonapeptide angiotensin 1–9, limiting angiotensin II synthesis by ACE, and with vasodilatory effects through angiotensin II type 2 receptor stimulation (Figure 2).

Thus, ACE2 can counteract the untoward effects of angiotensin II with vasodilatory, anti-inflammatory, antioxidant and antifibrotic effects.<sup>68–70</sup> In experimental models, ACE2 knockout mice were more likely to develop left ventricular systolic dysfunction and HF with reduced ejection fraction.<sup>63</sup> Overexpression of the ACE2 gene resulted in a more favourable post-myocardial infarction remodelling and recovery.<sup>71</sup> ACE2 may have a role also for

**Table 3** Mechanisms leading to myocardial injury during infective conditions including COVID-19

Study, year	Disease	Patients, n	Design	Mechanisms	Findings
Madjid <i>et al.</i> , 2007 <sup>45</sup>	Influenza	34 892	Retrospective pathology	Inflammation, platelet activation, endothelial dysfunction	Increased risk of MI and ischaemic cardiomyopathy
Corrales-Medina <i>et al.</i> , 2015 <sup>46</sup>	Pneumonia	1773	Observational prospective	Inflammation, hypercoagulation	Increased risk of CV disease (MI, stroke, and CAD)
Violi <i>et al.</i> , 2017 <sup>47</sup>	Pneumonia	1182	Observational prospective	Fever, inflammation, sympathetic activation, hypoxaemia	Increased risk of HF, AF
Milbrandt <i>et al.</i> , 2009 <sup>48</sup>	Pneumonia, sepsis	939	Observational prospective	Inflammation, endothelial dysfunction	Increased risk of coagulation abnormalities
Violi <i>et al.</i> , 2015 <sup>49</sup>	Pneumonia	432	Observational prospective	Inflammation	Increased risk of AF and HF via oxidative stress
Yu <i>et al.</i> , 2006 <sup>34</sup>	SARS-CoV disease	121	Retrospective	Direct viral damage, inflammation, therapy-related (corticosteroids, ribavirin)	Tachycardia, arrhythmia, hypotension, cardiomegaly, LV systolic dysfunction
Li <i>et al.</i> , 2003 <sup>50</sup>	SARS-CoV disease	46	Observational prospective	Inflammation, direct viral damage	Acute LV diastolic impairment
Takasu <i>et al.</i> , 2013 <sup>51</sup>	Sepsis	44	Post-mortem	Inflammation, hypoxaemia, vasoconstriction	Myocardial ischaemia with mitochondrial damage
Shi <i>et al.</i> , 2020 <sup>24</sup>	COVID-19	416	Retrospective	Inflammation, direct viral damage, endothelial dysfunction, hypercoagulation	Increased risk of myocardial damage
Zhou <i>et al.</i> , 2020 <sup>20</sup>	COVID-19	191	Retrospective	Inflammation, hypercoagulation, direct viral damage	Increased risk of myocardial injury
Guo <i>et al.</i> , 2020 <sup>25</sup>	COVID-19	187	Retrospective	Inflammation, direct viral damage, endothelial dysfunction, hypoxaemia	Increased risk of myocardial damage
Klok <i>et al.</i> , 2020 <sup>52</sup>	COVID-19	184	Retrospective	Inflammation, hypercoagulation, hypoxaemia	Increased risk of thrombotic complications
Wang <i>et al.</i> , 2020 <sup>12</sup>	COVID-19	138	Retrospective	Inflammation, hypoxaemia, viral damage	Increased risk of myocardial damage and arrhythmia
Varga <i>et al.</i> , 2020 <sup>43</sup>	COVID-19	3	Post-mortem	Inflammation, vasoconstriction, direct viral damage	Endotheliitis, endothelial virus inclusion, myocardial ischaemia
Xu <i>et al.</i> , 2020 <sup>38</sup>	COVID-19	1	Post-mortem	Inflammation	Cardiac interstitial inflammatory infiltrates

AF, atrial fibrillation; CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; LV, left ventricular; MI, myocardial infarction; SARS-CoV, severe acute respiratory syndrome coronavirus.

HF with preserved ejection fraction. ACE2 gene overexpression improved left ventricular diastolic function in experimental models through a reduction in reactive oxidative stress, fibrosis, myocardial hypertrophy.<sup>72,73</sup> Interestingly, ACE2 has also immunomodulatory properties both direct, through its interaction with macrophages, and indirect reducing angiotensin II which favours inflammation.<sup>74</sup>

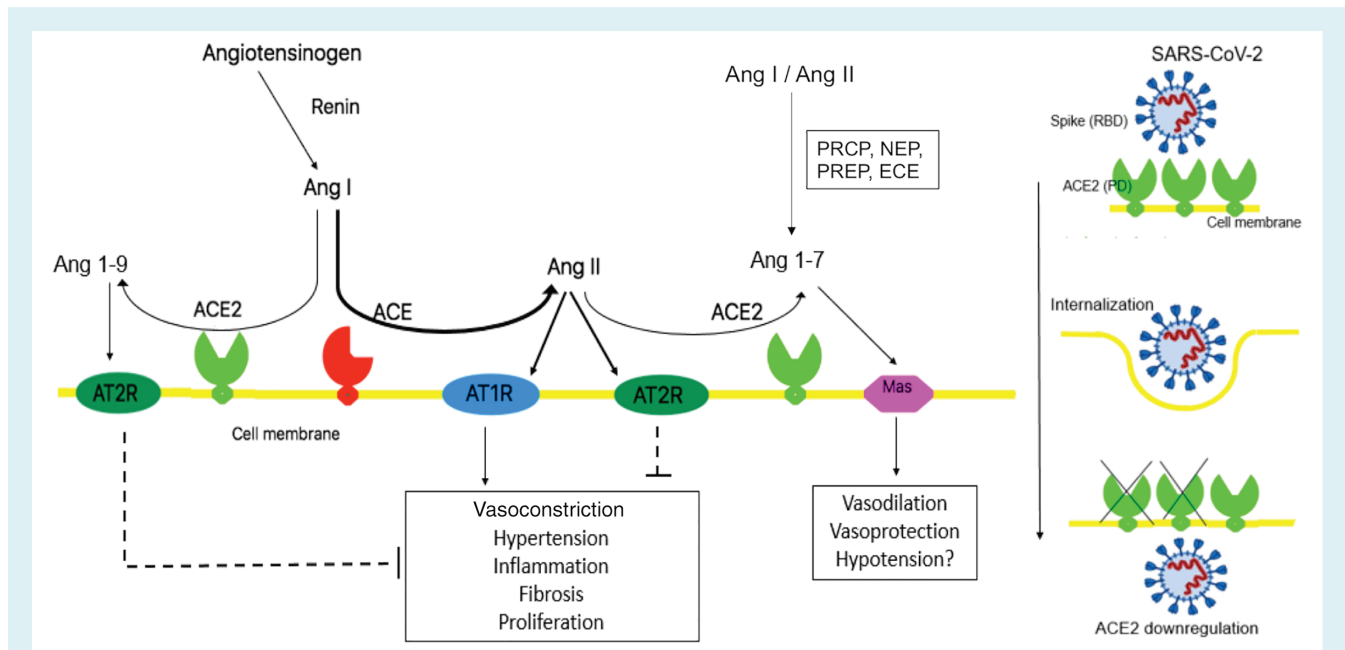
## Myocardial injury, angiotensin-converting enzyme 2 and COVID-19

In the heart, ACE2 is localized on the surface of coronary endothelial cells, cardiomyocytes and cardiac fibroblasts. ACE2 may have opposite effects in COVID-19. First, it is up-regulated in patients with cardiovascular disease, diabetes, and/or treated with ACEi or ARB.<sup>75–80</sup> This has been shown in experimental models,<sup>75,77</sup> tissue samples from the myocardium of patients with end-stage

HF,<sup>76,79</sup> and using assays of ACE2 plasma levels.<sup>78,80</sup> A first study, where circulating levels of ACE2 were measured in a large European population of 1485 men and 537 women with HF and results were validated in another, independent cohort, has been recently published.<sup>80</sup> Plasma levels of ACE2 were increased in patients with HF and, interestingly, their strongest predictor was male sex in both cohorts, consistently with the increased prevalence and severity of COVID-19 in males.<sup>9,18,23,80</sup> ACE2 up-regulation may thus increase the susceptibility to COVID-19 and favour a more severe clinical course of the illness through a larger viral burden into the cells. According to this hypothesis, which, however, remains to be proven, concerns regarding the administration of ACEi/ARBs, as a cause of ACE2 up-regulation, were expressed.<sup>81–84</sup>

Second, ACE2 is down-regulated by SARS-CoV-2 infection and this may potentiate angiotensin II release and favour angiotensin II type 1 (AT1) receptor stimulation, because of the loss of its counter-regulatory effects. Thus, ACE2 may have a protective





**Figure 2** Angiotensin-converting enzyme 2 (ACE2) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). ACE2 is involved in the renin–angiotensin–aldosterone system pathway but it is also a functional receptor for SARS-CoV-2. Ang I, angiotensin I; Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; ECE, endothelin-converting enzyme; NEP, neutral endopeptidase; PCRP, polycarboxypeptidase; PREP, prolylendopeptidase; RBD, receptor binding domain; PD, peptidase domain.

role, and heightened angiotensin II activity secondary to its downregulation may be a major mechanism leading to cardiac and/or lung injury, ARDS and other COVID-19 complications.<sup>83,85,86</sup> According to this second hypothesis, ARBs may have protective effects with respect of COVID-19 related organ damage.

## COVID-19 and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker treatment

Based on what stated above, treatment with ACEi/ARBs may either be considered as harmful, as it may increase susceptibility to COVID-19, or protective, as it may counteract increased AT1 receptor stimulation favoured by the loss of the counter-regulatory effects of the down-regulated ACE2. Mechanisms associated with potentially favourable or untoward effects of ACEi/ARBs in COVID-19 patients are reported in *Figure 3*.

Data from observational studies regarding plasma ACE2 levels and ACEi/ARB treatment in patients with COVID-19 suggest at least a neutral role of ACEi/ARB treatment. In two large cohorts of patients with HF (index cohort: 2022 patients, validation cohort: 1698 patients), circulating ACE2 levels were increased in HF patients but the use of ACEi or ARBs had no relation with them in the index cohort and was associated with lower ACE2 levels in the validation cohort, suggesting a protective effect of these drugs.<sup>80</sup>

Other studies regard the relation between ACEi/ARB treatment and the severity of COVID-19. In a retrospective, single-centre

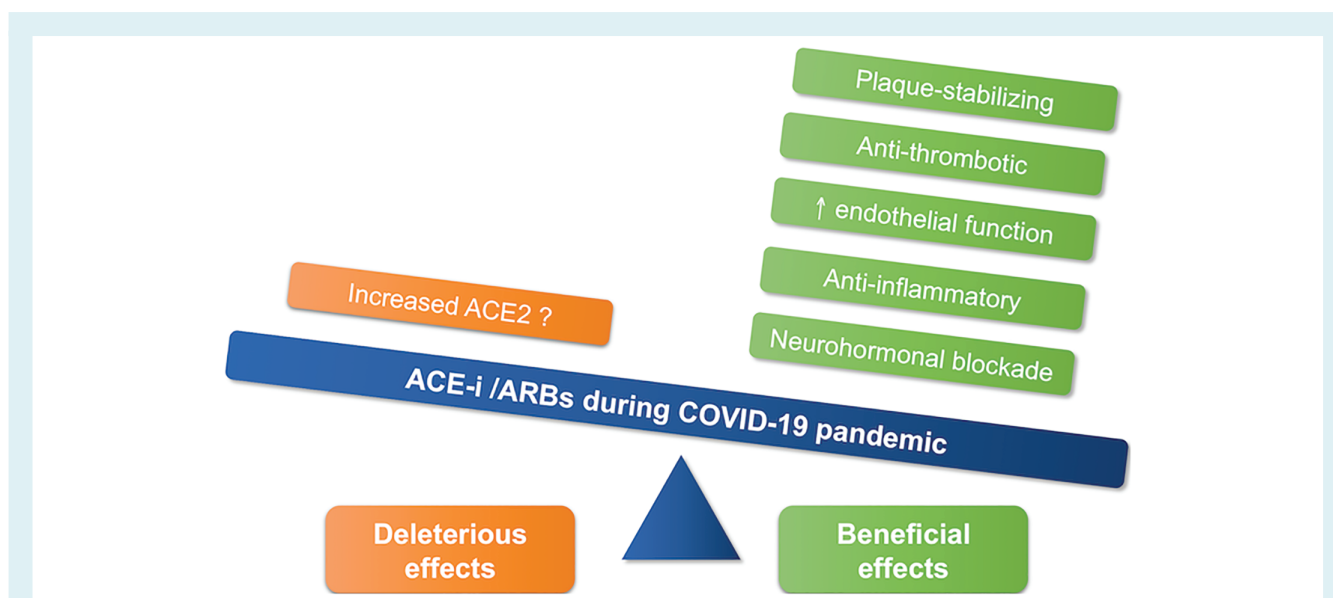
case series including 362 patients with hypertension hospitalized with COVID-19, no difference in infection severity and mortality was found between patients who were receiving ACEi/ARBs and the others.<sup>87</sup> A larger series of 1128 hypertensive patients with COVID-19 from a retrospective, multi-centre study from nine hospitals in Hubei, China, showed a lower mortality in patients receiving ACEi/ARBs vs. the others (3.7% vs. 9.8%;  $P = 0.01$ ). This difference remained significant after adjustment for risk factors and baseline variables at multivariable analysis and propensity analysis (adjusted hazard ratio 0.42; 95% confidence interval 0.19–0.92;  $P = 0.03$ , for ACEi/ARBs vs. non-ACEi/ARBs).<sup>88</sup>

Similar results came from non-Chinese series. A population-based case-control study from the Lombardy region of Italy compared 6272 patients with COVID-19 with 30759 control subjects. Use of ACEi/ARBs was more frequent among patients with COVID-19 than among controls because of their higher prevalence of cardiovascular disease. However, it was not an independent predictor of COVID-19 or its severity.<sup>27</sup>

Ongoing trials testing ACEi/ARB use/discontinuation in COVID-19 are reported in *Table 4*.

## Conclusions and practical implications

A few conclusions can be drawn at this stage. First, we have shown the high prevalence of cardiac injury following COVID-19 and this may be diagnosed only through biomarker measurements. This



**Figure 3** Deleterious and beneficial effects of angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARBs) in COVID-19 patients. ACE2, angiotensin-converting enzyme 2.

**Table 4** Ongoing trials testing angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use/discontinuation in COVID-19

NCT number	Study title	Status	Study type	Location
NCT04353596	Stopping ACE-inhibitors in COVID-19 (ACEI-COVID)	Recruiting	Interventional	Austria
NCT04351581	Effects of Discontinuing Renin–angiotensin System Inhibitors in Patients With COVID-19 (RASCOVID-19)	Recruiting	Interventional	Denmark
NCT04345406	Angiotensin Converting Enzyme Inhibitors in Treatment of Covid 19	Not yet recruiting	Interventional	Egypt
NCT04338009	Elimination or Prolongation of ACE Inhibitors and ARB in Coronavirus Disease 2019 (REPLACECOVID)	Recruiting	Interventional	USA
NCT04337190	Impact of Angiotensin II Receptor Blockers Treatment in Patients With COVID 19 (COVID-ARA2)	Recruiting	Observational	France
NCT04335786	Valsartan for Prevention of Acute Respiratory Distress Syndrome in Hospitalized Patients With SARS-COV-2 (COVID-19) Infection Disease	Recruiting	Interventional	Netherlands
NCT04335123	Study of Open Label Losartan in COVID-19	Recruiting	Interventional	USA
NCT04331574	Renin–Angiotensin System Inhibitors and COVID-19 (SARS-RAS)	Recruiting	Observational	Italy
NCT04330300	Coronavirus (COVID-19) ACEi/ARB Investigation (CORONACION)	Recruiting	Interventional	Ireland
NCT04329195	ACE Inhibitors or ARBs Discontinuation in Context of SARS-CoV-2 Pandemic (ACORES-2)	Recruiting	Interventional	France
NCT04322786	The Use of Angiotensin Converting Enzyme Inhibitors and Incident Respiratory Infections, Are They Harmful or Protective?	Active, not recruiting	Observational	UK
NCT04318418	ACE Inhibitors, Angiotensin II Type-I Receptor Blockers and Severity of COVID-19 (COVID-ACE)	Not yet recruiting	Observational	Italy
NCT04312009	Losartan for Patients With COVID-19 Requiring Hospitalization	Recruiting	Interventional	USA

may become indicated in all patients hospitalized for COVID-19 as independent prognostic markers. The clinical implications of the detection of myocardial injury remain, however, uncertain. No specific treatment is available. Agents with favourable effects on endothelial function may be tested in clinical trials.

A second aspect regards the role of ACEi/ARB treatment. No data have shown an increased COVID-19 susceptibility or

severity in patients receiving these agents. Therefore, these agents should not be discontinued during the COVID-19 pandemic. In addition, as they may have a protective role for angiotensin II-mediated organ damage during COVID-19, they should also be tested in clinical trials to improve the still dramatic patients' clinical course.

**Conflict of interest:** none declared.

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