# Lipid-lowering therapy and renin-angiotensin-aldosterone system inhibitors in the era of the COVID-19 pandemic

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The novel coronavirus (severe acute respiratory syndrome coronavirus 2 – SARS-Cov-2) disease 2019 (COVID-19) pandemic has been associated with severe respiratory disease incidence and increased mortality [1]. Angiotensin converting enzyme (ACE) 2 is a homologue of ACE, but also a receptor for the coronaviruses [2]. ACE2 is highly expressed in the lungs, heart, gastrointestinal (GI) tract and kidney, thus affecting the cardiovascular system (CV) and the immune system [3]. The overexpression of ACE2 was reported to enhance viral entry and replication intracellularly [4]. COVID-19, also called SARS-CoV-2, may also use ACE2 as a receptor to initiate infection, leading to severe complications from the heart (acute coronary syndrome (ACS) and fulminant myocarditis), lungs (pneumonia and acute respiratory distress syndrome (ARDS)) and GI tract (diarrhoea syndrome) [5].

ACE2 gene expression is affected by several factors, including gender (ACE2 gene is X-linked), ACE2 gene polymorphisms, comorbidities (increased in the presence of CVD, hypertension, diabetes), and drug therapy [6]. With regard to drugs, angiotensin II receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRA) have been reported to raise ACE2 activity in human and animal studies [7]. There are only a few animal studies available showing that statins may also increase ACE2 activity [8, 9]. In the era of the COVID-19 pandemic, such a drug effect may be considered as potentially worrying [10]. In this context, it was recently even suggested that ARBs could be replaced with ACE inhibitors and that statin treatment may be discontinued during the pandemic, particularly in primary prevention settings [11].

However, before implementing such strategies, we should consider several issues. Firstly, as the COVID-19 infection progresses, ACE2 is downregulated, thus potentially generating an inflammatory response leading to impaired cardiac contractility and acute lung injury [5, 7, 12]. Therefore, reduced ACE2 expression is linked to worse outcomes. On the other hand, ACE2 overexpression has been associated with several beneficial effects, i.e. prevention of adverse cardiac remodelling and fibrosis, improvement of vascular endothelial dysfunction, reduction of blood pressure, and protection from ARDS [7, 12]. Both statins and ARBs were reported to exert these benefits.

Secondly, a combination of statins/ARBs were used during the 2014 Ebola virus disease epidemic in Sierra Leone, leading to improved outcomes and increased survival [13]. These drugs can affect the host response to infection, not the virus, especially by preventing endothelial dysfunction, a shared feature of several virus infections [14]. Their combination seemed to promote a return to homeostasis, allowing patients with Ebola virus infection to recover on their own [15].

Third, patients with cardiovascular disease (CVD) were shown to be more prone to COVID-19 infection and with worse prognosis [16, 17]. Elevated inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been recognised as predictors of COVID-19 infection severity and mortality, suggesting a virus-activated "cytokine storm syndrome" [18, 19]. Therefore, as well as immunomodulation, COVID-19 treatment should also target reduction of inflammation. In this context, statins have been consistently reported to exert immunomodulatory and anti-inflammatory properties [20–30]. Also, it was previously suggested that statins could enhance host defence and suppress inflammation, thus representing a practical and inexpensive adjunctive or alternative host-directed treatment for infections by viruses, fungi, protozoa, and bacteria [31]. Similarly, there are data supporting an anti-inflammatory role for ARBs [32–34].

Fourth, statins may also prevent a viral-induced acute coronary syndrome (also in COVID-19 positive patients) by stabilising atherosclerotic plaques [35], as well as prevent acute kidney injury (AKI) [36]. Both acute cardiac injury and AKI are predictors of COVID-19-induced mortality [37]; statin therapy may prevent these complications and thus increase survival. Of note, statins can protect against contrast-induced AKI (CI-AKI) [38–41]. This is of clinical importance, especially in hospitalised patients who undergo diagnostic or therapeutic procedures involving the administration of contrast media (e.g. computed tomography of the lungs).

Fifth, effective lipid-lowering therapy (LLT) and significant cholesterol reduction might significantly suppress coronavirus infection. It was show that for infectious bronchitis virus (IBV) coronavirus, drug-related cholesterol reduction disrupts lipid rafts (an important element for the cellular entry of coronavirus) that enable the binding of the coronavirus with the host cells and, consequently, further infection [42]. It was also observed, in the studies with porcine deltacoronavirus (PDCoV), that cholesterol present in the cell membrane and viral envelope (coronaviruses are positive-sense enveloped RNA viruses) contributes to PDCoV replication by acting as a key component in viral entry. Thus, the pharmacological sequestration of cellular or viral cholesterol with effective LLT significantly blocked both virus attachment and internalisation [43]. All these mechanisms might suggest a critical role of statins and LLTs in the inhibition of coronavirus infection.

In COVID-19-positive patients, the majority of baseline CVD is of atherosclerosis origin, with the worst prognosis for patients being at the high, and especially very high and extremely high, risk of CVD [16]; thus, intensive LLT with statins and/or fixed combination with ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors seems to be critical. Indeed, we should do our best to maximally improve therapy adherence and thus have a better prognosis for the infected CVD patients [44, 45]. In this context, there are no premises that PCSK9 inhibitors, because they are monoclonal antibodies (in relation to the above-mentioned high cytokine storm during infection), should be discontinued. In contrast, PCSK9 inhibitors should be continued to achieve further low-density lipoprotein cholesterol (LDL-C) lowering (based on "the lower, the better" principle), because then we might significantly stabilise atheroma plaque, reduce the risk of CVD events, and reduce inflammation [46–48]. Recent available data have confirmed the role of PCSK9 inhibition in reducing the process of inflammation *via* decreasing main vascular inflammatory markers, reducing infiltration of monocytes into the subendothelial layer, and inhibiting monocyte migration. Apart from the reduction of pro-inflammatory mediators, PCSK9 inhibitors could ameliorate vascular inflammation [47]. Finally, a direct local anti-inflammatory action of PCSK9 inhibitors, independent of LDL-C reduction, has been shown in animal models; however, it still merits further investigation [47, 48].

It is of special interest now (due to the fact that coronavirus might also use different receptors to enter the host cell) that treatment with PCSK9 inhibitors has beneficial effects on LDL-C lowering via inhibition of LDL-receptors (LDL-R). This might exert an antiviral effect, among others, on hepatitis C viral (HCV) infection through down-regulation of the surface expression of LDL-R and cluster of differentiation (CD) 81 on hepatic cells, and a positive association with increased inflammatory responses, as well as with septic shock [48]. In a recent paper, we confirmed that there is no association between PCSK9 levels and resistance to antibiotics or the condition of patients hospitalised in intensive care units, a finding of clinical importance in the COVID-19 infection era [49].

Sixth, there are conflicting results regarding the possible effects of statins on ARDS development and outcomes [50, 51]. It was suggested

that statins act beneficially in 'hyper-inflammatory' ARDS patients (defined by increased biomarkers of inflammation, coagulation and endothelial activation) [52], but not in 'hypo-inflammatory' patients [53, 54]. A potential benefit of ARBs on survival in ARDS patients has also been reported [55, 56]. Nevertheless, there is a paucity of data on this field, and thus further research is needed to elucidate the association between statin therapy, ARBs, and acute lung injury.

Of note, drug-drug interactions should also be considered. In this context, simvastatin and lovastatin are contraindicated in patients on lopinavir/ritonavir therapy due to an increased risk of rhabdomyolysis [57]. Atorvastatin, rosuvastatin and other statins can be used at the lowest possible dose, based on the instructions included in the summary of product characteristics (spc) [58]. Taking this into account, we should be careful while treating COVID-19 disease patients with statins being on antiviral drugs and some antibiotics (including macrolides), because they might increase the risk of statin-associated muscle symptoms (SAMS) [59, 60]. Therefore, their careful monitoring is highly recommended to avoid unnecessary drug-related side effects, and at the same time optimising LLT therapy to achieve the individual's LDL-C goal. In this context, in patients at very high CVD risk, requiring intensive LLT, it is reasonable to initiate therapy with polypills/fixed combinations of statins (at lower doses) and ezetimibe, with or without PCSK9 inhibitors (as available), aimed at reducing the risk of SAMS [59, 60].

A position statement of the European Society (ESC) Council (on 13 March 2020) (as well as of other national and international societies) highlights the lack of evidence on harmful effects of ACE inhibitors and ARBs on the incidence and progression of COVID-19 infection and strongly supports the continuation of usual antihypertensive therapy [6, 61]. Regarding statins, their beneficial effects on inflammation, vascular, heart, and lung function strongly support the continuation of their use. Due to their significant effect on CVD prevention, PCSK9 inhibitors should also be continued, as available. Physicians should wait for strong evidence and recommendations from international scientific societies before altering their patients' drug therapy in the COVID-19 era.

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Dr Niki Katsiki and Maciej Banach contributed equally to this paper.

## Conflict of interest

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