

Cardiovascular diseases, lipid-lowering therapies and European registries in the COVID-19 pandemic

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Since December 2019 the coronavirus disease 2019 (COVID-19) which emerged in Wuhan, China, has rapidly spread around the globe. With >10 000 000 confirmed cases in >180 countries and an estimated mortality rate of 2–5%, it has had an enormous economic and social impact worldwide. Clinical risk factors and diseases which predispose to severe COVID-19 are pulmonary diseases, advanced age, hypertension, coronary artery disease, diabetes mellitus, and smoking (Figure 1).¹ These factors might affect the susceptibility to infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the subsequent critical clinical complications.² Approximately 80% of patients after SARS-CoV-2 infection develop mild to moderate symptoms, 15% severe, and ~5% life-threatening clinical complications. Severe clinical problems of COVID-19 patients could involve the difficult management of acute myocardial infarction, acute pulmonary embolism, cardiac tamponade complicating myo-pericarditis, and heart failure.

The infection involves binding of the SARS-CoV-2 spike protein to the cell receptor angiotensin-converting enzyme 2 (ACE2).³ Because ACE inhibitors and angiotensin receptor blockers (ARBs) can increase ACE2 expression in experimental studies, this observation has raised discussions about the safety of these important antihypertensive drugs in the current COVID-19 pandemic.³ It should be emphasized that such discontinuation of ACE inhibitor or ARB therapy in patients with heart failure or coronary disease could lead to unnecessary worsening of cardiac conditions and hospitalization. Recent position statements from the European Society of Cardiology ([https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang)), the European Society of Hypertension,⁴ the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology (<https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>) strongly recommend that patients

taking ACE inhibitors or ARBs who contract COVID-19 should continue treatment. Recent clinical studies support those recommendations.⁵

Statins are well-known and widely prescribed lipid-lowering drugs. However, statin treatment has increased ACE2 expression in the heart of experimental models via epigenetic histone modifications.⁶ This might raise concerns about the safety of statins in the current COVID-19 pandemic.

From our point of view, up-regulation of ACE2 by statins and ARBs might even be protective in the pathogenesis of COVID-19. Infection of experimental models with the closely related SARS-CoV and its spike protein reduced ACE2 expression. Furthermore, genetic deletion of ACE2 and ARBs reduced pathological lung alterations after SARS-CoV infection. A potential mechanism of the protective effects of ARBs during SARS-CoV infection could be an up-regulation of ACE2. ACE2 usually mediates the cleavage of angiotensin II into angiotensin(1-7). In contrast to the classical renin-angiotensin-aldosterone system, the ACE2/angiotensin(1-7)/Mas receptor axis is considered as protective in the cardiovascular system, the lung, and the kidney. In addition, statins are vasoprotective by lowering LDL, up-regulating nitric oxide, and mediating antioxidative and anti-inflammatory effects. Inflammation plays a major role in atherosclerosis and cardiovascular diseases.^{7,8} Statins and ARBs alone and synergistically improve endothelial function⁹ and the prognosis of cardiovascular patients.

The impact of the lipoprotein levels on the clinical outcome in COVID-19 patients is currently not well understood. Recently, the impact of underlying cardiovascular disease and myocardial injury on fatal outcomes in patients with COVID-19 has been described.¹⁰ This study compared patients with and without elevation of troponin T (TnT) levels. Total, HDL, and LDL cholesterol levels did not differ between both groups, but patients with elevated TnT levels showed higher triglyceride levels. The inflammatory biomarkers high-sensitivity C-reactive protein

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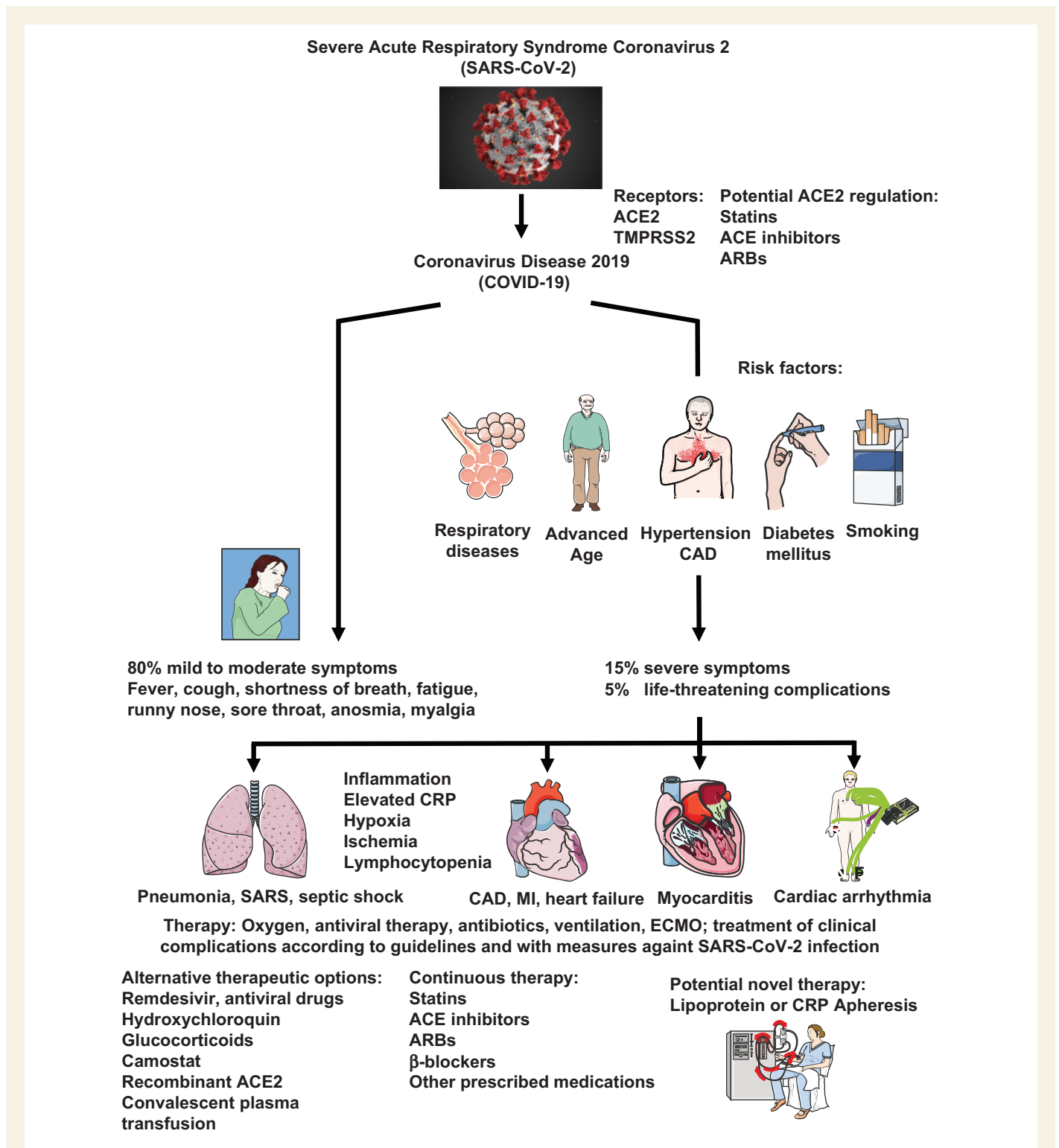


Figure 1 Conceptual figure highlighting risk factors, clinical characteristics, complications, and therapeutic approaches of severe coronavirus disease 2019 (COVID-19). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection involves binding to the cell receptor angiotensin-converting enzyme 2 (ACE2). Statins, ACE inhibitors, and angiotensin receptor blockers (ARBs) can increase ACE2 expression in experimental studies. This could theoretically increase viral load (without evidence), but ACE2 up-regulation has been shown to be protective in the cardiovascular system, the lung, and the kidney. Risk factors for severe COVID-19 are respiratory diseases, advanced age, hypertension, coronary artery disease (CAD), diabetes mellitus, and smoking. Approximately 80% of COVID-19 patients develop mild to moderate symptoms, 15% severe, and ~5% life-threatening clinical complications. They include pneumonia, severe acute respiratory syndrome (SARS), septic shock, and complications by viral infection in the treatment of CAD, myocardial infarction (MI), heart failure, myocarditis, and cardiac arrhythmias. Treatment of clinical symptoms according to the guidelines needs preventive measures against SARS-CoV-2 infections. Prescribed pharmacological therapy including statins should be continued, and novel therapeutic strategies including lipoprotein and CRP apheresis could be tested in clinical studies and documented in European registries. Parts of the figure are adapted from SMART – Servier Medical Art, Servier: <https://smart.servier.com>. The SARS-CoV-2 image was created and kindly provided by CDC / Alisa Eckert, MS, and Dan Higgins, MAMS.

(hsCRP), procalcitonin, and globulin were significantly increased in patients with elevated TnT levels. The authors suggest that in patients with COVID-19, the previous use of cardiovascular drugs should not be discontinued based on current data. Because SARS and COVID-19 patients are characterized by increased CRP levels and activation of proinflammatory pathways, statins with their anti-inflammatory potential might reduce corresponding severe clinical complications of COVID-19-induced acute lung injury and cardiovascular complications.

Therefore, we would recommend continuing statin therapy in COVID-19 patients to benefit from its well-documented protective effects. The statins will control LDL cholesterol levels, thus preventing lipoprotein-related cardiovascular complications. Immunomodulatory properties and multiple pleiotropic effects of statins include the inhibition of T-cell activation, antigen-presenting function, and leucocyte infiltration of target organs. They might also protect against myocardial damage after local inflammation, hypoxia, and ischaemia in response to severe SARS-CoV-2 infections. Finally, statins could up-regulate the protective ACE2 in severe lung injury and reduce the impact of inflammation in the lung, thus supporting beneficial effects. The protective effect of statins might even be dose dependent. Recently, it was described that statins may be associated with a lower risk of in-hospital death from COVID-19 than non-use.⁵ However, larger clinical trials will be necessary to study the impact of statin therapy on clinical parameters and the outcome in COVID-19 patients.

Other strategies to lower lipoprotein levels might represent interesting novel therapeutic approaches.^{11–13} In general, lowering LDL cholesterol and lipoprotein(a) levels could have beneficial effects such as up-regulation of ACE2 and prevention of cardiovascular complication during COVID-19 infection. The impact of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors on outcomes of COVID-19 patients is currently not known. Lipoprotein apheresis is an attractive alternative therapeutic approach to treat critically ill patients. Lipoprotein apheresis exerts lipid-lowering effects [especially LDL cholesterol and lipoprotein(a)] and anti-inflammatory effects (decrease of CRP and of proinflammatory cytokines), and improves the rheological properties of the blood.¹⁴ Because COVID-19 patients have elevated CRP levels and local inflammation, this therapy might be beneficial. It may contribute to the stabilization of atherosclerotic plaques which could be affected by the coronavirus and finally may rupture. Therefore, lipoprotein or even recently described CRP apheresis using rigidly implemented isolation measures might be a novel strategy in the treatment of COVID-19 patients.

European registries such as the recently created CAPACITY-COVID registry will be important measures to determine the role of cardiovascular diseases and therapeutic strategies in the COVID-19 pandemic.¹⁵ The European Group – International Society for Apheresis (E-ISFA) has recently joined the German Center for Infection Research, the ESCMID Emerging Infections Task Force, and a number of other institutions including the Robert Koch Institute in the LEOSS (Lean European Open Survey on SRAS-CoV-s Infected Patients) registry. This is an open, international, and anonymous registry covering all aspects of COVID-19 infections from diagnosis, laboratory measurements over medical treatments, to clinical outcomes (<https://leoss.net>). This initiative will help in

defining the impact of apheresis therapy on clinical parameters and outcomes in COVID-19 patients.

In summary, do not stop the ongoing pharmacological therapy including statins and ensure that lipoprotein levels of cardiovascular patients adhere to the European guidelines in the current COVID-19 pandemic. Apheresis might represent a promising novel therapeutic approach in severely ill COVID-19 patients. Recently created European registries including LEOSS will help to define the role of cardiovascular diseases and therapeutic strategies in the treatment of COVID-19.

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