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COVID-19: (mis)managing an announced Black Swan

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In late December 2019, the Chinese physician Li Wenliang warned of unusual cases of pulmonary infection, suspecting that a new, highly contagious coronavirus might be involved. He was not heard. Within weeks the unthinkable became reality and a pandemic evolved and took its path around the globe. What sounded initially like a harmless flu, and then suddenly arose as a Black Swan to the many unprepared, was an expected event to virologists and to philanthropists such as Bill Gates. As such, Nassim Taleb who popularized the term[1] introduced by Sir Karl Popper almost a century ago[2] refused to call it a Black Swan. Many national healthcare systems were not well prepared for such an event: disinfectant and masks were lacking, there were not enough hospital beds or intensive care units (ICUs), and ventilators were scarce. All things that costed many lives— for sure, the austerity politics did not pay off in healthcare as it killed many, indeed too many in affected countries.

For cardiologists, the pandemic was indeed a Black Swan as the vast majority had never dealt with viruses or epidemics (with the exception of a few interested in myocarditis).[3] As it turned out, cardiovascular diseases (CVDs) became *the* major risk factors for an unfortunate course of the pulmonary infection and a major cause of death in affected patients. Within weeks, CVDs came to centre stage in the pandemic, as outlined in a *Viewpoint* '**Coronaviruses and the cardiovascular system: acute and long-term implications**' by Bernard Prendergast *et al.* from the John Radcliffe Hospital in Oxford, UK.[4] The authors remind us that much has been learnt in the course of preceding epidemics, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and H1N1 influenza, and it is now recognized that their overall health burden may be underestimated, since extrapulmonary manifestations are frequent. Acute and chronic cardiovascular complications of pneumonia are common and result from various mechanisms, including relative ischaemia, systemic inflammation, and pathogen-mediated damage including myocarditis.[5–7] Of note, influenza vaccination reduces major cardiovascular events in patients with coronary disease.[8] Thus, the COVID-19 outbreak emphasizes the need for greater awareness of the acute and long-term cardiovascular implications of viral infections and the significant gaps in knowledge that future research will need to address for the benefit of such patients.

In a second *Viewpoint* entitled '**SARS-CoV-2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19?**', Gabriela Kuster *et al.* from the University Hospital Basel in Switzerland discuss the hypothesis that angiotensin-converting enzyme inhibitors (ACE-Is) could foster cell entry of the COVID-19 virus and in turn provide a risk factor for fatal outcomes due to up-regulation of ACE2 that the virus uses to dock on the cell membrane (*Figure 1*).[9] The authors discuss the knowns and unknowns regarding the renin–angiotensin system, ACE-Is, and SARS-CoV-2 interaction, and provide two interpretations, i.e. (1) a possible negative impact as ACE-Is (which in the meantime appears unlikely)in spite of the well established protective effects of the agents[10]or (2) reverse causality since patients on ACE-Is are commonly older and have more comorbidities.[11–13]

A Brief Communication entitled '**Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts**', Stefanie Dimmeler *et al.* from the Johan-Wolfgang Goethe Universität in Frankfurt am Main, Germany continue on the subject.[14] They determined the tissue levels of ACE2 where SARS-CoV-2 binds via its glycosylated outer membrane spike proteins. They found that ACE2 is highly expressed in the lung and heart, complementing previous observations that it is increased in myocardial infarction.[15] Although SARS-CoV-2 mainly invades alveolar epithelial cells, it can also cause myocardial injury, as assessed by increased troponin T and NT-proBNP levels in COVID-19-infected patients, as further outlined in this issue.[16]

The current pandemic coronavirus SARS-CoV-2 predominantly affects elderly individuals, especially men and those with CVD who are often receiving ACE-Is. In their manuscript '**Circulating plasma concentrations of ACE2 in men and women with heart failure and effects of renin–angiotensin–aldosterone-inhibitors: potential implications for coronavirus SARS-CoV-2-infected patients**' Adriaan Voors and colleagues from the University Medical Center Groningen in the Netherlands expand on this issue with heart failure patients.[17] They measured ACE2 in 1485

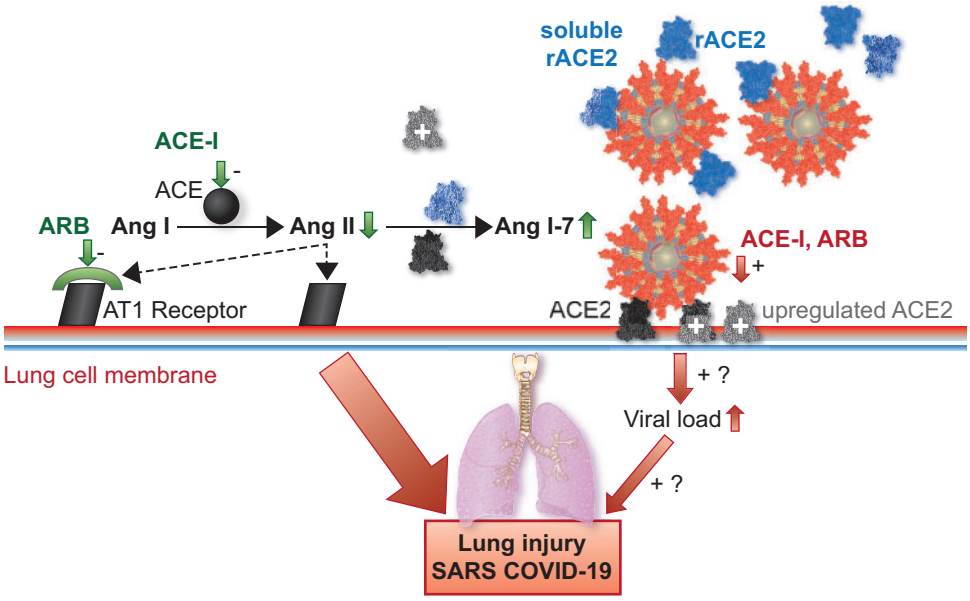

Figure 1 Conceptual figure highlighting the central role of ACE2 in the potentially deleterious (red) and protective (green) effects of the renin–angiotensin–aldosterone system (RAAS) and its inhibition in the development of severe acute respiratory syndrome (SARS) (from Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, Widmer AF, Osswald S. SARS-CoV2: should inhibitors of the renin angiotensin system be withdrawn in patients with COVID-19? See pages 1801–1803).

men and 537 women with heart failure as the index cohort and validated it in 1123 men and 575 women. The strongest predictor of elevated plasma levels of ACE2 in both the index and validation cohort was male sex. In the index cohort, use of ACE-Is, angiotensin receptor blockers (ARBs), or mineralocorticoid receptor antagonists was not an independent predictor of plasma ACE2. In the validation cohort, ACE-Is were independent predictors of lower plasma ACE2, and mineralocorticoid receptor antagonists of higher plasma ACE2 concentrations. Thus, surprisingly, in patients with heart failure, plasma concentrations of ACE2 were higher in men than in women, but use of neither an ACE-I nor an ARB was associated with higher plasma ACE2 concentrations. These data might explain the higher incidence and fatality rate of COVID-19 in men, but do not support previous reports suggesting that ACE-Is or ARBs increase the vulnerability for COVID-19 through increased plasma ACE2 concentrations. These provocative findings are further discussed by in an **Editorial** by Gavin Oudit from the University of Alberta in Edmonton in Canada and Marc Pfeffer from the Harvard Medical School in Boston, Massachuttets in the USA.[18]

The impact of CVD on COVID-19 outcomes has been investigated in the article '**Clinical characteristics and outcomes of Caucasian patients with COVID-19 and a history of cardiac disease in Northern Italy**' by Marco Metra and colleagues from the Università degli Studi di Brescia in Italy, one of the centres with the highest case load and mortality.[19] They analysed 53 consecutive patients with confirmed COVID-19 and a history of CVD admitted between 4 and 25 March 2020, when the epidemic reached its peak. Their mean age was 68 years and 81% were males. The main cause of admission was either COVID-19 pneumonia with a history of CVD in 47% or an acute cardiac condition with concomitant COVID-19 in 52%. Of note, 16 presented with acute heart failure, 6 with acute coronary syndrome (ACS), and 4 with pulmonary embolism (*Figure 2*). During hospitalization, 32% died, 11% developed thrombo-embolic events, 21% developed acute respiratory distress syndrome or ARDS, and 11% suffered septic shock. Non-survivors tended to be older, with a higher burden of cardiac comorbidities, impaired renal function, lower blood cells count, and higher D-dimer. Both high-sensitivity troponin and NT-proBNP were elevated at admission in both groups, with a trend towards higher levels among non-survivors. Patients who died were also more likely to have a lower PO_2/FiO_2 ratio and need for high-flow oxygen support, compared with those who lived. Thus, Caucasian patients with CVD and superimposed COVID-19 have an extremely poor prognosis, findings that are put into context in an **Editorial** by Pierpaolo Pellicori from the Hull and East Yorkshire Medical Research and Teaching Centre in Kingston upon Hull, UK.[20]

The impact of viral pneumonia on CVD through various mechanisms is then reviewed in the manuscript entitled '**Deleterious effects of viral pneumonia on the cardiovascular system**', by Ling Yang and colleagues from the Third Affiliated Hospital of Soochow University in Changzhou, China.[21] Even though viral pneumonia is regarded as a pulmonary disease characterized by dyspnoea and hypoxaemia, cardiovascular events outweigh all other causes of death in many viral pandemics. They pursued three aspects: (i) to summarize the knowledge about epidemiological characteristics and clinical manifestations of viral infections in recent pandemics; (ii) to explore the cardiovascular response to these infections; and (iii) to identify coping strategies as experienced in the Wuhan epidemic and future viral infection pandemics.

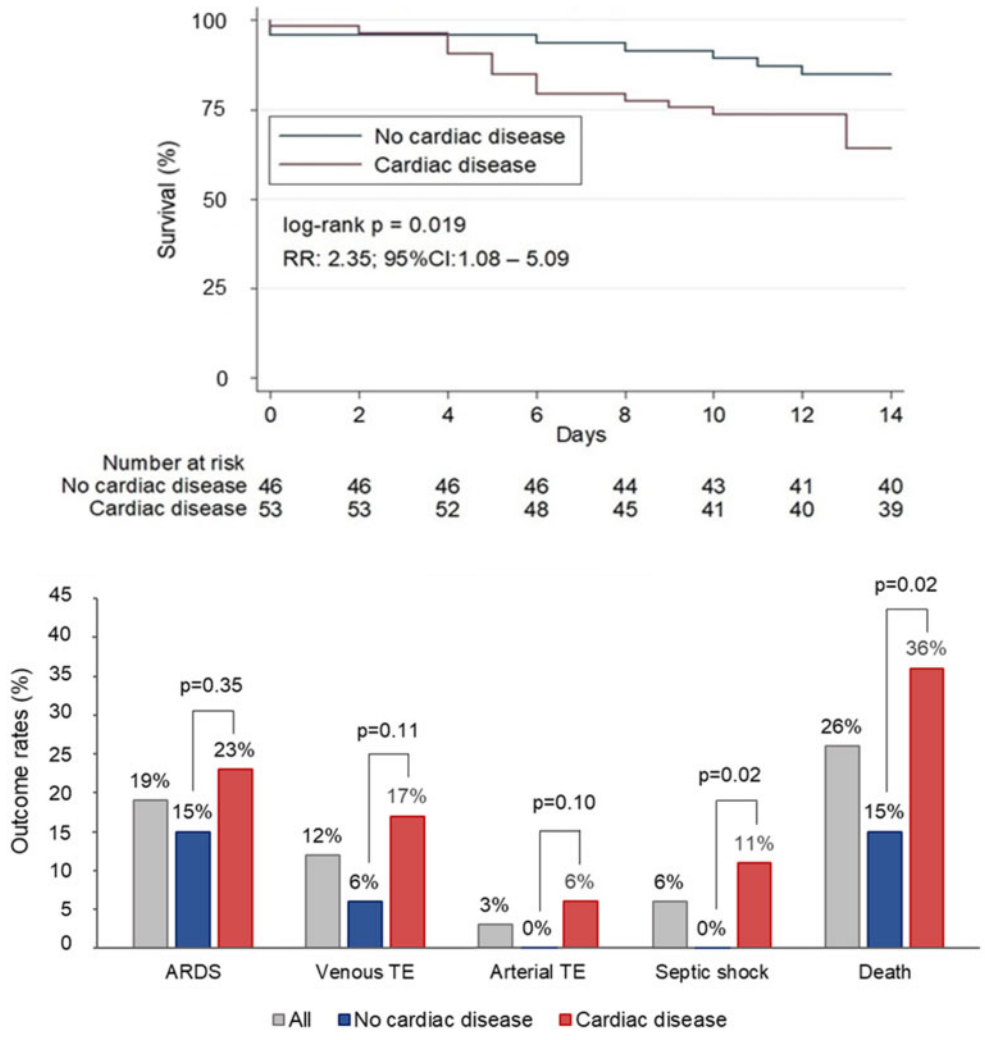

Figure 2 Top: Kaplan–Meier 14-day survival rates for the patients with and without concomitant cardiac disease. Bottom: 14-day outcomes (major complications and deaths) of all patients and the patients without and with concomitant cardiac disease. Abbreviations: ARDS, acute respiratory distress syndrome; TE, thrombo-embolism (from Inciardi RM, Adamo M, Lupi L, Cani DS, Pasquale MD, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. See pages 1821–1829).

Pandemics such as COVID-19 massively affect health services in general, as all efforts are focused on the patients affected by it. Furthermore, the outcome of interventions may be affected by COVID-19 for both patients and physicians in charge. The latter issue is addressed in the *Current Opinon* '**EAPCI Position Statement in Invasive Management of Acute Coronary Syndromes during the COVID-19 pandemic**' prepared by Andreas Baumbach from St. Bartholomew's Hospital in London, UK, and colleagues on behalf of EAPCI.[22] They note that the COVID-19 pandemic poses an unprecedented threat to healthcare worldwide as the number of patients requiring hospital admission and intensive care overwhelms many healthcare systems and negatively affects standard of care, leading to collateral clinical damage. This position statement aims to assist cardiologists in the invasive management of ACS in the context of the COVID-19 pandemic. Modified diagnostic and treatment algorithms are proposed to adapt evidence-based protocols for this unprecedented challenge. Various clinical scenarios, as well as management algorithms for patients with a diagnosed or suspected COVID-19 infection, presenting with ST-segment and non-ST-segment elevation ACS, are described, as well as scenarios for re-organization of ACS networks, with redistribution of hub and spoke hospitals, in addition to in-hospital reorganization of emergency rooms and cardiac units.

The issue is also complemented by various *Discussion Forum* pieces. In a first entitled '**Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage**', Bernhard Metzler and colleagues from the University Hospital Innsbruck in Austria discuss the pandemic based on the numbers from their country. In another contribution entitled '**Is fulminant myocarditis**

caused by circulating human coronaviruses?' Ryan Dare and colleagues from the University of Arkansas for Medical Sciences in Little Rock, Arkansas, USA comment on the recent contribution '**Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin**' by Yuan Fang and colleagues from the Sichuan University West China Hospital in Chengdu, Sichuan (China).[23,24] Fang *et al.* respond to the contribution in a separate piece.[25]

In '**Switching to another antihypertensive effective drug when using ACEIs/ARBs to treat arterial hypertension during COVID-19**', Michele Mario Ciulla from the University of Milan in Italy comment on the *Viewpoint* article also published in this issue entitled '**SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19?**' by Kuster *et al.* [9,26] Kuster *et al.* respond in a separate contribution.[27]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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