

The saga continues: is COVID-19 a cardiopulmonary disease?

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Since last November, almost 5.5 million confirmed COVID-19 infections and 350 000 deaths have been reported.¹ As evidence is mounting, it has become clear that while COVID-19 initially affects the airways and lungs, the inflammatory storm occurring later during the infection also involves the cardiovascular system and leads to venous thrombosis, pulmonary embolism,² heart blocks,³ myocardial infarction, as well as myocarditis^{4–6} and heart failure.⁷ Furthermore, any cardiac condition seems to represent a major risk factor for an unfavourable outcome of the COVID-19 infection.

Finally, and less apparent initially, the lockdown in all affected countries produced extensive collateral damage as patients were afraid to visit hospitals for acute cardiac conditions and were deprived of necessary care as outpatient and elective inpatient services had been cancelled. This second Focus Issue on COVID-19 and cardiovascular disease addresses all these issues and starts with the *Fast Track* 'Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study' by Fei Li and colleagues from China. They investigated whether the treatment of hypertension, especially with renin–angiotensin–aldosterone system (RAAS) inhibitors—as suggested initially⁸—would influence the mortality of all patients with COVID-19 infection admitted to the Huo-Shen-Shan Hospital in Wuhan, China.⁹ This hospital was designed only for treating COVID-19 and opened on 5 February 2020. Hypertension and its treatment were stratified according to medical history or medications prior to the infection. Among 2877 patients, 29.5% had a history of hypertension. After adjustment for confounders, patients with hypertension had a two-fold increased relative mortality risk as compared with those without hypertension. Patients with a history of hypertension, but without antihypertensive treatment, had an even higher risk of mortality compared with those with treatment, with a hazard ratio of 2.17. A quarter of the patients were treated with at least one RAAS inhibitor,

while the rest received beta-blockers, calcium antagonists, or diuretics. In those on RAAS inhibitors, mortality was numerically lower, but did not reach significance (Figure 1). Thus, in this largest cohort published so far on that issue, hypertension appears independently associated with mortality from COVID-19. Furthermore, these data do not support the hypothesis that RAAS inhibitors worsen outcomes among persons with this infection. These important findings are put into context of the debate on the role of ACE2 and COVID-19 in a thought-provoking **Editorial** by Luis Ruilope from the Hospital 12 de Octubre in Madrid, Spain.¹⁰

Troponins are known risk factors for outcome in patients with acute coronary syndromes,^{11,12} heart failure,¹³ valvular heart disease,¹⁴ pulmonary embolism,¹⁴ and even normal individuals. As such, it was important also to study this aspect in patients with COVID-19 infection. In their article entitled 'Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019', Bo Yang and colleagues from the Wuhan University Renmin Hospital in China investigated this aspect in 671 patients with severe COVID-19 infection.¹⁵ Of those, 9.2% died; these patients had more comorbidities and more commonly had myocardial injury (i.e. 75.8% vs. 9.9%) than survivors. The area under the receiver operator characteristic curve of high-sensitivity cardiac troponin I for in-hospital mortality was 0.92. The optimal cut-off points (i.e. >0.026 ng/mL) and high levels of high-sensitivity cardiac troponin I predicted in-hospital death, with a hazard ratio of 4.56 and 1.25, respectively. In multivariable logistic regression, older age, comorbidities such as hypertension, coronary artery disease, chronic renal failure, and chronic obstructive pulmonary disease, and a high level of C-reactive protein were predictors of myocardial injury. Thus, risk of in-hospital death among patients with severe COVID-19 is predictable by markers of myocardial injury, which were associated with an inflammatory response and cardiovascular comorbidities. These clinically important findings are accompanied by an **Editorial** by Hugo Katus from the University Hospital Heidelberg in Germany, and colleagues.¹⁶

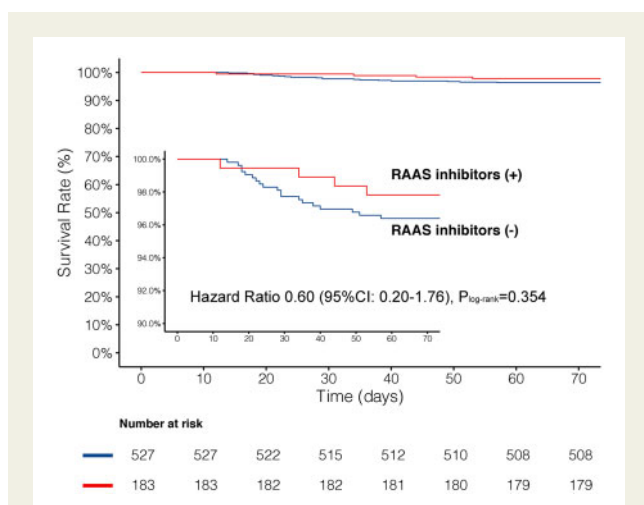


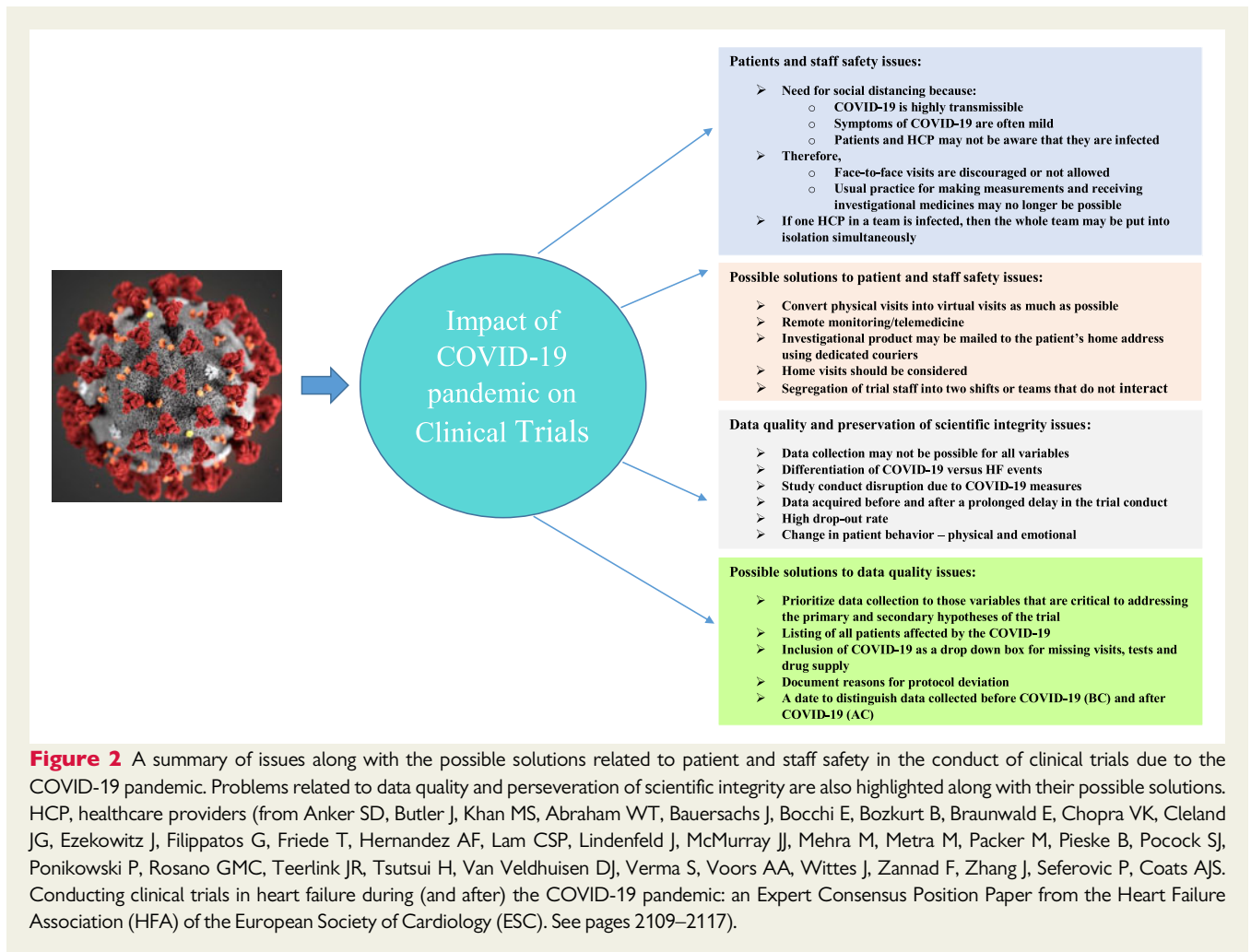
Figure 1 Kaplan–Meier survival curves for mortality from the time of symptom onset, patients with ACEI/ARBs (RAAS inhibitors) or beta-blockers, CCBs, or diuretics (non-RAAS inhibitors) (from Gao C, Cai Y, Zhang K, Zhou L, Zhang Y, Zhang X, Li Q, Li W, Yang S, Zhao X, Zhao Y, Wang H, Liu Y, Yin Z, Zhang R, Wang R, Yang M, Hui C, Wijns W, McEvoy JW, Soliman O, Onuma Y, Serruys PW, Tao L, Li F. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. See pages 2058–2066).

Additionally, the COVID-19 pandemic affected not only those with the infection, but also cardiac patients at large. It appears that the recommendations of governmental agencies to stay at home most probably deterred cardiac patients from visiting a hospital when acute symptoms occurred, as outlined in the article **‘Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era’** authored by *Ciro Indolfi* from the Division of Cardiology, Magna Graecia University in Catanzaro, Italy and colleagues of the Società Italiana di Cardiologia and the CCU Academy investigators group.¹⁷ They conducted a multi-centre, observational, nationwide survey on admissions for acute myocardial infarction at Italian intensive cardiac care units over a 1-week period during the COVID-19 outbreak, compared with the equivalent week in 2019. They observed a 48.5% reduction in admissions compared with the equivalent week in 2019. The reduction was significant for both ST-segment elevation myocardial infarction (STEMI) admission, with a 26.5% reduction, and non-STEMI (NSTEMI), with a 65.4% reduction. Among STEMI, the reduction was greater for women, with 41.2%, than for men, with 17.8%. A similar reduction in acute myocardial infarction admissions was registered in North Italy (52.1%), Central Italy (59.3%), and, surprisingly, also in Southern Italy (52.1%) where fewer COVID-19 cases were observed. Thus, the COVID-19 pandemic has led to a significant collateral damage even in non-COVID-19 patients with cardiac disease. As outlined in an insightful **Editorial** by *M. Chadi Alraies* from Wayne State University in Washington, DC, USA,¹⁸ the causes may be multifactorial and may be related to the fact that patients may have been afraid to visit hospital during the pandemic or that fewer plaque ruptures occurred due to the standstill of life during the lockdown.

Finally, a comprehensive review entitled **‘COVID-19: from epidemiology to treatment’** by *Jose Miro* and colleagues from the Hospital Clínic–IDIBAPS in Barcelona, Spain reminds us that cardiologists and cardiovascular surgeons must be aware now of virus infections in their patients and on their impact in general.¹⁹ Healthcare workers should be educated and trained to tackle the enormous challenge posed by SARS-CoV-2 and other viruses in wards, operating theatres, ICUs, and cardiac catheterization laboratories. This review provides the necessary knowledge about COVID-19 and focuses on relevant aspects on prevention and management for specialists within the cardiovascular field.

As much as patients and the clinical service suffered from the COVID-19 pandemic, so did research, and running clinical trials in particular. Indeed, in most countries, any running protocols were stopped, which impacted on the recruitment, follow-up, and eventually the integrity, safety, and results of such trials. This issue is discussed in the *Current Opinion* article **‘Conducting clinical trials in heart failure during (and after) the COVID-19 pandemic: an Expert Consensus Position Paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)’** by *Stefan Anker* from the Charité in Berlin, Germany and colleagues. (Figure 2)²⁰ For heart failure trials, COVID-19 may be particularly impactful as patients with heart failure are likely to be at greater risk of infection with COVID-19 and the consequences might also be more serious. Furthermore, they are also at risk of adverse outcomes if their clinical care is compromised. The authors note that as physicians and clinical trialists, it is our moral and ethical duty to ensure safe and effective care is delivered to trial participants without affecting the integrity of the trial. Many regulatory authorities from different world regions have issued guidance statements regarding the conduct of clinical trials during this COVID-19 crisis. However, international trials may benefit from expert guidance from a global panel of experts to supplement local advice and regulations, thereby enhancing the safety of participants and the integrity of the trial. Accordingly, the Heart Failure Association of the European Society of Cardiology conducted web-based meetings with clinical trialists in Europe, North America, South America, Australia, and Asia. In this article, the authors highlight the challenges this pandemic poses for the conduct of clinical trials in heart failure and offers advice on how they might be overcome, with some practical examples. While this panel of experts are focused on heart failure clinical trials, these discussions and recommendations may apply to clinical trials in other therapeutic areas.

The issue is further complemented by Discussion Forum contributions. In a contribution entitled **‘Clinically suspected myocarditis in the course of coronavirus infection’**, *Krzysztof Ozieranski* and colleagues from the Warszawski Uniwersytet Medyczny in Poland comment on the recent article **‘Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin’** by *Yuan Fang* and colleagues from the Sichuan University West China Hospital in China.^{21,22} *Fang et al.* respond to *Ozieranski* in a separate contribution.²³ In another contribution **‘Fulminant myocarditis in the time of coronavirus’** *Vittoria Cuomo* and colleagues from the Università degli Studi di Napoli Federico II Dipartimento di Medicina Clinica e Chirurgia in Italy also comment on the same article by *Fang et al.*²⁴ *Fang et al.* respond to this contribution as well.²⁵



In a contribution entitled **'Does SARS-CoV-2 cause viral myocarditis in COVID-19 patients?'**, Ruihai Zhou from the University of North Carolina at Chapel Hill in North Carolina, USA comment on the recent publication **'Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection'** by Giovanni Peretto and colleagues from the IRCCS San Raffaele Hospital and Vita-Salute University in Milan, Italy.^{5,26} Peretto *et al.* respond in a separate contribution.²⁷

Finally, in a contribution entitled **'Renin-angiotensin-aldosterone system dysregulation and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection'**, Thadathilankal John and colleagues from the Stellenbosch University Faculty of Medicine and Health Sciences in Bellville, South Africa comment on the recent Viewpoint article **'SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19?'** by Gabriela Kuster from the University Hospital Basel in Switzerland.^{8,28} Kuster *et al.* respond to this comment in a separate manuscript.²⁹

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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