ESC European Society of Cardiology
European Heart Journal (2020) **00**, 1–4
doi:10.1093/eurheartj/ehaa958

EDITORIAL

COVID-19 pandemic: complex interactions with the arrhythmic profile and the clinical course of patients with cardiovascular disease

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This editorial refers to 'Ventricular arrhythmia burden during the coronavirus disease 2019 (COVID-19) pandemic', by C.J. O'Shea *et al.*, doi:10.1093/eurheartj/ehaa893.

The implantable cardioverter defibrillator (ICD) is an effective treatment for patients with previous life-threatening ventricular tachyarrhythmias (VAs) or at high risk of developing this type of arrhythmic event potentially leading to sudden arrhythmic death.[1] The favourable outcome after implant of an ICD in patients appropriately selected according to guidelines has been confirmed in the real world, in the setting of both primary and secondary prevention.[2] An ICD constitutes a rescue treatment, and ICD firing reflects our inability to completely prevent the risk of life-threatening arrhythmias despite concurrent pharmacological treatments and, when needed, coronary revascularization.[3]

ICDs are generally accepted by implanted patients, without an important worsening in quality of life (QoL), although psychological problems linked to anxiety and depression have been reported in up to one-third of ICD patients, ranging from mild symptoms to severe post-traumatic stress disorder.[4] Indeed, the occurrence of ICD shocks, rather than reassuring physicians of the appropriateness of the indications, has a series of associated important and worrisome implications linked to the risk of shock-related psychological distress, impaired QoL,[5] and the risk of a worsening of the outcome in terms of expected survival.[6,7]

The physiology and pathophysiology of cardiovascular diseases (CVDs), including the occurrence of VA in patients with ICDs, may be influenced by triggers such as sympathetic tone, emotional factors and psychological distress, mental health status, chronic stress, physical activity intensity level, systemic illnesses and concurrent non-cardiovascular drugs, as well as air pollution and ionizing radiation through inhalation of particles.[8] All these factors have to be considered in any attempt to assess the impact of coronavirus disease 2019 (COVID-19) on the clinical course of patients with CVD implanted with an ICD. The COVID-19 pandemic is disrupting healthcare systems worldwide, and this unprecedented and challenging event is associated with a massive impact on welfare, social life, and the economy, especially in relation to the adoption of lockdown periods by many governments. Isolation, social distancing, and quarantine, typical of a lockdown period, may imply a series of deleterious effects on patients' psychological status, often combined with financial issues or unemployment, as well as a reduction in physical activity. It is possible to hypothesize that this can result in maladaptation to physical inactivity leading to psychological distress.[9] In general, it is unknown if during the lockdown period most of the patients applied the recommendation to maintain some level of physical activity, whose positive impact on physical and mental health is well recognized and has been demonstrated.[9]

In the current issue of the *European Heart Journal*, O'Shea *et al.*[10] report on a cohort of patients previously implanted with an ICD followed remotely by a vendor-neutral service receiving transmissions and alerts from multiple device platforms. The authors selected patients from the USA with transmissions during the 100 days following the first COVID-19 case identified in that country (21 January 2020) and compared transmitted data with two periods of 2019 corresponding to the last months of the year and to the same seasonal period of 2019. The aim of the study was to verify whether the period of the COVID-19 pandemic and the associated lockdown were related, as reasonably expected, to an increased burden of VAs, as detected by implanted devices (ICDs, including biventricular ICDs). The study question was very interesting and well motivated since it could be expected that the COVID-19 pandemic could result in adverse experiences and distress for the population of patients carrying an ICD, as has been reported for traumatic events such as

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natural disasters, earthquakes, wars, terroristic attacks, violent assaults, crashes, etc.[11] It is known from the literature that strong emotions, occurring in particular in patients with a psychological trait characterized by anger, may induce sympathetic arousal favouring the onset of VA, and therefore an ICD intervention in subjects with an arrhythmogenic substrate.[12]

In this study, the primary analysis was the paired comparisons between patients who underwent remote monitoring both during the COVID-19 period and in the two control periods of 2019, respectively. The authors should be congratulated for this interesting analysis which unexpectedly showed that the number of VAs treated by an ICD, with either antitachycardia pacing or shocks, was actually reduced during the period of the COVID-19 pandemic by 31–32% as compared with the two control periods. Additionally, the proportion of patients with treated VAs was lower in the states with the highest incidence of COVID-19. Overall, the number of patients who had VAs did not differ during the three study periods, but the number of arrhythmias declined during the COVID-19 pandemic, in parallel with the adoption of formal recommendations to stay at home (lockdown). The authors concluded that the coincidence of VA burden reduction with the measures of social isolation and lockdown may imply a causal relationship, linked to a reduced exposure to real-life stressors, usually acting as triggers of arrhythmogenesis. In summary, the study highlights that within the wide spectrum of the complex, even disruptive, effects of the COVID-19 pandemic on the natural course of CVD and specifically on arrhythmias, we should include a reduction in ICD interventions since, as found by this report, the net result of COVID-19 direct and indirect effects can be, in selected patients, a reduction of factors triggering or favouring VA. The findings reported by O'Shea *et al.*[10] are noteworthy, since the observed reduction in VA burden and the consequent reduction in ICD shocks may allow avoidance of the vicious cycle of distress enhanced by a depressive coping and dysfunctional appraisal that *per se* facilitates the risk of VA and adverse outcomes.[11] The lack of details on patient profiles and on the course of the underlying CVD during the study periods actually limits more detailed assessments of the multiple factors and interactions that are potentially involved. For instance, a condition of distress may derive from working activities and difficulties at work, up to the loss of work and unemployment, and in competitive environments, as in western countries and especially North America, working activities may facilitate arrhythmic events, as previously shown.[13] However, according to the average age of the study patients (69 ± 12 years), we can presume that most of them were retired. Despite these considerations, the hypothesis made by the authors that the reduced occurrence of VA is linked to the degree of social lockdown and the associated reduction in exposure to stressors and triggers is attractive. Anyway, it should be considered that these observational data are related to a selected group of patients who were free from a terminal course during the study periods that were analysed. Very recent data from the USA highlighted that mortality rates for heart disease increased during the first months of the COVID-19 pandemic[14] but, according to methods, patients who unfortunately died during this period were excluded from the analysis reported by O'Shea *et al.*[10] It is unknown what proportion of unselected patients carrying an ICD, in the so-called 'real-world', could present the unexpected finding of a reduced burden of VA reported by O'Shea *et al.*[10] Probably, an analysis focused on patients with a purely electrical disease (Brugada syndrome, long QT, channelopathies, etc.) vs. patients with left ventricular dysfunction/heart failure could help to estimate the variable impact of COVID-19 on these different underlying substrates, potentially exposed to differential effects of the COVID-19 pandemic. As a matter of fact, the latter patients, according to age and commonly associated comorbidities, fulfil the criteria for the most vulnerable patients if exposed to the direct effects of the COVID-19 pandemic,[15] while the former, more frequently younger and without heart failure or major comorbidities, are potentially more exposed to the 'social' effects rather than the direct 'clinical' effects of COVID-19.

The clinical status and evolution of diseases are complex and dynamic processes subject to a complex interaction of variables acting as modulators, as causative factors, or as triggers of acute exacerbation leading to disease progression. COVID-19 is disrupting social life, working activities, financial plans, and economic perspectives, as well as the organization of care across the world. However, apart from the direct effects and the impact on outcomes of affected patients, its effects on the full spectrum of patients with a CVD are not well defined, in view of the complex interplay of factors affecting health and the various trajectories of CVD. Indeed these trajectories are exposed to modulation and conditioning by clinical, psychological, environmental, social, and economic factors, with mutual and not fully understood complex interactions (*Figure 1*). The COVID-19 lockdown can be considered as a natural experiment that modifies a series of these variables leading to transition to a new situation of even increased complexity, which would have been unbelievable a few months ago. The natural course of CVD is variable, as depicted in *Figure 1*, but is usually characterized by predisposing factors, acute events, and a general course towards a progressive decline. This decline is accelerated by acute events related to multiple triggers and modulating factors, and can be influenced, in terms of delay or acceleration, in a way that is currently unpredictable as a consequence of COVID-19 and associated lockdown. Some manifestations of CVD, such as acute myocardial infarction (MI), both ST elevation MI and non-ST elevation MI,[16] as well as new-onset or worsening heart failure,[17] were actually reduced during COVID-19. On the other hand, an increase in out-of-hospital cardiac arrests (OHCAs) was reported, associated with reduced survival, with cases of confirmed or suspected COVID-19 accounting for only one-third of the increase in OHCA incidence during the pandemic.[18] These findings suggest that the assessment of the direct and indirect effects of COVID-19 is a very complex process, that at present is necessarily incomplete and defective. Only longitudinal studies will allow assessment of whether the lower occurrence reported for some acute events, such as VAs in selected ICD patients, MI, or acute heart failure, will substantially modify the known course of CVD, which as with any process involving humans is profoundly exposed to the direct or indirect influences of COVID-19. A more comprehensive assessment of the direct and indirect effects of COVID-19 on patients with CVD and on the trajectories that may differentially characterize the clinical course of real-life patients is needed, also focusing on the impact on long-term outcome.

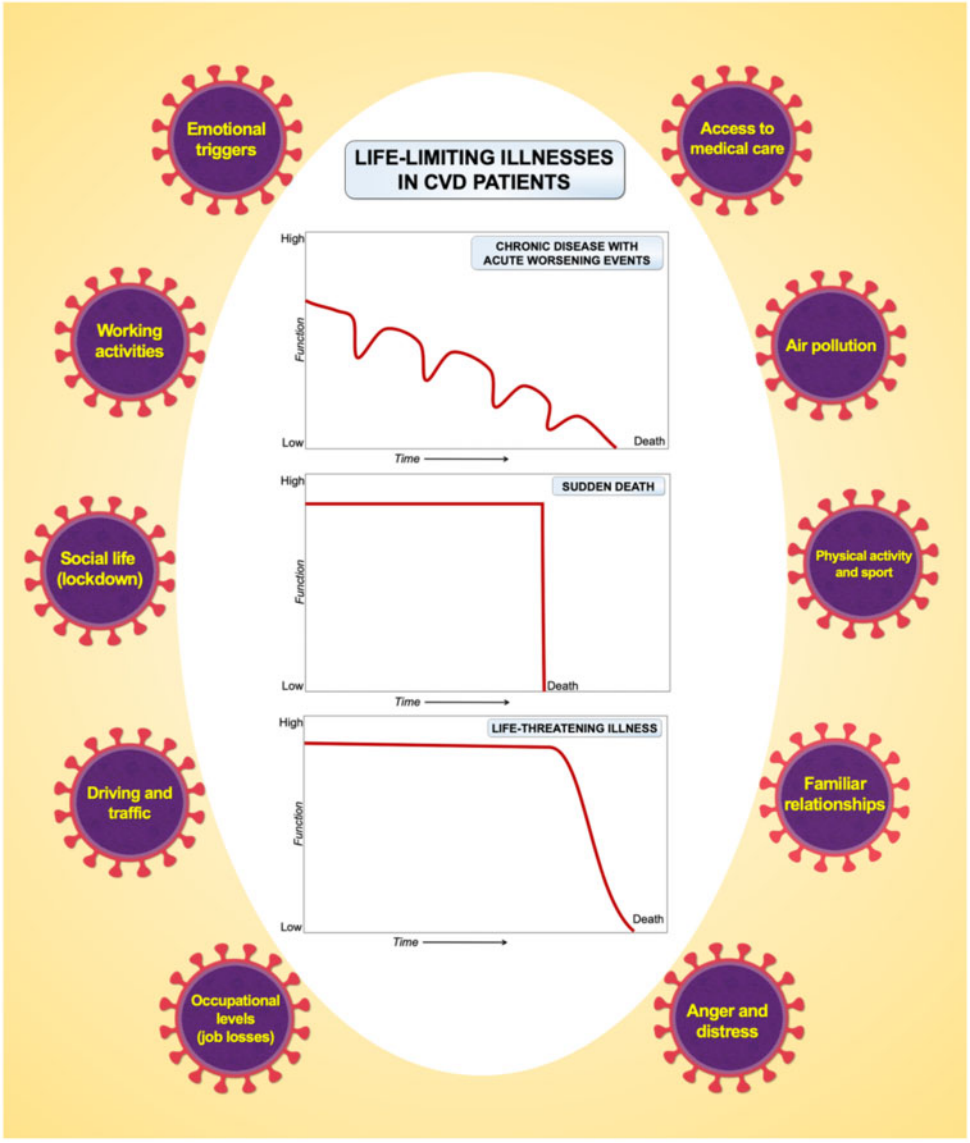

Figure 1 The direct and indirect impact of COVID-19 on life-limiting illnesses in patients with cardiovascular disease. The figure shows the many factors that may influence the different trajectories of life-limiting illnesses in patients affected by cardiovascular disease (CVD). Patients with an ICD may exhibit all the three trajectories, according to baseline profile, new events/comorbidities, and direct and indirect effects of COVID-19, dependent on the many variables shown in the figure.

Conflict of interest: G.B. reports no conflicts with regard to the content of the present work; outside this work, he has received small speaker fees from Medtronic, Boston, Biotronik, Boehringer Ingelheim, and Bayer. M.V. declares no conflicts of interest.

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