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REVIEW

# Cardiovascular disease and COVID-19: a consensus paper from the ESC Working Group on Coronary Pathophysiology & Microcirculation, ESC Working Group on Thrombosis and the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Heart Rhythm Association (EHRA)

**Edina Cenko [1]*, Lina Badimon [2], Raffaele Bugiardini [1], Marc J. Claeys [3], Giuseppe De Luca[4], Cor de Wit [5,6], Geneviève Derumeaux [7,8,9], Maria Dorobantu [10], Dirk J. Duncker [11], Etto C. Eringa [12,13], Diana A. Gorog [14,15], Christian Hassager [16,17], Frank R. Heinzel [18,19,20], Kurt Huber [21,22], Olivia Manfrini[1], Davor Milicic[23], Evangelos Oikonomou [24], Teresa Padro [2], Danijela Trifunovic-Zamaklar [25,26], Zorana Vasiljevic-Pokrajcic[26], Marija Vavlukis [27], Gemma Vilahur[2], and Dimitris Tousoulis [24]**

[1]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Giuseppe Massarenti 9, 40134 Bologna, Italy; [2]Cardiovascular Program ICCC-Research Institute Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, CiberCV, Barcelona, Spain; [3]Department of Cardiology, University Hospital Antwerp, Edegem, Belgium; [4]Cardiovascular Department of Cardiology, Ospedale "Maggiore della Carità", Eastern Piedmont University, Novara, Italy; [5]Institut für Physiologie, Universität zu Lübeck, Lübeck, Germany; [6]Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) e.V. (German Center for Cardiovascular Research), partner site Hamburg/Kiel/Lübeck, Lübeck, Germany; [7]IMRB U955, UPEC, Créteil, France; [8]Department of Physiology, AP-HP, Henri-Mondor Teaching Hospital, Créteil, France; [9]Fédération Hospitalo-Universitaire « SENEC », Créteil, France; [10]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [11]Division of Experimental Cardiology, Department of Cardiology, Thoraxcenter, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [12]Department of Physiology, Amsterdam Cardiovascular Science Institute, Amsterdam University Medical Centres, Amsterdam, The Netherlands; [13]Department of Physiology, Maastricht University, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands; [14]Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, UK; [15]Department of Postgraduate Medicine, University of Hertfordshire, Hatfield, UK; [16]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; [17]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [18]Department of Cardiology, Charité-Universitaetsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany[19]DZHK (German Centre for Cardiovascular Research), partner site Berlin, Berlin, Germany[20]Berlin Institute of Health, Berlin, Germany; [21]3rd Medical Department, Cardiology and Intensive Care Medicine, Wilhelminen Hospital, Vienna, Austria; [22]Medical School, Sigmund Freud University, Vienna, Austria; [23]Department of Cardiovascular Diseases, University Hospital Centre Zagreb, University of Zagreb, Zagreb, Croatia; [24]Department of Cardiology, 'Hippokration' General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [25]Cardiology Department, Clinical Centre of Serbia, Belgrade, Serbia; [26]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; and [27]University Clinic of Cardiology, Medical Faculty, Ss' Cyril and Methodius University in Skopje, Skopje, Republic of Macedonia

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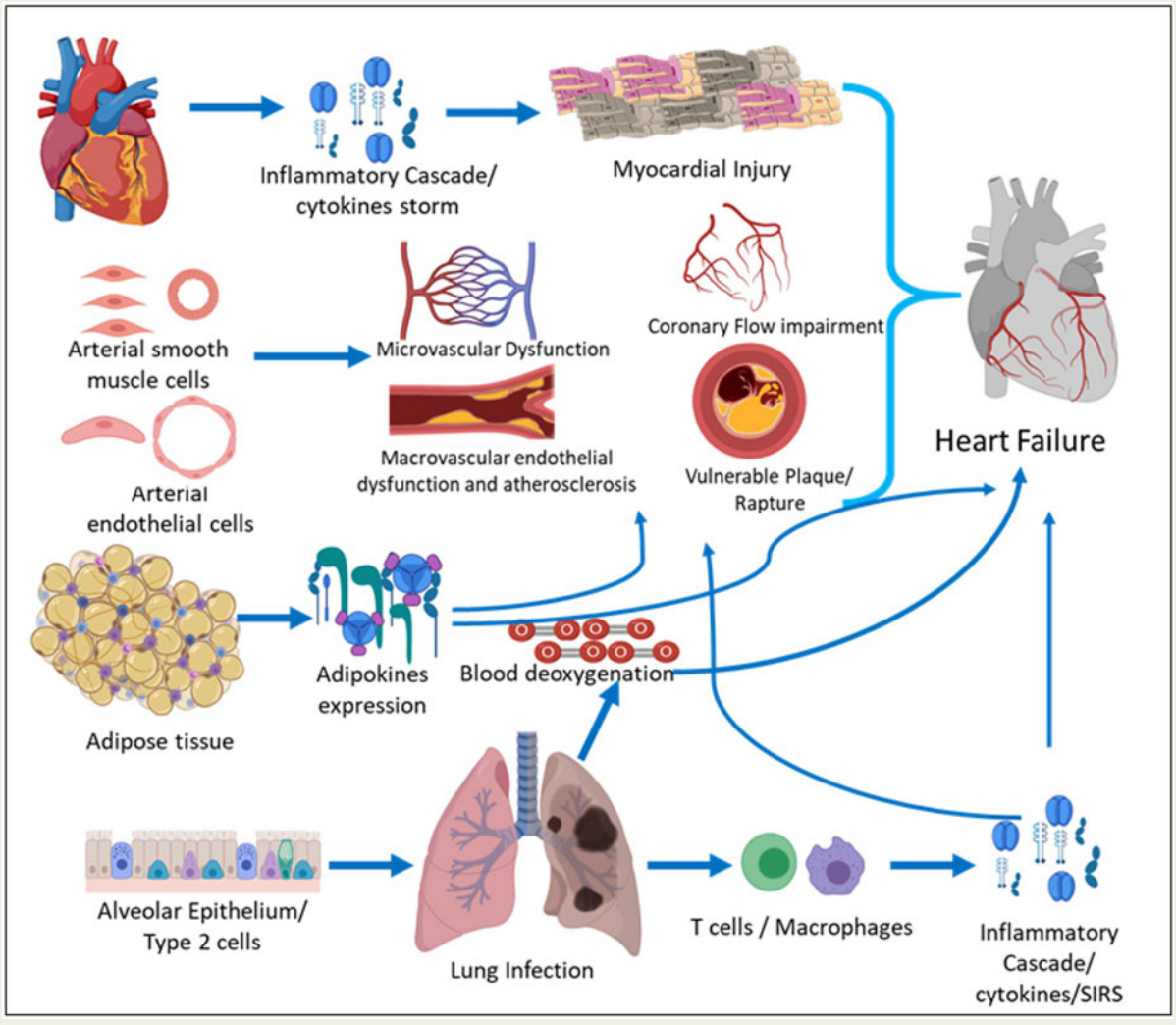
**Abstract**

The cardiovascular system is significantly affected in coronavirus disease-19 (COVID-19). Microvascular injury, endothelial dysfunction, and thrombosis resulting from viral infection or indirectly related to the intense systemic inflammatory and immune responses are characteristic features of severe COVID-19. Pre-existing cardiovascular disease and viral load are linked to myocardial injury and worse outcomes. The vascular response to cytokine production and the interaction between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and angiotensin-converting enzyme 2 receptor may lead to a significant reduction in cardiac contractility and subsequent myocardial dysfunction. In addition, a considerable proportion of patients who have been infected with

*Corresponding author. Tel: +39 0512144911, E-mail: edina.cenko2@unibo.it

SARS-CoV-2 do not fully recover and continue to experience a large number of symptoms and post-acute complications in the absence of a detectable viral infection. This conditions often referred to as 'post-acute COVID-19' may have multiple causes. Viral reservoirs or lingering fragments of viral RNA or proteins contribute to the condition. Systemic inflammatory response to COVID-19 has the potential to increase myocardial fibrosis which in turn may impair cardiac remodelling. Here, we summarize the current knowledge of cardiovascular injury and post-acute sequelae of COVID-19. As the pandemic continues and new variants emerge, we can advance our knowledge of the underlying mechanisms only by integrating our understanding of the pathophysiology with the corresponding clinical findings. Identification of new biomarkers of cardiovascular complications, and development of effective treatments for COVID-19 infection are of crucial importance.

## Graphical Abstract




**Keywords** Cardiovascular disease • COVID-19 • SARS-CoV-2 • cytokines • inflammation • Infection • endothelial dysfunction • microcirculation • thrombosis • Myocardial injury • post-acute COVID-19

## Introduction

To date, the coronavirus disease 2019 (COVID-19) pandemic, has affected over 214 million of people and caused over 4.4 million deaths since December of 2019.[1] Initially thought to be an acute respiratory distress syndrome (ARDS), it has since became clear that COVID-19 is in fact a multiple organ disease. The disease is characterized by cytokine storm, resulting in endothelial inflammation/dysfunction, micro- and macro-vascular thrombosis, which may damage organs other than the lung. Human studies have offered an alarming view of the risks of severe

complications in elderly patients and in those with underlying cardiovascular disease or who are at high cardiovascular risk due to one or more risk factors such as hypertension, diabetes mellitus, hypercholesterolaemia, or obesity. Moreover, recent studies revealed that some biological changes induced by COVID-19 throughout the organs are long-lasting.[2] Consistent with this finding, a large number of patients who have been infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continue to experience symptoms after the acute phase of the acute infection, which can evolve over time and persist for months. While still being defined, these effects are referred to as Post-Acute Sequelae of SARS-CoV-2 infection or 'Long COVID'.[3] Therefore, the magnitude of the problem is still unknown. Post-acute COVID-19 is a matter of major concern for patients affected by cardiovascular disease, given that the presence of underlying cardiovascular comorbidities in patients with COVID-19 is associated with high mortality and COVID-19 can cause cardiovascular disorders, including myocardial injury, arrhythmias, acute coronary syndrome (ACS), and venous thromboembolism (VTE). Cardiovascular disease remains the leading cause of morbidity and mortality globally and is associated with 17.8 million deaths annually.[4] We cannot predict the impact of post-acute COVID-19 on future cardiovascular outcomes. Nevertheless, to meet the urgent need for effective treatment and preventative strategies, rigorous efforts should be made to investigate and integrate biological and clinical findings related to COVID-19 in cardiovascular disease.

In this position paper, we assessed the evidence supporting the mechanisms of acute and post-acute cardiovascular injury among patients with COVID-19 and their clinical features to identify gaps that need to be addressed in future research.

## Inflammation and COVID-19

Severe COVID-19 patients have frequently lymphopenia, hypoalbuminaemia, and exhibit higher levels of transaminases, lactate dehydrogenase, C-reactive protein (CRP), ferritin, and D-dimer, as well as markedly higher levels of interleukin (IL)-2R, IL-6, Il-8, IL-10, and tumour necrosis factor-α (TNF-α). Cytokine production is induced by macrophage activation mediated by a disintegrin and metalloproteinase 17 (ADAM17) which is also responsible for the proteolytic cleavage of angiotensin-converting enzyme 2 (ACE2). In addition, $CD14^+$ $CD16^+$ monocytes producing high levels of IL-6 are observed in COVID-19 patients, suggesting that monocytes contribute to the cytokine storm.[5]

Increased activity of the angiotensin (Ang) II/Ang II receptor type 1 ($AT_1$) receptor axis, due to the loss of function of ACE2 in combination with cytokines-induced hyperinflammation (*Figure 1*) can trigger systemic endothelial injury, overexpression of inflammatory mediators in the interstitial space of various organs causing parenchymal injury, hypercoagulability, microvascular thrombosis in the pulmonary and coronary microcirculation,[6,7] myocardial injury, and multiple organ dysfunction in a positive feedback loop through circulating inflammatory mediators and organ dysfunction-mediated endothelial activation. Inflammation drives SARS-CoV-2-related mortality through pulmonary endothelial barrier dysfunction and left ventricular dysfunction.[6] Cardiac microvascular endothelial cells, exert a positive effect on cardiomyocyte contractility mainly mediated by endothelium-derived nitric oxide (NO). Cytokines reduce endothelium-derived NO delivery likely through increased cytoplasmatic and mitochondrial oxidative stress that results in the scavenging of NO thus reducing cardiomyocyte contractility and relaxation.[8] Pulmonary barrier dysfunction and left ventricular dysfunction may aggravate each other,[9] causing a vicious cycle that results in pulmonary oedema. Lymphopenia occurs early and it is a prognostic factor, potentially associated with reduction of $CD4^+$T and $CD8^+$T cells. Main mechanisms contributing to lymphopenia are thought to be as follows: (i) direct viral infection of lymphocytes, leading to apoptosis and pyroptosis; (ii) viral mediated bone marrow damage and thymus suppression; (iii) lymphocyte apoptosis induced by TNF-α, IL-2R, IL-6, and other pro-inflammatory cytokines; (iv) tissue re-distribution of lymphocytes; and (v) suppression of lymphocyte proliferation caused by metabolic and biochemical changes such as hyperlactic acidemia and hyperbilirubinaemia.[10] This leads to an imbalance of the innate/acquired immune response. Persistent immune activation in predisposed patients can lead to secondary haemophagocytic lymphohistiocytosis, an hyperinflammatory syndrome characterized by a cytokine storm that induces multi-organ failure and death similar to the events observed in septic patients.[6,11]

## ACE2 and cardiovascular manifestations

SARS-CoV-2 is a single-stranded ribonucleic acid (RNA) virus which shares 79.5% sequence identity with SARS-CoV.[12] The outer membrane structural spike (S) protein, which binds with high affinity to the ACE2 receptor, is inserted into the viral envelope. Following binding, the S protein is cleaved and thus activated for membrane fusion by the transmembrane protease serine 2 (TMPRSS2) in a process known as S protein priming (*Figure 1*).[13–15] Therefore, SARS-CoV-2 infection requires the co-expression of ACE2 and TMPRSS2. Spike protein/ACE2 internalization promote the up-regulation of ADAM17 and shedding of the extracellular domain of ACE2, increasing membrane ACE2 down-regulation and reducing surface ACE2 expression.[15] The increased ADAM17-mediated ACE2 shedding exacerbates inflammatory responses by TNF-α and IL6R initiating the cytokine storm.[15]

ACE2 is a master regulator of the renin–angiotensin system (RAS). The activity of the RAS depends on the balance between the ACE/Ang II/$AT_1$ and ACE2/Ang 1-7/Mas axes. ACE converts Ang I to the active vasoconstrictor Ang II, whose actions are mediated by $AT_1$ and Ang II receptor type 2 ($AT_2$). Activation of the ACE/Ang II/$AT_1$ receptor axis, leads to deleterious effects, including vasoconstriction, inflammation, fibrosis, cellular growth and migration, as well as fluid retention. ACE2 is the main Ang 1-7 forming enzyme and the G-protein coupled Mas is a functional receptor for Ang 1-7.[16] Angiotensin 1-7 binding to Mas induces several beneficial effects such as vasodilation, inhibition of cell growth, anti-thrombotic, and anti-arrhythmogenic effects[17] (*Figure 1*). Given that ACE2 is widely expressed in endothelial cells, cardiofibroblasts, cardiomyocytes pulmonary epithelial cells, pulmonary vasculature, kidney, adipose tissue, liver, gut, and central nervous system (*Figure 2*), the loss of ACE2 function following binding of the S protein and ADAM17-mediated shedding along with cytokine storm, are likely involved in the multiple organ dysfunction including the cardiovascular manifestations of COVID-19 (*Figures 1 and 2*). Even though infection of human cardiomyocytes by SARS-CoV-2 with deleterious effects has been shown *in vitro*,[18] clinical evidence of direct viral infection of cardiomyocytes has not been found, and myocarditis related to COVID-19 infection seems rare. As such the interaction between COVID-19 and ACE2 might affect the cardiovascular system in an indirect manner.[19] SARS-CoV-2 entry into cells has been shown to down-regulate ACE2 expression, which can lead to a significant reduction in cardiac contractility and progression of atherosclerosis.[20]

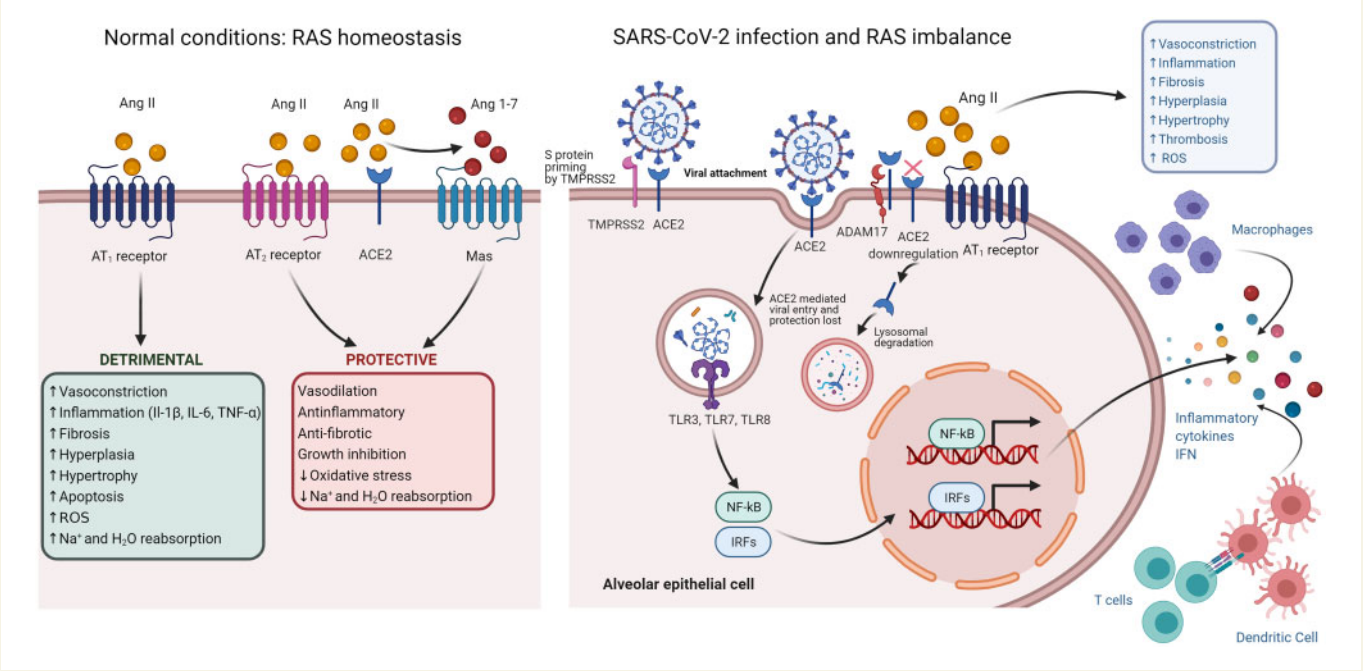



**Figure 1** Interplay between angiotensin II, ACE2 (angiotensin-converting enzyme 2), and SARS-CoV-2 binding in the pathogenesis of COVID-19, the inflammatory response and cardiovascular protection lost. *Left panel*: In physiological conditions, ACE2 balances renin–angiotensin system expression. Increased ACE2 increase the protective axis of ACE2/Angiotensin (Ang)1-7/Mas receptor axis counter-regulates the actions of the ACE/Ang II/angiotensin receptors 1 ($AT_1$) axis. *Right panel*: SARS-CoV-2 spike (S) protein has a strong binding affinity to ACE2 which facilitate viral entry into target cells by transmembrane protease serine 2 (TMPRSS2) priming. Following binding of ACE2 with S protein, down-regulation of ACE2 is observed. Accumulation of Ang II increases the activity of $AT_1$ receptors leading to internalization, down-regulation, and degradation of ACE2. In addition, endocytosed SARS-CoV-2 up-regulates the proteolytic cleavage of ACE2 mediated a disintegrin and metalloproteinase 17 (ADAM17), which activity is further increased by activation of $AT_1$ receptors due to the accumulation of Ang II. Viral RNA activates toll-like receptor (TLR) 3, TLR 7, TLR 8. These receptors activate interferon regulatory factors (IRFs) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) to induce inflammatory cytokines including interferons (INF). Dendritic cells are able to produce IFN and augment the IFN signal, which also represents a risk for immunopathology. Systemic cytokines release in combination with cardiovascular risk factor and comorbidities can lead to a cytokine storm, whereas increased activity of Ang II/$AT_1$ receptor axis, due to ACE2 loss of function, exerts vasoconstrictor, profibrotic, prothrombotic and proinflammatory effects. Figure created with BioRender.com. $H_2O$, water; IL, interleukin; $Na^+$, sodium; ROS, reactive oxygen species; SARS-CoV-2, Severe Acute Respiratory Syndrome-Coronavirus 2; TNF-α, tumour necrosis factor alpha.

## Underlying cardiometabolic risk factors associated with worse outcome in COVID-19

Several reports have consistently demonstrated that pre-existing cardiovascular disease and cardiometabolic risk factors such as hypertension, diabetes, obesity, and/or smoking are major risk factors for increased COVID-19 severity and mortality.[21–24] In a recent comparative risk assessment analysis of over 900 000 patients with COVID-19 from the USA, nearly 30% of COVID-19 hospitalizations were attributable to obesity, 26% to hypertension, 21% to diabetes mellitus, and 12% to heart failure. The study estimated that a 10% reduction in cardiometabolic risk factors could potentially prevent 11% of COVID-19 hospitalizations.[24] Therefore, patient's awareness of preventive lifestyle measures improves cardiovascular health at large and may reduce COVID-19 severity risk.

### Hypertension or age?

Globally, an estimated 1.13 billion individuals worldwide have hypertension, and the greatest burden is in individuals aged 60 years and older.[25] Early small case series offered an alarming view suggesting that people living with hypertension were at higher risk of severe COVID-19 and mortality. Preliminary data showed that the incidence of hypertension ranged from 32.6% to 34% among confirmed patients with COVID-19.[26,27] Among patients with myocardial injury and elevated cardiac troponin T levels, 63.5% had hypertension.[27] Similar findings were observed concerning mortality from COVID-19.[27] A meta-analysis incorporating early data of patients with COVID-19, demonstrated that the presence of hypertension was associated with nearly 2.5-fold higher risk of severe disease, intensive care unit (ICU) hospitalization, and mortality.[28] Altogether, these findings indicate that hypertensive patients have a higher risk of developing severe COVID-19. However, the mechanisms that link pre-existing hypertension and COVID-19 are yet to be fully elucidated as hypertension coexists with many other risk factors. One approach to disentangle the independent relationship between COVID-19 outcomes and exposure to hypertension is to study patients with hypertension while excluding those with other known risk factors of adverse outcomes. Recent evidence from the UK population-based study OpenSAFELY involving over 17 million patients was based on this approach.[29] OpenSAFELY quantified a wide range of clinical risk factors for death from COVID-19, some of which were not previously well characterized. There was no association between hypertension (defined as a

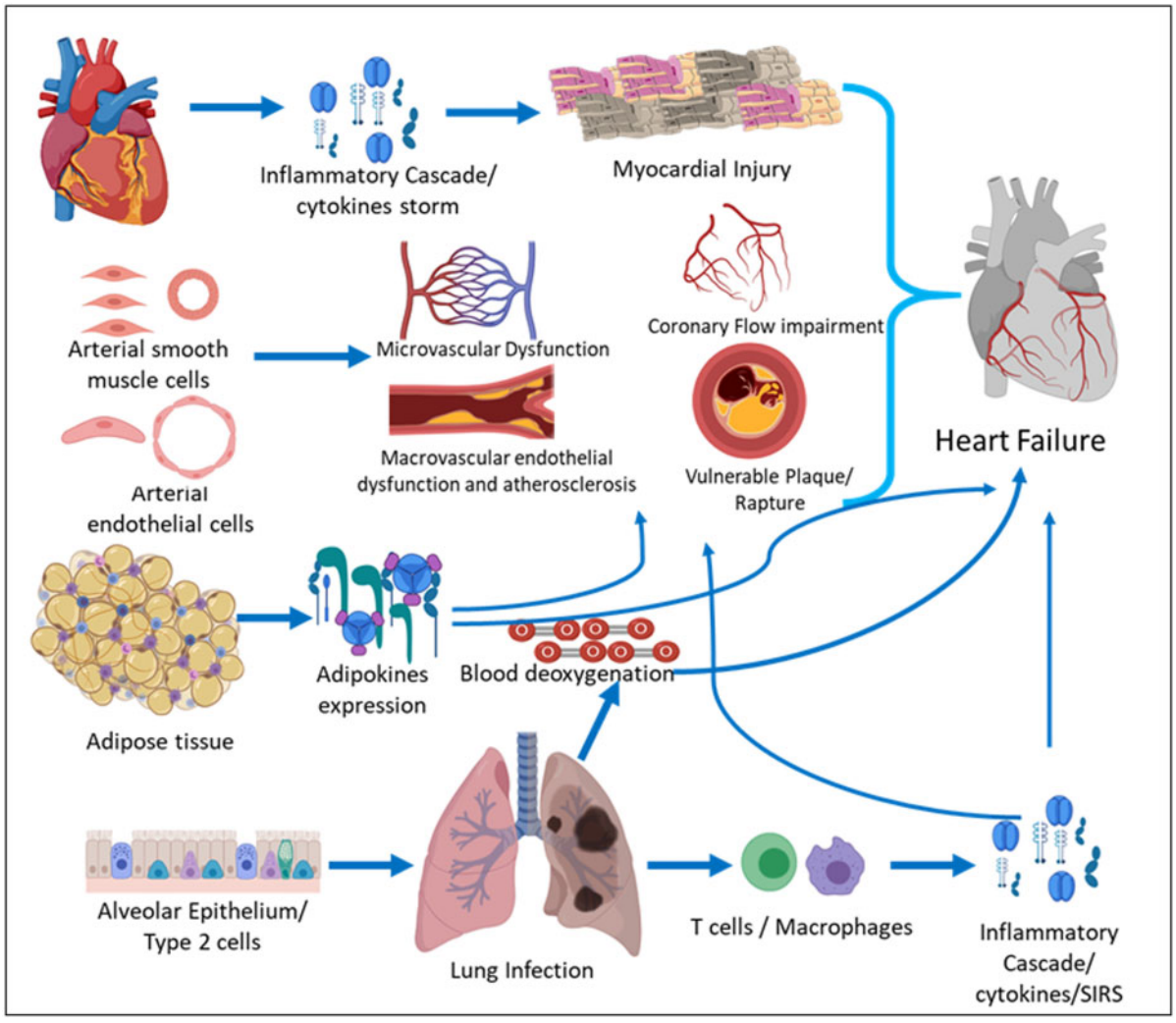



**Figure 2** Tissue expression of ACE2 and potential mechanisms involved in systemic inflammatory response and cardiovascular complications of COVID-19. ACE2 is widely expressed in endothelial cells, arterial smooth muscle cells, renal alveolar epithelial cells adipocytes, and cardiovascular system. Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) infection cause immune activation, tissue accumulation of T cells, and macrophages leading to myocardial injury. Cytokines release cause systemic inflammatory response which may cause further impairment in micro and macro-circulation and plaque rapture. Blood desaturation may further impair microcirculation and myocardial performance. SIRS, systemic inflammatory response system.

recorded diagnosis, or blood pressure ≥140/90 mmHg at the last measurement) and COVID-19 mortality (hazard ratio: 0.95, 95% confidence interval: 0.89–1.01). In contrast, age, cardiovascular disease, diabetes, obesity, respiratory diseases, history of malignancy kidney, liver, neurological, and autoimmune diseases were all associated with increased risk of death. The strongest predictor of mortality was age.

Other recent studies reinforced these observations reporting that age >60 years, overweight/obesity and, diabetes but neither hypertension nor anti-hypertensive treatments were associated with adverse prognosis.[30,31] Poor blood pressure control is associated with target end-organ damage, and mean blood pressure increases with age.[32] Additionally, age-related low-grade chronic inflammation with enhanced pro-inflammatory cytokines and chemokines, underlie several cardiovascular diseases including hypertension, which in turn is associated with senescence of $CD8^+$T cells, a mainstay of antiviral immunity.[33–35] A small study showed that macrophages and neutrophils of hypertensive patients with COVID-19, exhibit higher expression of pro-inflammatory chemokines such as ligands for chemokines with two adjacent cysteines (CCL3, CCL4) and the chemokine receptor CCR1.[36] A recent study showed an age-related increase of ACE2 expression in human kidney and lung tissues and lack of association between hypertension, RAS blockers, and renal expression of ACE2.[30] These findings are in agreement with previous reports suggesting that RAS blockers use were not associated with higher ACE2 and TMPRSS2 expression in lung tissues, nor with increased circulating plasma concentrations of ACE2.[37,38] Taken together, these observations may explain the reported associations between age, hypertension, and severity of COVID-19 infection. In sum, hypertension is very strongly associated with age and although many studies adjusted for this, disentangling the effects of each other is difficult. Age appears to be the strongest predictor for severe disease and mortality in COVID-19, which may be due to immunosenescence, inflammaging,[39] exaggerated $AT_1$ pro-inflammatory, pro-thrombotic, and pro-fibrotic signalling.[17]

## Diabetes mellitus

The estimated global prevalence of type 2 diabetes is 9.3% (463 million people)[40]; therefore, it is not surprising that diabetes is a common cardiometabolic risk factors in patients with COVID-19.[24,29,41–44] Early data reported a higher prevalence of diabetes in patients with severe disease as compared to those with mild to moderate disease (16.2% vs. 5.7%).[41,45] Moreover, the unadjusted case fatality rate of COVID-19 was higher among diabetic patients than non-diabetic patients (7.3% vs. 2.3%).[46] As the global COVID-19 pandemic progressed, a similar pattern of worse prognosis in patients with diabetes was reported across European and USA studies.[24,29,42,47] The OpenSafely[29] study showed a linear relationship between measured glycated haemoglobin (HbA1c) level of ≥58 mmol/mol (≥7.5%), recorded in primary care, and risk of COVID-19-related mortality, suggesting an association with hyperglycaemia. Other studies have provided similar results showing that the risk of COVID-19 related morbidity and mortality is independently associated to hyperglycaemia.[47–49] Another UK population-based study using the QResearch database (QCOVID, $n = 6\,083\,102$) reported 4.74-fold to 6.29-fold higher risk of age-specific mortality for type 2 diabetes in men and women, respectively.[44] Interestingly both OpenSafely and QCOVID reported a higher excess of death risk in younger patients with diabetes compared with older patients with diabetes, hypothesizing that the effective/biological age of a young patient with diabetes matches the chronological age of an older patient without diabetes.[50] Although the absolute risk of COVID-19-related death in younger patients with diabetes is not as high as that in elderly, these observations along with the potential modulatory effect of hyperglycaemia on immune and inflammatory responses suggests that the relationship between COVID-19 and diabetes entails a more complex pathophysiology.

Potential mechanisms thought to increase susceptibility and disease severity of SARS-CoV-2 in patients with diabetes include: (i) cellular binding with higher affinity and efficient virus entry, due to glycosylation of S protein and ACE2.[51,52] Circulating levels of furin, a cellular protease involved in facilitating viral entry by cleaving the S1 and S2 domain of the S protein and cell-to-cell spread, are elevated in patients with diabetes[51,53,54]; (ii) expression of ACE2 on pancreatic islets cells may lead to a direct effect of SARS-CoV-2 causing decreased β-cell insulin reserve.[55] Interestingly, insulin administration attenuates ACE2 expression.[56] (iii) Delayed SARS-CoV-2 clearance[21]; (iv) immunomodulation, cytokine-mediated dysregulation of glucose metabolism, and hypercoagulability.[57] Patients with diabetes are at increased risk of infection due to impaired innate immunity with reduced neutrophil chemotaxis, phagocytosis, and intracellular killing of pathogens resulting in an impairment in adaptive immunity that is characterized by an initial delay in the activation of Th1 cell-mediated immunity and a late hyper-inflammatory response. This further increases insulin resistance and may results in endothelial dysfunction and injury, thereby ultimately promoting thrombotic microangiopathy.[58] Additional mechanisms of adverse outcomes in COVID 19 include the effects of hyperglycaemia and glycolysis in monocytes, which may promote viral replication, cytokine production, and subsequent T-cell dysfunction through mitochondrial reactive oxygen species (ROS) production, and activation of hypoxia-inducible factor-1α[52]; and (v) higher prevalence of cardiovascular comorbidities that may help to explain the association with disease severity and adverse prognosis.

## Obesity

Obesity and particularly metabolically unhealthy obesity are major contributors to cardiovascular disease, and mortality. Achieving a metabolically healthy weight is a risk modifier associated with improved cardiac and vascular function.[59,60]

Epidemiological data show a J-shaped relationship between body mass index (BMI), COVID-19 severity and mortality, with lower risks at BMI thresholds near normal weights.[61–66] Interestingly, this relationship was more pronounced among younger patients (<65 years old).[62,67,68] In COVID-19 patients from New York City, those aged under 60 years with a BMI ranging from 30 to 34 kg/m$^2$ had a 2-fold increase in the probability of ICU admission compared to patients with a BMI <30 kg/m$^2$. This likelihood increased to 3.6-fold in patients with a BMI ≥35 kg/m$^2$.[68] Likewise, a BMI >35 kg/m$^2$ increased the risk of invasive mechanical ventilation 7-fold and was associated with lower survival rates.[69] In the OpenSafely study, adjusted mortality rates increased with increasing BMI ranging from 1.05 for BMI <34.9 kg/m$^2$ to 1.92 for BMI ≥40 kg/m$^2$ when compared with non-obese patients.[70] Thus, the relationship between obesity and severe COVID-19 and whether obesity could shift this increased risk into younger age groups is still a matter of concern given the high burden of obesity. Some studies addressed the question of why COVID-19 is deadlier in people with obesity, even if they are young. These studies noted that fat distribution and an impaired adipose tissue function, rather than total fat mass and BMI are related with COVID-19 complications at the individual level especially in younger patients.

In one small study of patients with COVID-19, 10 cm$^2$ of increase in visceral adipose tissue area, measured by computed tomography (CT), was associated with a 1.36-fold increase in risk for ICU hospitalization.[71] In contrast, BMI and total adipose tissue area showed weak association with COVID-19 severity.[71]

A combination of physiological and social factors likely drives the grim numbers of obesity-related COVID-19 risk. The biology of obesity includes impaired immunity, chronic inflammation, and increased risk of thrombosis, all of which can worsen COVID-19 outcomes. The devastating impact of obesity, particularly in younger people may have further explanations. A recent study found an increased epicardial adipose tissue attenuation index in the epicardial coronary arteries, which may reflect inflammation within the fat depot, with increasing COVID-19 severity.[72] Of note, epicardial adipose tissue attenuation was similar to that observed in many patients with coronary artery disease despite most of COVID 19 patients having no prior history of coronary artery disease and no coronary artery calcification.[72] In a recent multicentre study of 119 patients with COVID-19 increasing epicardial adipose tissue volume and attenuation were associated with increasing burden of COVID-19 pneumonia, clinical deterioration, or death.[73]

The physical pathologies that render people with obesity vulnerable to severe COVID-19 are multiple. Adipose tissue is among the tissues with the highest expression of ACE2 receptors.[74] It is also an important source of cytokines, known as adipokines, which in turn are involved in the regulation of glucose level, lipid metabolism, blood pressure (e.g. through angiotensinogen, angiotensin-II, ACE2 receptors), inflammation (e.g. through modulation of TNF-α, IL-6, macrophage chemo attractant protein-1), thrombosis, and oxidative stress.[59] Moreover, prior studies have shown that adipose tissue may act as a virus reservoir.[75] In particular, coronaviruses can infect bone marrow-derived macrophages and replicate in them.[76] Therefore, abnormal adipose tissue distribution, composition and function, rather than total body fat, may play an important role in COVID-19 infection and related complications, amplifying the inflammatory response in a positive feedback loop.[59] Accumulation and inflammation of perivascular, pericardial and epicardial fat surrounding the heart and connecting vessels, may increase local ACE2 expression and associate with an increased leptin/adiponectin ratio, which, in

turn, enhances the effects of some pro-inflammatory cytokines with lipotoxicity, such as TNF-α and IL-6.

Pro-inflammatory cytokines increase oxidative stress and decrease glucose utilization exerting detrimental effects on endothelial function. They also increase myocardial inflammation and impair myocardial energetics[59] which may result in negative inotropy and myocardial dysfunction.[77] Ultimately, pro-inflammatory cytokines triggered by abnormalities in perivascular, pericardial and epicardial fat may aggravate hypoxia and increase arrhythmias.[6,78] Other issues aggravate these physio-pathological problems. Obesity may alter the balance between pro and anti-thrombotic mechanisms and may be complicated by higher rates of thromboembolic events including pulmonary embolism.[59,79] Yet larger studies are needed to support the hypothesis that visceral, perivascular, pericardial, and epicardial obesity plays an essential role in COVID-19 myocardial injury.

### Smoking

Smoking remains a leading risk for early death and disability with 6.4 million deaths per year attributable to smoking worldwide.[80] Smoking is an independent risk factor for atherosclerotic cardiovascular disease and a factor positively associated with respiratory diseases, impaired immune system and consequently increased incidence of infectious diseases.[60] Smoking has been shown to up-regulate ACE2 expression especially in the lower respiratory tract which might make current smokers vulnerable to infection by COVID 19 compared with former/never smokers.[81,82]

However, data on this issue are controversial. Several early observational studies[41,83,84] and subsequent meta-analyses[85–87] based on these reports found an inverse relationship between smoking and severe COVID-19 leading to the misconception that current smoking is of benefit during COVID 19 infection. In contrast, other reports linked current smoking with severe clinical course of COVID-19 and need of ICU care.[88,89] Among of 8910 hospitalized patients with COVID-19 current smokers accounted for 5.5% of the study population. A 1.79-fold increase in inhospital mortality was observed in current smokers as compared with former/never smokers.[90] The same may also be the case for waterpipe, electronic cigarettes or 'heat-not-burn' IQOS users.[82] Of note, the prevalence of smokers was higher amongst those patients with myocardial injury as assessed by increased cardiac troponin T levels compared with non-smokers (13.5% vs. 8.1%).[27] In sum, further studies are needed to clarify the reasons behind the reported low prevalence of current smokers among hospitalized patients with COVID-19. The effect of current smoking on SARS-CoV-2 infection is a delicate and complex topic that should be addressed rigorously before delivering messages that could be misinterpreted.

## Mechanism of disease in relation with the cardiovascular system

### Endothelial injury and thrombosis

The prothrombotic and procoagulant state of COVID-19 entails a crucial role in the clinical manifestations of this disease. Viral infection with COVID 19 injures endothelial cells, which respond to the insult by activating the coagulation system.

Endothelial cell dysfunction induces the expression of tissue factor (TF) (through IL-1, TNF-α, and IL-6-mediated mechanisms), releases von Willebrand factor (vWF) from the Weibel-Palade bodies, and enhances surface expression of selectin class of leucocyte adhesion molecules such as P-selectin and E-selectin, overall promoting thrombus formation and leucocyte recruitment (i.e. thrombo-inflammation; *Figure 3*).[91,92] Virus engagement with ACE2 endothelial receptor may also reduce angiotensin II conversion to angiotensin 1-7. Angiotensin II not only promotes thrombus formation but induces plasminogen-activator inhibitor-type 1 (PAI-1) production hampering fibrinolysis and thrombus dissolution.[93] On the other hand, platelets are able to sense the viral infection and become activated through pattern recognition- [toll-like-receptors (TLR)], immunoglobulin Fc- and complement receptors. Activated platelets facilitate pathogen clearance by forming platelet aggregates and microthrombi, and by promoting the formation of neutrophil extracellular traps (NETs), web-like structures of decondensed chromatin containing DNA, histones, and granular components, inducing the so-called NETosis.[94,95] NETs provide a scaffold and stimulus for thrombus formation by different mechanisms including: (i) the delivery of active TF, (ii) activation of the intrinsic (contact) coagulation pathway through electrostatic interactions between the histones and platelet phospholipids, (iii) induction of platelet activation through histone interaction with platelet TLR, and (iv) blockade of the endogenous anticoagulant antithrombin III and TF pathway inhibitor (TFPI) through activated serine proteases.[94] Severe inflammation is also associated with deregulation of the coagulation and fibrinolytic systems by affecting key components involved in the atherothrombotic process such as TF, antithrombin-III, and protein C.

### Recent insights on prothrombotic state in COVID-19

Many studies have provided essential insights into the prothrombotic state in COVID-19. Clinical studies demonstrated significantly elevated markers of endothelial and platelet activation such as VWF, PAI-1, soluble thrombomodulin, soluble P-selectin and soluble CD40 ligand, as well as proinflammatory cytokines, components of NETs including cell-free DNA, nucleosomes, myeloperoxidase-DNA, TFPI, complement 5a, and membrane attack component (C5b-9) in severe COVID-19 patients suggesting 'endotheliopathy' and thrombo-inflammation as the main contributors of COVID-19 related severity and mortality.[95–98] Furthermore, the cytokine storm induces coagulation disorders favouring the appearance of VTE or disseminated intravascular coagulation (DIC) leading to an increase in Factor VIII clotting activity, widespread thrombin formation and consequent elevated D-dimer levels, associated also with a reduced platelet count (*Figure 3*). In this regard, IL-6 levels have been shown to correlate with a procoagulant profile.[99] Thrombocytopenia, which is secondary to excessive platelet consumption in the injured tissue or a result of immune-mediated haematopoietic stem cell damage, was associated with a 3-fold increased risk of severe COVID-19.[100] Of note, in patients with SARS a negative correlation was reported between platelet count and circulating levels of the T-cell immunosuppressor soluble vascular cell adhesion molecule-1.[101] Additionally, evidence suggests that ACE2 is highly expressed in cardiac pericytes which, when exposed to COVID 19, may lead to endothelial destabilization due to their firm interactions with endothelial cells.[74] The interaction between angiopoietin ligands (ANGPT1/2) and Tie receptor (TIE2) appears to be responsible for the endothelial dysfunction that ensues, resulting in reduced endothelial cell survival and increased vascular permeability. Presence of viral elements within the endothelial cells as well as accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death (lymphocytic endotheliitis) were observed in

histopathology specimens of patients with COVID-19.[102–104] A recent study suggested that the S protein can exert endothelial cell damage manifested by decreased mitochondrial function and eNOS activity, leading to increased redox stress and ultimately impaired NO bioavailability and ACE2 down-regulation. Of note, the endothelium-dependent vasodilation induced by acetylcholine was impaired in isolated pulmonary arteries of hamsters, but not the endothelium-independent vasodilation induced by sodium nitroprusside.[105] It is important to note that endothelial inflammation–endotheliitis affects many vascular beds, resulting in global microcirculatory dysfunction. Recently, soluble thrombomodulin has been suggested as a surrogate marker of endotheliopathy in COVID-19 and seems to provide prognostic information.[97] However, this marker still needs further validation.

In summary, multiple pathogenic mechanisms seem to predispose COVID-19 patients to endotheliopathy and thrombosis. Future studies are clearly warranted to fill the current knowledge gaps and identify mechanism of short- and long-term effects of SARS-CoV-2 on endothelial function and novel prognostic endothelial biomarkers.

## Myocardial injury

The Fourth Universal Definition of Myocardial Infarction defines myocardial injury (acute or chronic) as at least one cardiac troponin (cTn) value above the 99th percentile upper reference limit (URL).[106] Recent reports indicate that myocardial injury, manifested by elevated levels of circulating cTn, electrocardiographic or imaging criteria is frequent among patients with COVID-19. Still there is much confusion about the pathophysiological entities underlying this injury. Here, we summarize few key points about myocardial injury and COVID-19.

## Myocardial injury is common and impairs prognosis

The exact frequency of myocardial injury in patients with COVID-19 is difficult to ascertain due to variations in cTn assays, thresholds, studied populations, and clinical conditions. Myocardial injury has been demonstrated in 7–40% of patients with COVID-19 depending on the geographic areas, with a higher prevalence among those patients requiring intensive care.[88,107–112] Mortality is approximately 22% among patients with cTn above the URL and 61.5% for those with cTn levels >10 times the URL.[107,110,111,113]

Mechanisms of elevated troponin in COVID-19 are likely to be multifactorial including sepsis-related cardiomyopathy triggered by the systemic hyperinflammatory state, coronary thrombotic and plaque rupture events, microvascular injury due to DIC and thrombosis, supply–demand mismatch, ARDS related hypoxia, and direct viral cardiotoxicity.[114,115] Whether the hypercoagulable state and systemic inflammation observed in COVID-19 are unique features causing myocardial injury should be further investigated.

## Clinical classification of acute myocardial injury

Following careful clinical evaluation and understanding of the clinical context in which cTn measurements were obtained, patients with cTn increases should be classified as having (i) Type 1 acute myocardial infarction (MI), (ii) Type 2 acute MI, or (iii) acute non-ischaemic myocardial injury.

## Myocardial infarction

*Type 1 MI*: Immune response, acute infections, as well as local and systemic inflammation resulting in especially those of the respiratory tract are associated with an increased risk of ACS.[116] Observational studies on prior virus epidemics support the concept of an association between viral infections affecting the respiratory tract and MI, as is the case of influenza A infections.[117] In agreement with such prior observations, a recent systematic review with meta-analysis of self-controlled case series based on five independent studies found an increased risk of MI during the first week following influenza infection.[118]

As discussed above, a massive systemic inflammatory reaction associated with severe pneumonia as in COVID-19 may lead to an increased propensity for plaque disruption,[116] and thrombus formation[119] leading to type 1 MI.[106] Histopathologic examination of autopsy specimens has evidenced that patients dying of acute systemic infections have consistently higher content of macrophages and T cells in the coronary adventitia and periadventitial fat than non-infected deceased patients, establishing a link between acute systemic infections and local increase of inflammatory cells in coronary arteries.[116] In addition, patients with ACS have higher inflammatory activity across the coronary tree than those patients with chronic coronary syndrome. Arterial segments presenting culprit lesions are enriched in infiltrating inflammatory cells, such as macrophages, T cells, and neutrophils, when compared with other areas of the coronary bed.

Inflammatory cells may contribute to plaque instability by expressing active molecules including, cytokines, proteases, coagulation factors, oxygen radicals, and vasoactive molecules. In this respect, experimental studies in mice have demonstrated that infection with the influenza A virus associates with higher immune cell influx, increased production of inflammatory cytokines, and active metalloproteinases in the atherosclerotic plaque, which may account for a higher atherosclerotic plaque vulnerability.[120] Evidence of concomitant COVID-19 in ACS patients has been reported.[121–126] Higher troponin levels, D-dimer, and CRP, higher rates of multivessel thrombosis, stent thrombosis and higher thrombus burden have been reported in MI patients with COVID-19 as compared with non-infected.[125] Additionally, MI patients with COVID-19 showed significantly higher rates of coronary no-reflow (myocardial blush grade 0 or 1) and lower left ventricular function after revascularization, despite similar ischaemic times, suggesting impaired myocardial perfusion at tissue level likely due to microvascular thrombi.[125] Thus, MI patients with COVID-19 represent a high-risk group of patients with unique characteristics resulting in increased mortality risk.[122–126] Yet, these reports are limited to a few small retrospective observational studies of ST-segment elevation myocardial infarction patients with a scarcity of data on non-ST elevation-acute coronary syndrome.[121–126] As such these reports are unable to capture the real magnitude of the problem. Reasons behind this lack of data could be: (i) a decrease in health care–seeking behaviour in asymptomatic/suspected COVID-19 patients, as suggested by concerning reports of an increase in out-of-hospital cardiac arrests (OHCA) and sudden death that could have been secondary to MI[127]; (ii) difficult differential diagnosis as non-localized chest pain maybe present also in acute COVID-19 due to the underlying hypoxaemia and tachycardia, which in turn may also induce electrocardiographic changes suggestive of myocardial ischaemia.[33] On the other hand, dyspnoea may be the only symptom of ACS which in turn in asymptomatic COVID-19 patients could be attributed to the underlying pneumonia; (iii) due to

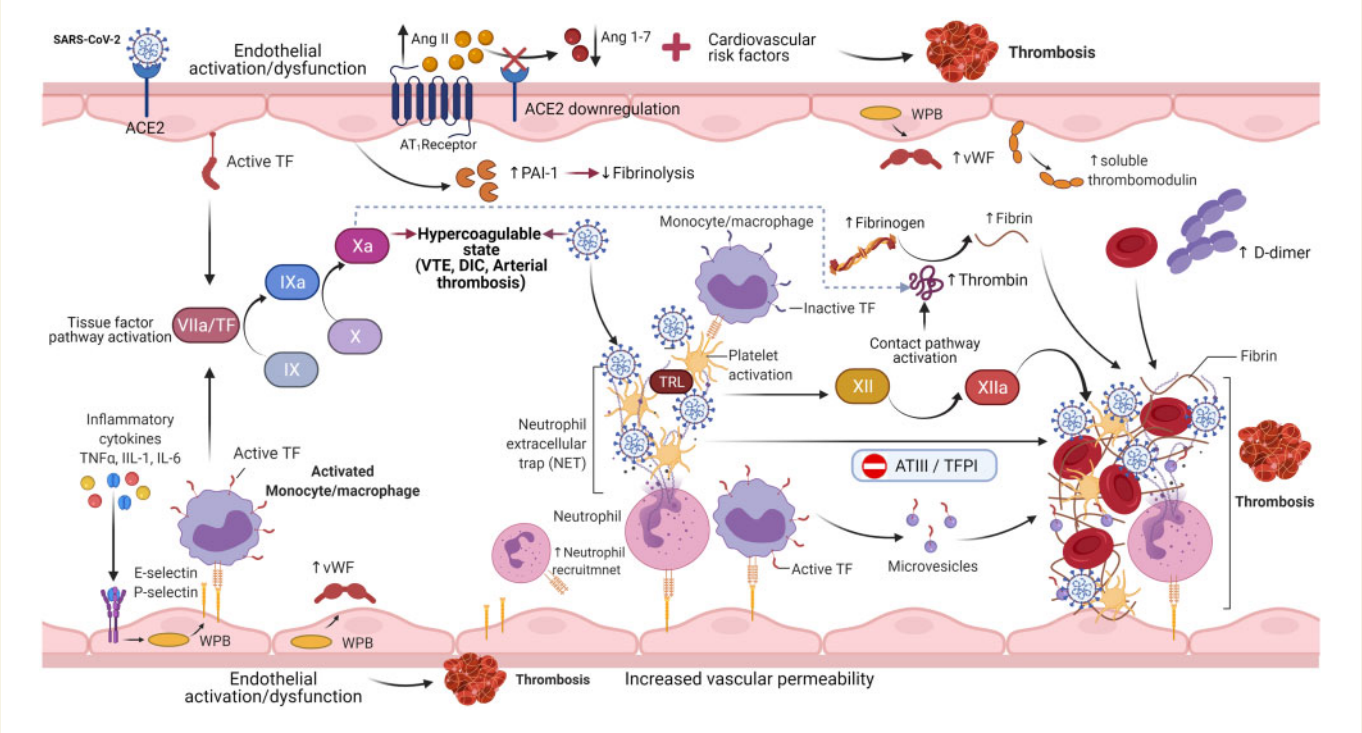



**Figure 3** Mechanisms of endothelial activation/dysfunction and immunothrombosis in COVID-19. SARS-CoV-2 activates the endothelium, either directly by interacting with angiotensin-converting enzyme (ACE) 2 receptor or indirectly by triggering hyperinflammation. Inflammatory cytokines induce the activation of tissue factor (TF) and exocytosis of Weibel Palade bodies (WPB) from endothelial cells, enhancing expression of P-selectin and E-selectin which in turn recruits' neutrophils and monocytes/macrophages. Monocytes/macrophages activate and deliver through their microvesicles, TF to the sites of SARS-CoV-2 exposure, initiating the TF pathway activation (or extrinsic pathway). Neutrophils release neutrophil extracellular traps (NETs), which capture SARS-CoV-2, promote thrombus formation activation of factor XII (contact or intrinsic pathway of coagulation cascade), and promote platelet recruitment by binding von Willebrand factor (vWF). The NETs propagate coagulation by inactivating endogens anticoagulants such as tissue factor pathway inhibitor (TFPI) and antithrombin III (ATII). Concomitantly, thrombomodulin is shed from endothelial cells, which further promotes a procoagulant and pro-inflammatory milieu. Spike (S) protein binding to ACE2 endothelial receptor reduce angiotensin (Ang) II conversion to Ang 1-7. Accumulation of Ang II leads to plasminogen-activator inhibitor-type 1 (PAI-1) production inhibiting fibrinolysis and thrombus dissolution. Figure created with BioRender.com. IL, interleukin; TNF-α, tumour necrosis factor alpha; TLR, toll-like receptors.

appropriate concerns regarding the safety of health care workers, COVID-19 positive patients with symptoms and electrocardiographic evidence of acute myocardial injury, were less likely to undergo invasive coronary angiography.[126]

*Type 2 acute MI*: Studies report that patients with COVID-19 often have chronic cardiovascular conditions such as hypertension, cardiomyopathy, coronary artery disease, or heart failure. All these conditions can be explanations for chronic stable increases >99th percentile URL in Type 2 MI for a number of reasons. First, systemic inflammation is associated with marked haemodynamic changes including sympathetic activation-mediated tachycardia, which results in increased myocardial oxygen requirements.[128,129] Second, the direct effects of pathogens and/or their indirect effects through inflammatory cytokines and chemokines promote ROS which are associated with mitochondrial dysfunction including mitochondrial uncoupling, leading to increased mitochondrial oxygen utilization and hence myocardial oxygen demand.[130,131] Furthermore, acute respiratory infections can cause ARDS that can result in hypoxia and consequent lowering of arterial oxygen content, thereby potentially further limiting myocardial oxygen delivery.[128]

As with other coronaviruses, COVID-19 can elicit an intense release of multiple cytokines and chemokines that can lead not only to vascular inflammation but also to abnormal regulation of vascular tone leading to coronary vasospasm. These abnormalities, in turn, can cause cardiac perfusion abnormalities and even MI.

Cardiogenic shock in those patients may also be precipitated by a myocardial demand-supply mismatch. Increased cardiometabolic demand associated with the systemic infection or sepsis coupled with hypoxia caused by acute respiratory illness can impair myocardial oxygen demand-supply relationship and lead to additional myocardial injury.

## Acute non-ischaemic myocardial injury

Emerging reports suggest that acute non-ischaemic myocardial injury is likely the predominant reason for cTn increases. Common cardiac aetiologies include myocarditis, Tako-Tsubo syndrome, and acute heart failure due to either systolic or diastolic dysfunction.[106] Primary non-cardiac conditions, such as pulmonary embolism, critical illness, and sepsis, probably cause myocardial injury as well.[106,111] Myocarditis and myopericarditis are causes of acute non-ischaemic myocardial injury that warrant particular concern in COVID-19. Depression of myocardial function can result in increased left ventricular diastolic filling pressures, and in combination with systemic vasodilation can cause lowering of

diastolic arterial blood pressure, thereby further reducing effective coronary driving pressure. These haemodynamic changes affect particularly the left ventricular subendocardial layers, that are most dependent on perfusion during diastole and hence most vulnerable to ischaemia.[132] Accordingly, COVID-19 studies have shown marked increases in N-terminal pro-B-type natriuretic peptides (NT-pro-BNP) in patients with myocardial injury, with studies reporting mean NT-pro-BNP concentrations of 72 pg/mL in patients who recovered compared with 800 pg/mL in those who died.[26] Another cause for acute non-ischaemic myocardial injury is pulmonary embolism. In a study of 184 ICU patients with COVID-19 pneumonia, pulmonary embolism was the most frequent thrombotic complication (81%). These data have led to the recommendation to use prophylactic anticoagulation in the absence of randomized evidence.[7] Another potential mechanism leading to acute non-ischaemic myocardial injury is direct injury by COVID 19 through ACE2 receptors, which are present in the myocardium and are functional receptors for COVID 19. Patients with heart failure have a higher expression of ACE2, which may explain their increased risk for myocardial injury following COVID-19.

## Acute myocarditis

To date, a few cases-series of 'COVID-19-related myocarditis' with diverse clinical presentations, have been published.[133–136] Patients with an exuberant immune response can manifest acute myocarditis with profound myocardial injury or cardiogenic shock.[128,134] However, it is worth remembering that the available findings are more consistent with 'clinically suspected myocarditis' or possible Tako-Tsubo syndrome.[133,137] A molecular analysis showed the absence of the SARS-CoV-2 genome in the myocardium of a patient diagnosed with COVID-19 and endomyocardial biopsy-proven lymphocytic myocarditis, indicating that the identification of SARS-CoV-2 in the respiratory tract is insufficient to prove that clinically suspected myocarditis is caused by SARS-CoV-2.[133] Furthermore, the epidemiological features of COVID-19 do not fit well with the 'classical' biopsy-proven myocarditis. According to the current ESC guidelines, the diagnosis of viral myocarditis is a diagnosis of exclusion made with certainty only in the case when a viral genome is proven in endomyocardial specimens along with the histological findings of active myocarditis.[137] SARS-CoV-2 infection of induced pluripotent stem cell-derived cardiomyocytes has been shown *in vitro*[18] and SARS-CoV-2 genome has been identified in endomyocardial biopsies of patients with suspected myocarditis.[135] However, there is no direct evidence of SARS-CoV-2 within cardiomyocytes as virus presence has been documented in interstitial cells within cardiac tissue but not in cardiomyocytes, suggesting that viral genome presence was due to infected macrophage migration.[138]

Recently, rare and self-limiting cases of myocarditis with temporal association to immunization with an mRNA-based COVID-19 vaccine have been reported, especially in young men (mean age 25 years old).[139,140] Data from the Israeli Ministry of Health suggest a crude incidence rate of approximately 24 cases per million following a second dose.[139,140] Still, the true incidence of this adverse event is unknown at this time. Although the specific mechanisms are unclear an immune-mediated mechanism is likely.[141]

In summary, to date, there is scarce evidence supporting direct myocardial injury through COVID 19 infection. Given the risks of COVID-19, including the risk of myocardial injury from COVID-19 infection, concerns about rare or even extremely rare adverse events following immunization should not undermine confidence in the value of vaccination.

## Thromboembolism in patients with COVID-19

Coagulation abnormalities including arterial and especially VTE are recognised features of severe COVID-19 infection, manifesting in deep venous thrombosis, pulmonary embolism, and DIC. As discussed above, inflammation, endothelial activation, increased platelet reactivity, NETosis, alterations in coagulation factors, and stasis predispose to both arterial and venous thrombosis. In the setting of COVID-19 several studies have shown that the hyperinflammatory state may lead to pulmonary microthrombosis and pulmonary intravascular coagulopathy. Acquired antiphospholipid antibodies have been identified in 45–90% of COVID-19 patients, but the exact mechanism of antibody formation and its associated thrombogenicity remain unclear.[142]

Whilst all hospitalized patients are at risk of VTE, those with ARDS, severe sepsis and/or on ICU are at much higher risk, due to both patient-specific factors (including age, obesity, sepsis, hypoxia, due to concomitant respiratory or heart failure) and ICU-related factors (sedation, immobilization, vasopressors or central venous catheters). Coagulopathy is reflective of more severe disease and adverse prognosis, with DIC reported in 71% of COVID-19 patients who died compared to only 0.6% of survivors.[119] Furthermore, fibrin-platelet microthrombi deposition in the pulmonary vasculature is apparent at autopsy in COVID-19 patients.[143] Those presenting with myocardial injury appear to have elevated D-dimer, fibrinogen, low antithrombin levels, prothrombin time (PT), and activated partial thromboplastin time (APTT) compared to those without cardiac involvement.[107]

In recent meta-analyses, hospitalized patients have an overall estimated incidence of COVID-19 related VTE ranging from 15% to 21%. This is four-fold higher in critically ill patients admitted to the ICU compared with non-ICU settings (23–31% vs. 7–9%).[144–146] Studies have also shown that age and coagulopathy, defined as spontaneous prolongation of PT > 3 s or APTT > 5 s, are associated with thrombotic complications and higher mortality.[7,147] Furthermore, the true incidence of VTE may be underappreciated as it is often challenging to detect it in ICU patients. Moreover, pulmonary embolism may be under-diagnosed since respiratory deterioration is a prominent feature of the concomitant ARDS. The increased risk of thromboembolism that is known to be associated with COVID-19 can be appreciated also in other clinical conditions.[148,149] The overall incidence of ischaemic stroke and MI is reported to be nearly 4% across studies.[7,146] In a single-centre case series, 20 patients with COVID-19 developed acute limb ischaemia over a 3-month period.[149] In a multicentre case-series of 209 critical COVID-19 patients, 9.6% developed atypical severe arterial thrombotic events.[148] Of note, thrombosis occurred mainly in non-atherosclerotic vessels[148] and successful revascularization was lower than expected probably due to the immunothrombosis model.[149]

In order to mitigate the prothrombotic state associated with COVID-19, guideline and consensus statements recommends standard thromboprophylaxis with low-molecular weight heparin (LMWH), unfractionated heparin, or fondaparinux over oral anticoagulants, in the absence of contraindications, in all acutely hospitalized patients with COVID-19.[33,150,151] Unfractionated heparin and LMWH have anti-inflammatory effects being able to down-regulate TNF-α induced inflammatory responses and partially inhibit IL-6, and IL-8 release.[152,153] Some studies have reported that heparin bind to the S protein of SARS-CoV-2, thus potentially blocking cellular invasion.[154,155] Fibrinolytic therapy with tissue plasminogen activator (tPA) in refractory COVID-19 acute lung injury and ARDS has been reported to be associated with improved

oxygenation, ventilation, and haemodynamic status,[156] which supports that fibrin deposition in the airspaces and lung parenchyma, along with fibrin-platelet microthrombi in the pulmonary microvasculature contributes to ARDS and right heart failure.[102,104,143] However, optimal thromboprophylaxis including regimen, intensity, and duration have yet to be established. Several other consensus statements, guidelines and reviews have also made similar recommendations for thromboprophylaxis in COVID-19 especially in hospitalized patients.[150] Of note, the role of direct oral anticoagulants is still unproven. Nevertheless, they are increasingly adopted. Similarly, the role of fibrinolytic therapy for critically ill patients remains to be established. Results of ongoing randomized clinical trials will help to clarify these uncertainties.[157]

## Acute heart failure: the right ventricle in COVID-19

A growing number of studies show evidence of heart failure in COVID-19 patients even without pre-existent cardiovascular diseases.[26] Cardiac involvement in patients infected with SARS-CoV-2 may manifest as acute COVID-19 cardiovascular syndrome (ACovCS) that among other presentations also encompasses the whole spectrum of acute heart failure symptoms.[158] Among hospitalized patients with COVID-19 the reported rates of acute heart failure varied from 23% to 33%.[84,108] As previously mentioned acute heart failure may be due to negative inotropic effects of cytokines and pro-inflammatory ACE/angiotensin II, or myocardial injury.

However, in the setting of COVID-19 the right ventricle is at higher risk of failure due to its physiological relationship with the pulmonary circulation. Right ventricular (RV) dysfunction and failure may contribute to the rapid haemodynamic deterioration, arrhythmias, and sudden death seen in patients with COVID-19. Early post-mortem studies from severe COVID-19 patients showed evidence of RV dilatation.[104,159] As the pandemic progressed, larger echocardiographic studies demonstrated that COVID-19 patients had RV dilation (12 to 15%), RV dysfunction (16–35%), and elevated pulmonary artery systolic pressure, even in the absence of known cardiomyopathy.[160–165] In these patient's adverse RV remodelling was associated with over two-fold increase in mortality risk.[161,165] Additionally, many severe COVID-19 patients require positive pressure ventilation, which in turn affects preload, afterload and ventricular compliance and may further contribute to RV failure.

In summary, these observations highlight the clinical implications of RV dysfunction assessments and the possibility to risk-stratify COVID-19 patients based on this assessment.[166–168]

## Arrhythmic manifestations

Arrhythmias are a common complication in patients with COVID-19. Early case-series of hospitalized patients reported rates ranged from 8–17% and 44–60% in ICU setting and fatal cases, respectively.[169–173] In a recent international large survey of over 4500 patients, arrhythmias occurred in 18% of cases, with atrial fibrillation/flutter being the most common disorder in COVID-19.[174] Atrial fibrillation/flutter, left bundle branch block, electrocardiogram (ECG) signs suggesting acute right ventricular pressure overload (e.g. right bundle branch block or S1Q3T3 pattern), premature ventricular contractions, and ST-segment deviation have been all associated with elevated troponin levels and mortality, in COVID-19 pateints.[175] Life-threatening arrhythmias (ventricular tachycardia/ventricular fibrillation) can occur in 4–6% of hospitalized COVID-19 patients and are more common in those with elevated cardiac troponins[27,174] thus the diagnostic workup for cardiac injury should be always accompanied by concurrent rhythm monitoring.[176]

Although the exact nature of these arrhythmias is currently unknown, there are several mechanisms by which arrhythmias may occur in COVID-19. Five pathophysiological conditions align with the clinical course of COVID-19 and may predispose to arrhythmias: (i) pre-existing pro-arrhythmic conditions (structural heart disease, ion channel disorders)[177]; (ii) direct cardiotropic effects of the SARS-CoV-2 virus or hyperinflammation response it evokes. Cytokines such as, IL 2, IL-6, and IL-8 as well as TNF-α may cause heart rhythm disorders.[178,179] Cytokines may favour the development of long QT syndrome (LQTS) by affecting the function of the cardiomyocyte $K^+$ and $Ca^{2+}$ ion channels (inflammatory cardiac channelopathies).[180] IL-6 enhances the L-type $Ca2^+$ current and inhibits the rapidly activating repolarizing $K^+$ current by targeting the human Ether-à-go-go-Related Gene (hERG) thus prolonging ventricular action potential duration.[180] In addition, inflammation-associated tachycardia resulting either from increased sympathetic activation of β-adrenergic receptors,[181] or direct activation of cardiac pacemaker cells by cytokines,[182] may precipitate life-threatening arrhythmias, especially in patients with underlying heart disease. Beta-blockers were associated with a reduced risk of death in critically ill patients with COVID-19[183]; however, a protective effect needs to be confirmed in prospective studies. Ongoing studies will also determine if selected immune proteins may qualify as biomarkers for an increased arrhythmogenic risk or immunomodulating therapy; (iii) cardiorespiratory instability requiring critical care and positive pressure ventilation.[176,184] Arrhythmias may indicate worsening of the patient's underlying condition. Electrolyte abnormalities due to rapidly worsening renal function may act as potential triggers and should be closely controlled. Nevertheless, whether the incidence of arrhythmias is higher in COVID-19 than in other conditions of cardiorespiratory distress is currently unknown; (iv) medical therapy with QT-prolonging drugs. Several explorative treatments for COVID-19 such as hydroxychloroquine and azithromycin, may induce QT-prolonging culminating in torsades de pointes.[185] A baseline ECG is warranted, if patients are receiving antiarrhythmic or psychotropics therapy. More importantly, QT-prolonging drugs, should be reconsidered if QTc >500 ms or QTc increase by ≥60 ms.[33,176] (v) finally, residual myocardial dysfunction and arrhythmic risk following COVID-19 with cardiac involvement. In analogy to myocarditis, patients with reduced left ventricular ejection fraction, persistent ECG changes or cardiovascular magnetic resonance (CMR) evidence of fibrosis may qualify for long-term follow-up for potential arrhythmic complications post COVID-19.[186] In this regard, digital health and remote monitoring has been accelerated by the pandemic, providing an opportunity to enhance the use of remote services in everyday medical practice worldwide.[176]

## Cardiac arrest

Cardiac arrest, either in or out of hospital, is common in critically ill patients with COVID-19 and is associated with poor survival, particularly among women and men aged 80 or older.[127,187] Initial experience from a tertiary teaching hospital in Wuhan, China, has demonstrated a very poor survival after in hospital cardiac arrest (IHCA).[188] Only 4 out of 136 patients with IHCA survived for 30 days and only 1 with a favourable neurological outcome even though 93% of the patients were monitored and resuscitation was initiated in less than 1 min in 89%. A recent study from Sweden included 3027 people who suffered a cardiac arrest (OHCA 64.3% and IHCA 35.7%). COVID-19 patients, had a 3.4-fold and 2.3-fold increased risk of 30-day mortality after an OHCA and IHCA,

respectively, compared with non-infected cases.[127] Of note this study showed that witnessed IHCA were less common in COVID-19 cases, as were in-hospital ECG monitoring, shockable rhythm and defibrillations,[127] highlighting the need for rhythm monitoring which is potentially life-saving.[176] Respiratory failure and prothrombotic events that have been extensively described in patients with COVID-19 are probably major contributors to in-hospital cardiac arrest in this setting. Although there is no direct evidence that SARS-CoV-2 directly causes cardiac arrest, cytokine storm could contribute to multi-organ dysfunction and cardiac arrest. Some previous observations may strengthen such hypothesis. Thus, cardiac arrest and subsequent resuscitation is often followed by the so called 'post cardiac arrest syndrome' (PCAS).[189] A dominating feature of the PCAS is a systemic inflammatory response syndrome with high levels of cytokines circulating in the blood associated with endothelial activation and endothelial injury.[190,191] Adding COVID-19 to PCAS the systemic inflammatory response may be more pronounced. Further in a recent phase II trial, blocking of IL-6 signalling pathway with tocilizumab, reduced systemic inflammation after cardiac arrest and showed an apparent cardioprotective effect.[192] The same reasoning applies to LQTS and Torsades de Pointes.[174,180]

Finally, in high prevalence areas it reasonable to encourage compression only resuscitation and public access defibrillation of adults with OHCA for lay people, as it has already been implemented in many first responder programmes in Europe.[193,194]

## Sex differences of cardiovascular injury in COVID-19 and potential mechanism of sexual dimorphism

Robust sex-specific risk estimates for confirmed infection and preliminary case fatality for COVID19 are still lacking, with available data likely biased by incomplete outcome data and differences in testing policies within and between countries. Growing evidence in USA and western European countries documented a greater susceptibility to SARS-COV-2 infection among women compared with men at least in those aged up to 50 years. In contrast, men across all ages are 20% more likely than women to be hospitalized with COVID-19, to require intensive care and are reported to have a 1.74-fold increased risk of mortality compared with women.[195,196] Similarly, hyperinflammation and myocardial injury are more pronounced in men.[197] On the opposite, COVID-19-related endotheliopathy and thrombosis were not found in clinical studies so far.[197] The reasons behind this increased risk are not completely understood. A possible explanation of the observed effect on mortality after infection with SARS-COV-2 is that comorbidities, such as hypertension, cardiovascular disease, chronic lung diseases, and tobacco smoking are more common among men than women.[197] Alternatively, the finding of increased COVID-19 infection among young women and the higher risk of severe disease and death among men in all age groups suggests a potential role for sex differences in biology and pathophysiology in COVID-19 infection. Yet, several studies have hypothesized that sex differences in COVID-19 may result from an interplay between preexisting comorbidities and sex-based biological factors, including sex chromosomes, sex hormones, and genomic and epigenetic differences, underlying viral entry and the immune response, which in turn also modulate cardiovascular disease. Some of these observations require further discussion.

i. Androgen signalling up-regulate ACE2 and TMPRSS2 expression in pulmonary and prostate tissues.198 Androgen-deprivation therapy/androgen receptor antagonists have shown to reduce the SARS-CoV-2 S-mediated cellular entry.[198] Similarly, oestrogen can up-regulate the expression of ACE2 in human atrial tissue and has shown immune modulating activity.[195,199] In a pilot trial, progesterone therapy reduced the need for supplemental oxygen and hospitalization. Therefore, the effects of oestrogen on ACE2 expression may have paradoxical effects, aiding COVID-19 viral infection, yet conversely limiting viral pathogenicity.[200] These insights could, at least partially, account for the better outcome and the lower myocardial injury and death rate in women compared with their male counterparts.

ii. Furthermore, the gene encoding ACE2 is located on the X chromosome and is regulated by oestrogens.[201] Inactivation silences transcription from one of the two X chromosomes in women (XX) and avoids redundant gene expression compared with men (XY). However, the silencing is not complete but about 10% of the genes escape the inactivation.[201] Thus, XX cells over-express genes encoding ACE2 in women.[201] Studies are mandatory to evaluate the role of inactivation of transcription of X genes, and of their regulators, which might represent a major challenge to understand the sex-specific pathogenic determinants of COVID-19 disease progression.

iii. In addition, it is known that innate and acquired immune responses are more intense and stronger in women than in men. This can provide women with a more effective tool to fight infective pathogens, favouring viral clearance. There are a variety of X-linked genes, such as IL-13, IL-4, IL-10, XIST, TLR7, FOXP3, which may underlie sexually dimorphic responses that contribute to stronger cellular, and humoral immune responses which also enhances the susceptibility of women to autoimmune diseases in women compared with men.[201] For example, recognition of viral RNA by TLR 7 is enhanced in women compared with men leading to a more robust, type I IFN secretion and response. Women show higher neutrophil and macrophage phagocytic capacity and IL-10 production, higher B-cell numbers, and antibody production and higher number of CD4+ T cells and activated T cells and T-cell proliferation than men.[202]

iv. Sex is known to be associated with longevity. Immune-inflammatory responses play a key role in successful ageing. While men are usually physically stronger, women live longer. The variation in sex hormones levels over the course of life may partially contributes to sex differences in immune profiles and disease susceptibility to infection at different ages.[195] Aging induces a decline in the proportion of naïve T cells and enhanced monocyte and cytotoxic cell functions that is more prominent in men, and a male-specific B cells decline after age 65 years old.[202,203] In addition, a trend of age-related decrease was observed in the production of some cytokines. In particular, the rate of decline in IL-10 is greater in men than in women. Because IL-10 acts as an immune-inflammatory suppressor,[204] this relatively lesser production can be consistent with the fact that the age-related decline of various immunological parameters is less pronounced in women than in men.[202,203]

In sum, unless the effects of biological sex are studied, we will continue to have gaps in the knowledge, which may result in missed opportunities for a better health care system response to the pandemic of COVID-19. Having greater awareness of the roles that sex may play, may guide personalized preventive measures and therapeutic options in women and men.

## Therapy and clinical trials: where are we with treatments?

The urgent need for effective treatments has resulted in the implementation of potential therapies lacking strong scientific evidence. There are

thousands of clinical trials investigating treatments and preventative measures for COVID-19. We summarize the most important features.

## Remdesivir

Following the results of the Adaptive COVID-19 Treatment Trial (ACTT)-1 and 2 supportive trials GS-US-540-5774 and GS-US-540-5773, The European Medicines Agency (EMA), approved a conditional marketing authorization remdesivir for the treatment of COVID-19 in adults with pneumonia who require supplemental oxygen.[205–207] The ACTT-1 which had the most robust study design, provided the most convincing evidence reporting a shorter time to recovery in the remdesivir group when compared with the placebo group (10 vs. 5 days), no differences in mortality risk were observed. Yet, on November 2020, the WHO issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.[208] Interim results from the WHO Solidarity trial suggest that remdesivir has little or no effect on mortality in patients who are hospitalised with COVID-19.[209] Larger randomized controlled trials (RCTs) are needed to approve or refute treatments that unintentionally may be damaging for the patients.

## Corticosteroids

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicentre, randomized, open-label trial in hospitalized patients with COVID-19, showed that the mortality from COVID-19 was lower in patients who were randomized to receive dexamethasone than among those who received the standard of care.[210,211] However, in the subgroup of participants who did not require supplemental oxygen at enrolment, no survival benefit was observed for dexamethasone. Thus, WHO has recommended dexamethasone plus remdesivir or dexamethasone alone only for hospitalized patients with severe or critical COVID-19.[208,211] If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone, may be used instead.[208,211]

Recently, the Steroids in COVID-19 (STOIC), a phase 2, open-label, randomised controlled trial, showed that early administration of inhaled budesonide when compared with usual care, reduced the likelihood of needing urgent medical care and reduced time to recovery in adult's outpatients with mild COVID-19.[212] However, STOIC data are insufficient and cannot exclude the possibility of harm from the use of inhaled corticosteroids, such as budesonide or ciclesonide, in outpatients with mild COVID-19 who have normal oxygen levels. As such EMA advise against the use of inhaled corticosteroids in this population.[213] Therefore, more robust evidence from clinical trials is still needed, to establish the benefits of inhaled corticosteroids in outpatients with COVID-19.

## Chloroquine/hydroxychloroquine, azithromycin, lopinavir/ritonavir

In the early phase of the pandemic hydroxychloroquine and chloroquine were widely used for COVID-19 patients. These two drugs have been used for decades in therapy and control of malaria and autoimmune diseases. Small early trials that evaluated hydroxychloroquine demonstrated no clinical benefits.[208,214,215] The subsequent large multicentre RECOVERY trial showed that the 28-day mortality rates of hospitalized patients with COVID-19 in the hydroxychloroquine treatment group were even higher than those in the usual-care group (62.9% vs. 59.6%).[214] Furthermore, combined use of hydroxychloroquine and the antibiotic azithromycin may prolong the QT-interval resulting in an increased risk of sudden death, and other adverse events.[13] Following a review of emerging data from the RECOVERY trial, there was also no beneficial effect of lopinavir/ritonavir on 28-day mortality in patients hospitalised with COVID-19 compared to usual care alone.[216] These data were confirmed by the Interim WHO Solidarity Trial.[209] This trial concluded that remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on COVID-19 mortality, initiation of ventilation, and duration of hospital stay.[209] These disappointing results highlight the question whether it is appropriate to use any drug on COVID-19 patients before large-scale RCTs are completed.

## Inhospital immunomodulatory therapies

The intense hyperinflammatory response to viral infections, led in the early stages of the pandemic to the drug repurposing of several agents able to modulate the immune response, including IL-1 (anakinra) or IL-6 (sarilumab, siltuximab, tocilizumab) inhibitors.[5] Recent trials of these immunomodulatory therapies showed conflicting results.[217–221] Tocilizumab intervention was frequently associated with improved outcomes and reduced mortality, whereas evidence for the efficacy of anakinra, siltuximab, or sarilumab in COVID-19 is currently insufficient[217–221] An important concern on IL blockade in patients with COVID-19 is the risk of mid and long-term adverse events from secondary infections which is still under investigation. Further research is needed to identify participant and disease characteristics where immunomodulatory therapy is likely to be of maximal benefit, perhaps exploring the relationship of the effects of such drugs with baseline inflammatory biomarkers such as IL-1, IL-6 and CRP and myocardial healing.

## Neutralizing monoclonal antibodies for high risk COVID-19 outpatients

Data suggesting that persistent SARS-CoV-2 replication portends severity of COVID-19 led to the development of treatments with the aim to prevent the progression of COVID-19 from the beginning of infection. In three trials early treatment with neutralizing monoclonal antibodies (mAb) REGN-COV2 (combination of casirivimab and imdevimab) or a combination of bamlanivimab and etesevimab significantly reduced SARS-CoV-2 viral load, COVID-19-related hospitalization and death compared to placebo in outpatients with recently diagnosed COVID-19 without need of supplemental oxygen.[222–224] No benefit and possible worse clinical outcomes were shown in hospitalized patients requiring high flow oxygen or mechanical ventilation, most likely because inflammation and thrombosis, rather than viral replication, play a greater role in later stages of the disease.[222–224]

The EMA granted a conditional marketing authorization and FDA approved these neutralizing mAbs with an emergency use authorization in mild to moderate COVID-19 patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.[225–228]

SARS-CoV-2 mAbs have the potential to be used for both prevention and treatment of infection, as they are designed to block viral attachment and entry into human cells, thus neutralizing the virus. Bamlanivimab/etesevimab and casirivimab/imdevimab are recombinant, neutralizing human IgG1 mAb which are unmodified in the Fc regions. The mAbs bind to different sites on the receptor binding domain of the spike protein of SARS-CoV-2, blocking the binding of the virus to the ACE2 host cell surface receptor.[229] Several factors still limit the successful contribution of

approved mAbs to the control of the COVID-19 outbreak including the need for very-large-scale manufacturing and the need to rapidly shift to modalities of administration not requiring hospital settings.

## Serine protease inhibitor therapy

Camostat mesylate and nafamostat mesylate are clinically proven inhibitors of TMPRSS2, used for the treatment of pancreatitis and DIC. Recently, both compounds have been identified as a promising antiviral therapy for COVID-19.[230] Animal and *in vitro* human cell studies have shown that nafamostat mesylate, camostat mesylate, and its active metabolite 4-(4-guanidinobenzoyloxy)phenylacetic acid (GBPA), blocks TMPRSS2 thus inhibiting viral protein S priming and hence virus-cell membrane fusion.[14,198,230] Moreover, animal studies have shown that camostat mesylate may reduce transforming growth factor-β production and associated fibrosis.[231] Nevertheless in a recent small multicentre RCT, 200 mg camostat mesylate failed to show clinical improvement, progression to ICU admission or mortality when compared with placebo in hospitalized patients with COVID-19.[232] Ongoing clinical trials will help to assess whether camostat mesylate or nafamostat mesylate administered in higher doses or during the very early phase of COVID-19 might be effective in reducing disease progression.

## Cell-based therapy in COVID-19

Mesenchymal stem cells (MSCs) and cardiosphere-derived cells (CDCs), have been widely studied for clinical application in regenerative medicine and for their anti-inflammatory, immunomodulatory, anti-fibrotic and regenerative properties.[233] MSCs can be isolated and grown from multiple human tissues, including the human umbilical cord (hUC).[233] CDCs are intrinsic cardiac stem cells, with a distinctive antigenic profile ($CD105^{+}$, $CD45^{-}$, $CD90^{low}$) and contain a small minority of $c\text{-}kit^{+}$ cells putative cardiac progenitors.[233,234] It has been hypothesized that MSCs and CDCs could reduce inflammation, ARDS and attenuate scar formation and fibrosis after myocardial injury in COVID-19.[234–237] Furthermore, because they express low levels of ACE2 and TMPRSS2, MSCs and CDCs are thought to be resistant to SARS-CoV-2 infection.[236,238]

Data supporting the use of intravenous hUC-MSCs in patients with COVID-19 are limited to small pilot open-label uncontrolled trials.[235–237] These studies reported improvement of inflammatory biomarkers such as CRP and cytokines,[235–237] improved survival[237] as well as a potential to reduce fibrosis associated with post-acute COVID-19.[236,237] It should be noted, however, that results did not reach statistical significance. Data supporting intravenous allogeneic CDCs (known as CAP-1002) are limited to a single compassionate-use cohort of 6 severe COVID-19 patients pre-treated with tocilizumab.[234] The study reported a good safety and tolerability profile of CAP-1002, followed by improvement in clinical status, pro-inflammatory biomarkers, cardiac troponin and D-dimer levels in most patients during hospitalization.[234]

Interpretation of these studies is further limited lack of randomization,[234–236] small sample size,[234–237] and shift in eligibility criteria from enrolling solely patients on invasive mechanical ventilation to including those on non-invasive ventilation.[237] Moreover, a concern on cell-based therapy is the safety profile at long-term follow-up.

To date, no MSCs or CDCs products are approved for the treatment of COVID-19. Multiple ongoing trials, including the Intravenous Infusion of CAP-1002 in Patients With COVID-19 (INSPIRE) trial will help to assess the role of cell-based therapy for the treatment of COVID-19.

# Post-acute sequelae of COVID-19

A large proportion of patients who have been infected from SARS-CoV-2 do not fully recover in the months after hospital discharge and continue experiencing debilitating symptoms such as fatigue, dyspnoea, chest pain, palpitations, thromboembolic events, myalgia, anxiety, depression and impaired quality of life.[2] These symptoms, often referred to as 'Long COVID' or 'Post-acute COVID-19 syndrome', can persist for months in the absence of detectable viral infection and vary in form and severity. Recent data have shown that over 13% of infected individuals are likely to report symptoms of post-acute COVID-19 that persist over 4 weeks, 4.5% over 8 weeks, and 2.3% of individuals report symptoms over 12 weeks.[239] These post-acute effects of COVID-19 are a matter of significant concern, as they potentially affect millions of people worldwide, increasing healthcare costs and disability.

The first major challenge in treatment of post-acute COVID-19 is establishing a universally accepted definition still need to be established. Recently, the NIH has proposed the term 'Post-Acute Sequelae of SARS-CoV-2 infection (PASC)' to collectively refer to these effects.[3] Recent studies have suggested to include two categories to define the syndrome: (i) subacute or persistent symptomatic COVID-19, which includes signs and symptoms lasting from 4 to 12 weeks beyond acute infection and attributable to COVID-19; and (ii) chronic or post-COVID-19 syndrome, which includes signs and symptoms persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses.[2,240–243]

Reports on 2- to 6-month outcomes from hospital discharge showed that fatigue/muscle weakness (50–63%), cough (15%), dyspnoea/exertional dyspnoea (23–43%), arthralgias (27%), chest pain (22%), ongoing palpitations/arrhythmias (5%), loss of memory (34%), anxiety/depression (23%), concentration difficulties (28%), and sleep disorders (26–31%) were the most common patient-reported symptoms.[244–248] Two recent large cohort studies showed that 14–30% of COVID-19 patients developed clinical sequelae that required medical care or hospital admission during the 4 months after the acute phase of the diseases.[244,249]

As the definition of long COVID or PASC is developing, the underlying causes of post-acute COVID-19 symptoms are poorly understood. Various mechanisms might be involved such as cellular injury due to direct viral invasion, systemic hyperinflammation, a procoagulant state leading to post-inflammatory cardiac and pulmonary fibrosis, impairment of pulmonary diffusion capacity, cardiac dysfunction, partially dissolved *in situ* thrombotic microangiopathy or emboli with flow limitation, and post-acute thromboembolism.[243,250,251] Time course progression and most frequent symptoms and complications of post-acute COVID-19 syndrome are summarized in *Figure 4*.

## Potential mechanisms of post-acute COVID-19

Post-acute COVID-19 may very well have multiple causes. For example, autoantibodies may have a role. Perhaps viral reservoirs or lingering fragments of viral RNA or proteins contribute to the condition. Systemic inflammatory response to COVID-19, involving IL-1, IL-6, and TNF-α have the potential to increase myocardial fibrosis in cardiac remodelling.[252,253] Emerging evidence suggest that post-acute COVID-19 symptoms could be caused also by inappropriate sinus tachycardia (IST) and postural orthostatic tachycardia syndrome (PoTS).[254,255] Autonomic dysfunction after viral infection, resulting in IST and PoTS, has previously been reported in SARS-CoV-1 infection.[256] These are likely the result of

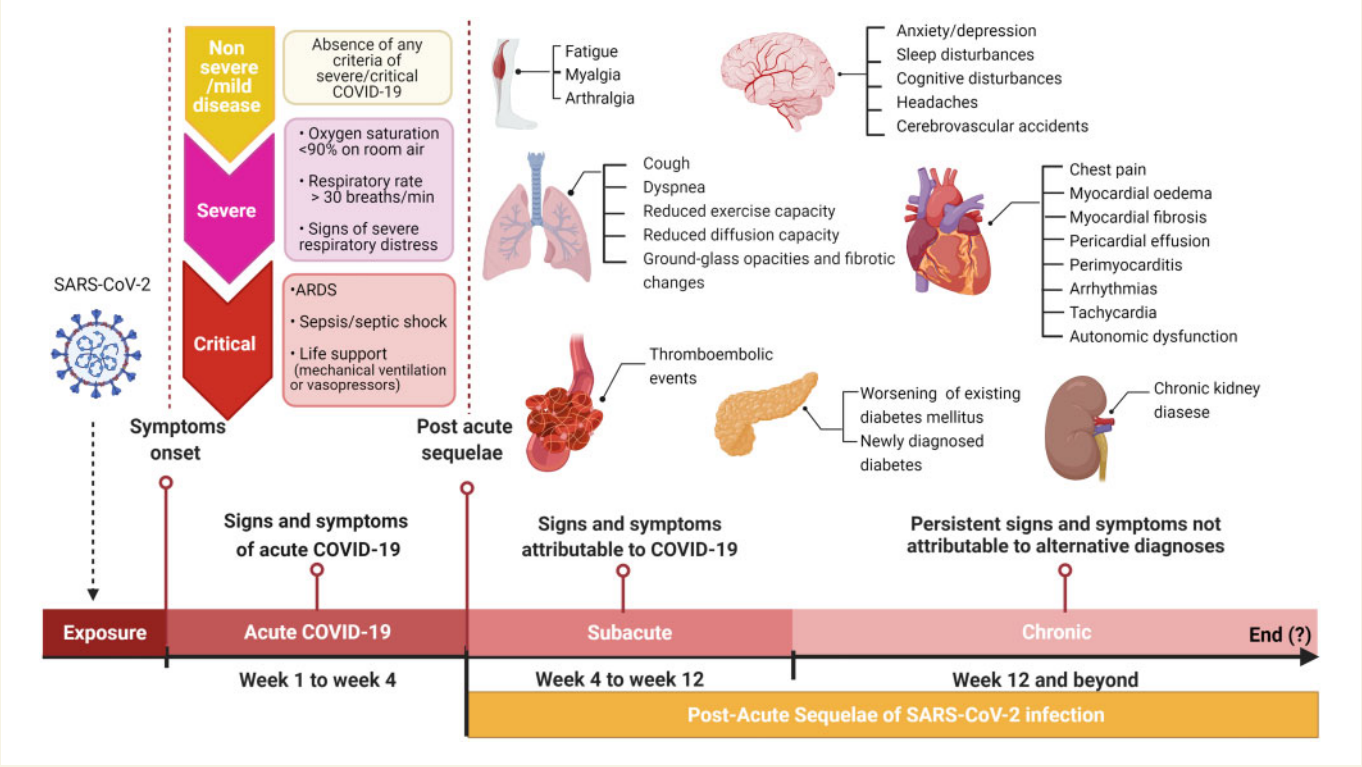



**Figure 4** Post-acute sequelae of SARS-CoV-2 infection. As for the current literature, post-acute sequelae of SARS-CoV-2 infection may be defined as persistent signs and symptoms or long-term complications beyond 4 weeks from symptoms onset. The most frequent symptoms and complications are summarized in the figure. Figure created with BioRender.com.

increased catecholaminergic state and inflammatory cytokines such as IL-1, Il-6, TNF-α and autoantibodies that target cardiac $Ca2^{+}$, $K^{+}$ or $Na^{+}$ channels leading to arrhythmogenic effects in the absence of evident changes in the myocardium.[180] In summary, the exact cause of post-acute COVID-19 is currently unknown and it will take substantial efforts to uncover mechanisms invoked. This may require a multidisciplinary approach considering the multiple targets being affected by COVID-19. Below we will report early approaches to this issue.

## Cardiac sequelae and complications

There is a bidirectional relationship between COVID-19 and the heart. Patients living with cardiovascular diseases are at higher risk of severe COVID-19 and death. On the other hand, myocardial oedema, fibrosis and related complications are observed in patients recovering from COVID-19.[257] CMR data suggest that cardiac involvement is present in approximately 80% of patients and ongoing myocardial inflammation in 60% of patients, at a median time interval of 71 days since COVID-19 diagnosis, even in asymptomatic patients.[258] Of note, when compared with healthy controls, patients who have recovered from COVID-19 have lower left ventricular ejection fraction, higher left ventricular volumes, late gadolinium enhancement (LGE) reflecting irreversible previous myocardial injury (necroptosis, fibrosis), and pericardial enhancement indicating pericardial inflammation. Additionally, these patients show raised native T1 signal suggesting expansion of the interstitial space due to fibrosis and native T2 signal suggesting myocardial oedema or necrosis. These findings correlate with higher levels of high-sensitivity troponin.[114] In addition, active lymphocytic inflammation was observed in a subgroup of patients who underwent endomyocardial biopsy.[258] Similar results were reported in other small studies of patients who recovered from COVID-19[259–261] It should be noted that up to 12% of these patients had a history of coronary revascularization or MI.[261] In contrast, another study did not show evidence of myocarditis, although CMR signs of subtle changes in myocardial structure and function and resolving pericardial inflammation were present in 30% of cases.[262]

Taken together, these observations support the hypothesis that abnormalities of myocardial tissue identified by CMR are common during COVID-19 recovery. These observations of myocardial fibrosis are worrisome, as resulting heart failure can lead to cardiac arrhythmias.

Yet, a raised T1 signal on CMR is not specific for oedema or acute myocardial inflammation, as it is observed in diffuse fibrosis or infiltration. Likewise, LGE reflects previous myocardial injury of any age.[263] Furthermore, the differentiation of ischaemic or non-ischaemic LGE in high-risk patients may reflect events prior to SARS-CoV-2 infection. For example, it is well known that 15% to 33% of patients with at least one cardiovascular risk factor have silent ischaemia, and potentially may have ischaemic LGE.[264,265]

## Imaging abnormalities and risk of future cardiac events

The relationship between imaging abnormalities and risk of future cardiac events are a matter of future research. A systematic evaluation of myocardial fibrosis (imaging/histology) may guide post-acute follow-up in COVID-19 patients with cardiac involvement and is clearly warranted.

In addition, innovative biomarkers for cardiovascular disease are also warranted. In this regard circulating RNAs biomarkers represent a valuable tool due to their biological relevance, dynamic regulation in response to disease, tissue-specificity, and accessibility. For instance, a recent study showed that has-miR-Chr8:96, a human microRNA, was able to distinguish patients with myocarditis from those with MI with a sensitivity and specificity of over 90%.[266]

## Post-acute pulmonary manifestations and risk future of cardiac events

Cohort studies have shown that at 6-month follow-up chest CT, residual ground-glass opacification and progression of fibrotic-like changes were present in one third of patients.[243,250] Additionally, impaired pulmonary diffusion capacity was the most common physiological finding occurring more frequently in those patients with fibrosis-like changes, suggesting unresolved microvascular injury.[243,250,251]

Some investigators have proposed a combined physiological approach to follow-up imaging to determine tissue perfusion, such as novel CT perfusion methods and combinations of standard methods of ventilation/perfusion (VQ) single-photon emission computed tomography with CT pulmonary angiogram, with the potential to inform the underlying pathophysiology of prolonged symptoms and therapeutic strategies.

Given the patterns of *in situ* thrombotic microangiopathy and vascular endotheliitis the impact of residual thrombus burden and potential haemodynamic sequelae such as chronic thromboembolic embolism, chronic pulmonary hypertension and adverse RV remodelling in COVID-19 remain a topic of future research.[267]

## Post-acute thromboembolic events

Most investigations have focused on the risk of thromboembolic events during the acute COVID-19 phase, while a few have focused on the post-acute phase of the disease. Current evidence shows conflicting results. In one study, 45-day post-discharge cumulative risk of VTE was 0.2%.[268] In another cohort, rates of VTE post-discharge were reported to be 4.8 per 1000 discharges and were not significantly different from post-discharge VTE associated with other acute diseases in 2019.[269] In a single-centre study, the cumulative incidence of thrombosis (including, pulmonary embolism, intracardiac thrombus, and ischaemic stroke) at day 30 post-discharge was 2.5%.[270] Similar results were reported in another cohort.[271]

As described above the COVID-19 related thrombosis suggests an immunothrombotic pathophysiology either directly by interacting with ACE2 receptor or indirectly by triggering hyperinflammation (*Figure 3*). Similarly, the risk of post-acute COVID-19 thrombotic events may be linked to the duration and the severity of hyperinflammation. Unfortunately, lack of data on the duration of the hyperinflammatory state after the acute phase, and lack of large prospective cohorts and randomized controlled trials, limits our ability to risk stratify post-acute thromboembolic events, highlighting the need to answer the unsettled question of extended post-discharge thromboprophylaxis.

## Metabolic sequelae of COVID-19 and diabetes

The relationship between COVID-19 and diabetes is complex and bidirectional. Patients with diabetes are at increased risk of severe COVID-19 and mortality. In turn, COVID-19 disrupts glucose metabolism which is a known feature of systemic infections. New-onset diabetes and severe complications of pre-existing diabetes such as insulin resistance, diabetic ketoacidosis, hyperosmolarity, microvascular and macrovascular complications have been described in patients with COVID-19.[272–275] Similarly, during the SARS-CoV-1 outbreak, acute diabetes was frequently reported in patients with no history of diabetes or steroid use.[276] ACE-2 and TMPRSS2 are expressed in pancreatic β cells,[277] but whether this is sufficient to trigger new-onset diabetes in COVID-19 is uncertain.[278] One study showed that SARS-CoV-2 infects and replicates in human pancreatic islet cultures inducing morphological, transcriptional and functional changes, including reduced numbers of insulin-secretory granules in β cells and impaired glucose-stimulated insulin secretion.[277] This investigation also described detection of the N protein of the virus in pancreatic exocrine and homeobox protein NKX6.1-positive β cells, a transcription factor that plays a critical role in pancreatic β cell function and proliferation, in postmortem examinations. Another proposed mechanism include increased insulin resistance due to cytokinemia such as IL-6 and TNF-α, an oxidative stress storm, glycation of ACE2 receptors, activation of the Ang II–ACE2–MasR axis due to binding of ACE2 receptor of β-cells and vascular endothelial cell/pericyte cells promoting fibrosis through islet amyloid polypeptide and collagen types I and III deposition.[274] These observations support the hypothesis of the potential diabetogenic effect of SARS-CoV-2 infection and are of particular concern given that diabetes promotes atherosclerosis and ischaemic heart disease.

Yet, there are several questions that remain unanswered: (i) What is the exact risk of new-onset diabetes in COVID-19? (ii) Does COVID-19 worsen the natural history of the disease in patients with pre-existing diabetes? (iii) Does COVID-19 increase long-term predisposition to diabetic ketoacidosis? and (iv) Can COVID-19-associated diabetes be reversed after the acute phase?

# Conclusions and future directions

Given that we have only known about the SARS-CoV-2 for only one and a half year, it is actually quite remarkable how much we have learned about its epidemiology and pathophysiology. As we increase our understanding of the disease there is growing consensus that COVID-19 is a macro- and micro-vascular disease and as such the cardiovascular system is largely affected. While, both clinical and basic research has been very responsive to tackle the challenge, most questions, however, remain unsolved, as our understanding of the pathophysiology of the disease is still under evolving and needs to be addressed and expanded in future research efforts. The most pressing questions are:

i. What causes elderly patients, men and those with cardiometabolic risk factors to be at higher risk of severe—COVID-19? Observations suggest the importance of a 'metabolic disease exposome',[279] including dietary lifestyle, glycaemic disorders, obesity, and sedentariness, among other potential disease severity modifiers such as systemic hypertension and aging, leading to chronic low grade inflammation, which may aggravate COVID-19-induced acute organ failure. Therefore, it is essential to precisely identify the factors underlying the severity and the clinical presentation of the disease, especially when considering the risk of COVID-19 epidemics.[280] Aging has also a significant effect on the response to pharmacological interventions. It may be necessary to design trials that focus exclusively on elderly. Finally, ageing is associated to oxidative stress and immune-senescence impairing therefore the answer of the immune system against the viral insult. The study population of an RCT should ideally reflect the population that is at the highest risk of the disease and that is most difficult to treat in clinical practice.

ii. How can we better address failure of the microcirculation in COVID-19 and personalize potential therapeutic approaches? Persistence of SARS-CoV-2 and viral RNA may act as potential viral reservoirs. They tend to induce an inflammatory response, stimulating endothelial dysfunction, accelerated atherosclerosis, hypercoagulability, and microvascular thrombosis. Thus, novel and prognostic biomarkers, combined with genetic differences and functional testing are required. To tackle the challenge, a large international interdisciplinary network of clinical and non-clinical scientists is needed. Initial examples of such cooperation is the EU-CardioRNA COST Action CA17129 which would try to identify RNA biomarkers combined with artificial intelligence.[5,281]

iii. What will be the impact of myocardial injury on long-term functional status, quality of life and risk for arrhythmias? What makes some people more vulnerable than others? What are the biological mechanisms underlying this? Exercise intolerance, for example, is a condition that a cardiologist in this group of post-acute COVID patients faces. The diagnostic and prognostic role of pulmonary and myocardial fibrosis in COVID-19 remains to be established. The systematic follow-up of COVID-19 patients with a deep and complete clinical and biological phenotype will enable the identification of individuals at risk in order to provide personalized care and with the aim of preventing further vulnerability for-and exposure to long-term sequela.

iv. Are SARS-CoV-2 infected persons without symptoms at a similar and proportional increased long-term risk of PASC compared with those with symptoms? Approximately 25% of individuals who had COVID-19 still have physical symptoms one month after they became ill, and about 10% have symptoms that persist after 12 weeks. COVID-19 is a 'new disease' that pushes the research community and the world more generally into 'uncharted territories'. We should commit to set up a network of scientists and laboratories around Europe taking a multidisciplinary approach.

## Authors' contributions

E.C. and D.T. conceived and designed the manuscript, drafted the manuscript, and revised it for important intellectual content. L.B., R.B., M.J.C., G.D.L., C.d.W., D.D., M.D., D.J.D., E.C.E., D.A.G., C.H., F.R.H., K.H., O.M., D.M., E.O., T.P. D.T.Z., Z.V.P, M.V., and G.V. made substantial contributions to the conception and design of the manuscript, drafted the manuscript, and revised it for important intellectual content. All authors approved the final version of the manuscript.

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