Invited Review

COVID-19 and the heart

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Received 6 April 2022; Revised 26 August 2022; Accepted 2 September 2022

Abstract

Background: There is evidence for a bi-directional relationship between COVID-19 and the cardiovascular (CV) system.

Source of data: Published literature.

Areas of agreement: Pre-existing heart failure (HF) increases the risk of mortality with COVID-19. CV complications are recognized, including increased rates of acute coronary syndromes, HF, arrhythmia and myocarditis. Drugs targeting the angiotensin system are safe and may provide prognostic benefit.

Areas of controversy: Vaccination as a cause of myocarditis remains a key area of contention.

Growing points: As the pandemic progresses, we are gaining more data about the long-term effects of COVID-19 on the CV system: long COVID, and medium-to-long-term increases in CV risk.

Areas timely for developing research: Large-scale longitudinal studies will shed light on long-term CV outcomes with COVID-19. Furthermore, the differential effects of COVID-19 variants on the CV system must be investigated.

Key words: COVID, COVID-19, SARS-CoV-2, heart, long Covid, myocarditis
Introduction

On 31 December 2019, the World Health Organisation announced a cluster of cases of viral pneumonia in Wuhan Province, China. Shortly after, it was discovered that this clinical syndrome was due to a novel coronavirus, SARS-CoV-2. Within 2 months a global COVID-19 pandemic was announced, to date infecting almost half a billion people worldwide and causing in excess of 6 million deaths.

Although primarily a respiratory disease, concerns regarding the effect of COVID-19 on the cardiovascular (CV) system were present from a very early stage. On a mechanistic level, the virus was found to use the Angiotensin-Converting Enzyme II receptor (ACE2r) to facilitate entry into the host cell. ACE2r is widely expressed throughout the CV system and is a target for a commonly prescribed class of antihypertensive drugs, ACE inhibitors (ACEi). From a clinical perspective, early case series from China noted that patients admitted to the intensive care unit (ICU) with COVID-19 had increased serum levels of cardiac troponin, a marker of myocardial injury. This raised concerns that infection with SARS-CoV-2 may lead to direct myocardial involvement. Furthermore, early data showed that patients with CV disease (CVD) were at increased risk of severe COVID-19, implying a potential bi-directional relationship between the virus and the CV system. In this paper, we review the complex relationship between COVID-19 and the heart, discussing the acute and long-term effects of COVID-19 on the CV system, as well as reviewing CV considerations relating to vaccination against COVID-19.

The renin-angiotensin-aldosterone system and the safety of ACEi and ARB in the era of COVID-19

As noted above, there was significant concern in early 2020 that, due to the mechanistic involvement of the ACE2r in viral entry into the host cell, the widely used antihypertensive agents ACEi and angiotensin receptor blockers (ARBs) may be dangerous in the setting of COVID-19. This was based on animal and human data demonstrating that use of ACEi and ARB results in an increase in ACE2r expression, and the hypothesis was therefore that these medications could facilitate viral entry into cells. However, early data did not support this theory, and in fact data emerged to suggest that the opposite is true i.e. discontinuation of ACEi/ARB in patients hospitalized with COVID-19 contributes to an increased risk of death. It is now widely accepted that ACEi and ARB are safe in COVID-19, and there are data to suggest that these classes of drug may be protective, or even actively therapeutic. It has been suggested that by inhibiting action of Angiotensin II, ACEi and ARB mitigate pro-inflammatory and profibrotic damage to the lung, a mechanism by which these drugs could exert their protective effects.

It has been proposed that an imbalance in the renin-angiotensin-aldosterone system (RAAS) may be a pathological hallmark of COVID-19. Indeed, RAAS imbalance contributes to the hyperinflammatory state seen in patients with severe COVID-19, with pro-oxidative and fibrotic effects leading to multi-organ damage seen in severe COVID-19. Furthermore, derangement in RAAS balance has been postulated as a contributor to the common findings of hypokalaemia and fluid retention in COVID-19 patients, suggesting a possible mechanism by which inhibition of the RAAS may provide clinical benefit. The link between COVID-19 and the RAAS, and the multi-system effects of the RAAS may represent a common explanation for the cardiac and renal manifestations of COVID-19. Indeed, patients with severe COVID-19 are commonly seen to display kidney injury, and patients with chronic kidney disease have worse outcomes than those without.

Contribution of CVD to severity of COVID-19

It is widely accepted that patients with an increased burden of comorbidities are at higher risk of severe COVID-19. Early in the pandemic, cohort studies from the UK showed the association between pre-existing CVD and poor outcomes with
COVID-19, including increased requirement of mechanical ventilation and risk of death. However, a large multi-national cohort study using data from the CAPCITY-COVID registry and LEOSS study showed that only heart failure (HF), and in particular severe HF (NYHA class III/IV), was associated with increased in-hospital mortality after multivariable regression analysis.\textsuperscript{13}

Interestingly, data from our hospital suggest that although risk factors for CVD are not associated with inpatient mortality, pre-existing CVD is, implying that link between CVD and poor outcomes may be mediated in part by new CV complications.\textsuperscript{14}

### Acute coronary syndromes

Understanding the true effect of COVID-19 on acute coronary syndromes (ACSs) is hampered both by the high prevalence of elevated serum troponin levels amongst patients with COVID-19 but also by the competing effect of social containment (‘lockdown’) measures on ACS presentations.

It is well-established that patients admitted to the ICU with respiratory and/or infective illnesses commonly display a raised serum troponin, which acts both as a marker of underlying CVD and as a predictor of mortality.\textsuperscript{15} In COVID-19, although associated with worse prognosis, elevated serum troponin levels are non-specific and may correspond to a variety of causes of myocardial injury, not necessarily with acute ischaemia.\textsuperscript{16} These include type 1 myocardial infarctions, but also supply:demand mismatch due to hypoxia and/or shock related to severe COVID-19, myocarditis, Takotsubo cardiomyopathy, pulmonary embolism and sepsis. Nevertheless, studies have shown the increased risk of acute myocardial infarction with COVID-19, including events due to coronary thrombosis without plaque rupture. The mechanism behind this increased risk of acute myocardial infarction in COVID-19 is postulated to be similar to that implicated in increased risk of stroke and venous/pulmonary embolism: the hyperinflammatory and hypercoagulable state induced by COVID-19 infection, with endothelial dysfunction and platelet activation resulting in a pro-thrombotic picture\textsuperscript{17} (although it is known that inflammation is associated with atherosclerotic plaque vulnerability and rupture).\textsuperscript{18,19}

COVID-19 has been seen to directly infert the vascular endothelial cells, causing apoptosis and altered interaction with platelets and leukocytes in the circulation.\textsuperscript{20} Furthermore, imbalanced endothelial release of vasoactive substances including nitric oxide and prostaglandins, and increases in reactive oxidative species lead to the ‘immunothrombosis’ that is thought to contribute to many of the multi-system manifestations of COVID-19 described here. These effects are seen both within the microvascular system (evidenced by microvascular angiopathy seen in lungs of patients affected by severe COVID-19 with acute respiratory distress syndrome), but also in larger vessels causing ACSs, but also acute limb ischaemia, venous and pulmonary embolism and stroke.\textsuperscript{21}

COVID-19 has had effects on ACS beyond biological mechanisms. A significant reorganization of ACS networks and their workings was required at the peak of successive waves,\textsuperscript{22} exemplified by the European Association of Percutaneous Coronary Intervention’s position statement on strategical categorization of coronary interventions during the COVID-19 pandemic.\textsuperscript{23} Elective coronary intervention, as well as other aspects of CV care including valve intervention and imaging needed to be delayed. Subsequent presentations may have been delayed and further along the natural progression of disease, with knock on effects of morbidity and mortality. So-called quiescent periods, where the frequency of ACS presentations decreased during early peaks in the pandemic,\textsuperscript{24} are likely to have contributed to late-presenting ACS events. Reductions in presentation may also be due to a combination of fear of contagion and overburdening already stretched healthcare systems amongst the population, but also a possible true reduction in ACS events with lower physical stressors and lifestyle changes whilst in social containment.

### Heart Failure

The relationship between heart failure (HF) and COVID-19 is complex. As discussed above, pre-
existing HF is associated with increased mortality in patients hospitalized with COVID-19, and data have shown that increasing NYHA class is associated with a greater duration of hospitalization, need for mechanical ventilation and mortality—this effect is independent of other comorbidities. Indeed, patients with HF show a reduced immunity and haemodynamic reserve and are at risk of exacerbations and deterioration when faced with concurrent illness.\textsuperscript{25}

Furthermore, new-onset of HF has been seen amongst patients hospitalized with severe COVID-19, presenting with right ventricular dysfunction, as well as left ventricular systolic and diastolic dysfunction.\textsuperscript{26} Suggested mechanisms include direct myocardial injury (presenting as myocarditis), as well as the effects of pro-inflammatory cytokine storm seen in patients with severe COVID-19, and finally right ventricular strain caused by pulmonary emboli commonly seen in COVID-19.

In addition to the detrimental effect of pre-existing HF in patients with COVID-19, an effect was seen whereby patients who were hospitalized for HF during the UK’s first COVID-19 wave in 2020 had poor in-hospital outcomes compared with historical controls, with this effect persisting even after discharge.\textsuperscript{27,28} As described above, the mechanism may relate to the reluctance to attend hospital during the height of the pandemic, with patients presenting later along the natural history of their illness, thereby suffering from higher mortality. Furthermore, the lower availability of specialist in- and out-patient care for patients during this period may have contributed. It will be crucial to ensure that, as vaccination becomes more widespread and healthcare systems begin to normalize the delivery of care, this vulnerable group of patients is monitored closely.

**COVID-19 and myocarditis: Clinical disease presentation and complication of vaccination**

From early in the pandemic, published reports highlighted individual cases of clinical myocarditis and pericarditis in patients with acute COVID-19.\textsuperscript{29} These findings raised the possibility that there would be a significant number of similar cases during waves of infection. Subsequent data suggest that across the spectrum of disease severity, clinically confirmed myocarditis is an uncommon presentation of COVID-19, with an incidence of < 1% in hospitalized patients.\textsuperscript{14} In patients with life-threatening or fatal COVID-19, sub-clinical myocardial involvement can be detected in a higher proportion of cases, either by cardiac magnetic resonance imaging, endomyocardial biopsy or post-mortem examination.\textsuperscript{30,31}

Acute myocarditis following vaccination against SARS-CoV-2 is a contentious issue. Two early studies from Israel reported on post-vaccine myocarditis in the Israeli population following rapid rollout of the BNT162b2 mRNA vaccine (Pfizer-BioNTech).\textsuperscript{32,33} Both studies found that vaccination to SARS-CoV-2 conferred an increased risk of myocarditis, with the highest prevalence in young adult males. However, in the vast majority of cases, the clinical course was self-resolving and uncomplicated. Subsequent data on post-vaccine myocarditis in adolescents showed that there is a strong male preponderance, with the incidence being much higher after the second dose compared with the first, however overall numbers are still low.\textsuperscript{34}

Data on risk of myocarditis following vaccination have raised the question of the relative risk compared with that of myocarditis following COVID-19 infection. Recent data from England suggest that there is a substantially higher risk of myocarditis, pericarditis and cardiac arrhythmia from COVID-19 infection than from vaccination against SARS-CoV-2.\textsuperscript{35}

**Arrhythmias**

Arrhythmias have been recognized in patients with COVID-19 since early on in the pandemic.\textsuperscript{36} A retrospective analysis of COVID-19 patients worldwide found that 18% of patients suffered from arrhythmia, with the majority developing atrial and supraventricular arrhythmias, and fewer developing ventricular arrhythmias and bradycardhythmias (sinus or atrioventricular block).\textsuperscript{37} Many of these
arrhythmias were new, although patients were noted to be more likely to have pre-existing CVD. Patients with CVD and COVID-19 infection are inherently high risk for arrhythmias due to a combination of increased pre-morbid susceptibility, critical illness and potential myocardial injury as discussed above. Furthermore, some medications that were considered by some to have potential benefit in the treatment of COVID-19 early in the pandemic (including azithromycin and hydroxychloroquine) have known QT prolonging effects, thereby increasing risk of ventricular tachycardia. However, use of these classes of medications has reduced after multiple randomized control trials failed to show any evidence for their benefit in COVID-19.

COVID-19 in children: PIMS-TS

A post-infectious syndrome known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was described in case series of children early in the pandemic. PIMS-TS shares characteristics with Kawasaki disease, commonly manifesting with pyrexia, rashes, gastrointestinal, respiratory and CV involvement. From a CV perspective, PIMS-TS can cause myocarditis, pericarditis, valvulitis, as well as left ventricular failure and coronary artery aneurysms or dilatation (similar to those seen in Kawasaki disease).\textsuperscript{38,39} Due to the multi-system and heterogeneous nature of the syndrome, the reported incidence of cardiac involvement in PIMS-TS varies from 12 to 100%. Children with cardiac involvement have elevated serum troponin, NT-pro B-type natriuretic peptide and D-dimer. A cohort study in the UK has shown favourable CV outcomes for patients with PIMS-TS at 6 months, although longer term outcomes remain to be seen, especially for those developing coronary artery aneurysms.\textsuperscript{40}

Long-term CV effects of COVID-19

From an epidemiological perspective, it is clear that COVID-19 can have lasting effects on the CV system. A large cohort study in the USA showed that 1 year after infection with COVID-19, risk of HF, ischaemic heart disease, arrhythmia, pericarditis, myocarditis and cerebrovascular disease is increased compared with a control cohort.\textsuperscript{41} This risk was higher with worsening severity of COVID-19 infection, with patients admitted to the ICU faring worse than hospitalized patients, but importantly is also seen to a lesser extent in non-hospitalized patients (who make up the majority of patients who have been infected with COVID-19). Furthermore, this effect was present in those without CVD prior to COVID-19 infection. These findings have important public health implications given the vast number of people who have been infected by COVID-19 (almost half a billion by April 2022), and who therefore will be vulnerable to increased CVD in the future. The duration of this effect remains to be elucidated and should be a focus of future research.

In addition to the heightened CV risk post-COVID-19, many patients continue to experience symptoms for weeks or months after the acute illness, a phenomenon termed ‘Long COVID.’ Although the study of severe and/or life-threatening acute COVID-19 is a diminishing field due to the effectiveness of vaccination, research into Long COVID is (currently) limited by the novelty of the disease. Long COVID is a multi-system condition with a range of neurological, cognitive, respiratory, gastrointestinal, cardiac and autonomic symptoms having been reported.\textsuperscript{42} The risk of developing Long COVID is associated with having more than five symptoms during the first week of the acute illness; age; body mass index; and female sex.\textsuperscript{43} Relating specifically to the CV system, a number of patterns emerge:

- A PoTS-like (postural tachycardia) syndrome\textsuperscript{44}
- Persistent myocardial inflammation
- Ongoing symptoms such as chest tightness/pain and palpitations\textsuperscript{45}

The efficacy of vaccination against Long COVID remains to be fully investigated. A 2022 review by the UK Health Security Agency reviewed 15 studies investigating the effectiveness of vaccination.
against Long COVID, reporting that vaccinated people are less likely to develop the disease following COVID-19 infection.46 This effect is in addition to the reduction in incidence of COVID-19 seen with vaccination, and is therefore likely to underestimate the importance of vaccination in preventing Long COVID. However, amongst those already suffering from Long COVID, it is unclear whether vaccination can improve symptoms, and the mainstay of treatment remains supportive in this population.

**Mechanisms linking COVID-19 to CVD**

The mechanisms which link COVID-19 infection and CVD are complex and remain incompletely characterized. There are many putative mechanisms, some of which are common to respiratory viruses and/or critical illness, and others which seem to be unique to COVID-19. Critically unwell patients are at risk of cardiac complications due to the excess metabolic demands on the heart, hypoxia, sepsis-induced myocardial dysfunction, poor physiological reserve due to pre-morbid conditions and many more.

Severe COVID-19 infection has been associated with a dysregulated immune response, involving cytokine storms made up release of cyto- and chemokines including tumour necrosis factor-α, interleukin-1, interleukin-6 (providing a rationale for interleukin antagonism as a therapy in COVID-19). These cytokine storms and associated immune response involving neutrophils and macrophages have been implicated in CV complications. Macrophages release collagenases which can destabilize atherosclerotic plaques, as well as tissue factor increasing thrombosis.47 Similarly, neutrophil extracellular traps, webs of chromatin and bactericidal components released by neutrophils have been implicated in thrombosis associated with COVID-19.47 Finally, endothelial dysfunction due to damage by SARS-CoV-2 may also play a role in the hyper-coagulable state seen in COVID-19.

As mentioned above, early autopsy-based data suggested the possibility of SARS-CoV-2 directly infecting the myocardium and causing cell injury. The high CV expression of the ACE2r, used by the virus to enter the host cell, provides a potential mechanism for this. However, subsequent data have shown that myocardial infection is only inconsistently associated with myocarditis (on autopsy and cardiac MRI), limiting the plausibility of this as a major cause of CV complications in COVID-19.48

**COVID-19 variants and differential effects on the CV system**

It is important to acknowledge that different variants of COVID-19 clearly present with different clinical phenotypes. Indeed, mortality and severity vary significantly between COVID-19 variants, and it is therefore appropriate to expect that CV implications will differ as well. It is unclear, for example, whether newer and future variants will have similar long-term effects on Long COVID, and the interplay between the COVID-19 and the heart can be expected to change as future variants emerge. More recent variants, such as the Omicron variant, are associated with a lower mortality than those variants which have generated much of the currently available data. It is crucial, therefore, that future research aims to clearly define which variant of COVID-19 is being investigated.

**Conclusions**

The COVID-19 pandemic has represented a unique public health and clinical challenge in our lifetimes. During this time, CV health both of patients with and without COVID-19 has been in the spotlight. Certain pre-existing CVDs such as HF increase the risk of poor outcomes with COVID-19, and COVID-19 itself can manifest with cardiac complications including new-onset of HF, ACS, arrhythmias and myocarditis. As the pandemic progresses, we are gaining a better understanding of the long-term effects of COVID-19 infection; these have manifested as Long COVID, and an increased risk of CVD sustained at least in the medium-term. However, certain elements remain to be fully elucidated: how
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successful will vaccination against COVID-19 be at mitigating CV effects of the virus, and will COVID-19 variants differentially affect the CV system? Finally, the longer-term implications of the public health effects of lockdown and the pandemic on CVD need to be considered too. Future research should aim to address these considerations.

Data Availability
No new data were generated or analysed in support of this review.

References

1. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
2. Reynolds HR, Adhikari S, Pulgarin C et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020;382:2441–8.
3. Singh S, Offringa-Hup AK, Logtenberg SJJ et al. Discontinuation of antihypertensive medications on the outcome of hospitalized patients with severe acute respiratory syndrome-coronavirus 2. Hypertension 2021;78:165–73.
4. Lee T, Cau A, Cheng MP et al. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors in COVID-19: meta-analysis/meta-regression adjusted for confounding factors. CJC Open 2021;3:965–75.
5. Duarte M, Pelorosso F, Nicolosi LN et al. Telmisartan for treatment of Covid-19 patients: an open multicenter randomized clinical trial. EClinicalMedicine 2021;37:100962.
6. South AM, Tomlinson L, Edmonston D et al. Controversies of renin-angiotensin system inhibition during the COVID-19 pandemic. Nat Rev Nephrol 2020;16:305–7.
7. Rysz S, Al-Saadi J, Sjostrom A et al. COVID-19 pathophysiology may be driven by an imbalance in the renin-angiotensin-aldosterone system. Nat Commun 2021;12:2417.
8. Henry BM, Vikse J, Benoit S et al. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta 2020;507:167–73.
9. Chen D, Li X, Song Q et al. Assessment of Hypokalemia and clinical characteristics in patients with coronavirus disease 2019 in Wenzhou, China. JAMA Netw Open 2020;3:e2011122.
10. Legrand M, Bell S, Forni L et al. Pathophysiology of COVID-19-associated acute kidney injury. Nat Rev Nephrol 2021;17:751–64.
11. Docherty AB, Harrison EM, Green CA et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ 2020;369:m1985.
12. Williamson EJ, Walker AJ, Bhaskaran K et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.
13. Consortium C-CC, Group LS. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries. Eur Heart J 2022;43:1104–20.
14. O’Gallagher K, Shek A, Bean DM et al. Pre-existing cardiovascular disease rather than cardiovascular risk factors drives mortality in COVID-19. BMC Cardiovasc Disord 2021;21:327.
15. Vestjens SMT, Spoorenberg SMC, Rijkers GT et al. High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia. Respirology 2017;22:1000–6.
16. Shi S, Qin M, Shen B et al. Association of Cardiac Injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802–10.
17. Nishiga M, Wang DW, Han Y et al. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020;17:543–58.
18. Libby P, Tabas I, Friedman G et al. Inflammation and its resolution as determinants of acute coronary syndromes. Circ Res 2014;114:1867–79.
19. Timpau AS, Miftode RS, Leca D et al. A real Pandora’s box in pandemic times: a narrative review on the acute cardiac injury due to COVID-19. Life (Basel) 2022;12:1085. https://doi.org/10.3390/life12071085.
20. Osuchowski MF, Winkler MS, Skirecki T et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med 2021;9:622–42.
21. Gavriliak E, Anyfanti P, Gavriliaki M et al. Endothelial dysfunction in COVID-19: lessons learned from coronaviruses. Curr Hypertens Rep 2020;22:63.
22. Raisi-Estabragh Z, Mamas MA. Cardiovascular health care implications of the COVID-19 pandemic. Cardiol Clin 2022;40:389–96.
23. Chieffo A, Stefanini GG, Price S et al. EAPCI position statement on invasive Management of Acute Coronary
Syndromes during the COVID-19 pandemic. *Eur Heart J* 2020;41:1839–51.
24. De Filippo O, D’Ascenzo F, Angelini F et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in northern Italy. *N Engl J Med* 2020;383:88–9.
25. Bader F, Manla Y, Atallah B, Starling RC. Heart failure and COVID-19. *Heart Fail Rev* 2021;26:1–10.
26. Szekely Y, Lichter Y, Taieb P et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. *Circulation* 2020;142:342–53.
27. Bromage DI, Cannata A, Rind IA et al. The impact of COVID-19 on heart failure hospitalization and management: report from a heart failure unit in London during the peak of the pandemic. *Eur J Heart Fail* 2020;22:978–84.
28. Ta Anyu A, Badawy L, Cannata A et al. Long-term outcomes after heart failure hospitalization during the COVID-19 pandemic: a multisite report from heart failure referral centers in London. *ESC Heart Fail* 2021;8:4701–4.
29. Hua A, O’Gallagher K, Sado D et al. Life-threatening cardiac tamponade complicating myo-pericarditis in COVID-19. *Eur Heart J* 2020;41:2130.
30. Knight DS, Kotecha T, Razvi Y et al. COVID-19: myocardial injury in survivors. *Circulation* 2020;142:1120–2.
31. Kawakami R, Sakamoto A, Kawai K et al. Pathological evidence for SARS-CoV-2 as a cause of myocarditis: JACC review topic of the week. *J Am Coll Cardiol* 2021;77:314–25.
32. Mevorach D, Anis E, Cedar N et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med* 2021;385:2130–9.
33. Withberg G, Barda N, Hoss S et al. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med* 2021;385:2132–9.
34. Mevorach D, Anis E, Cedar N et al. Myocarditis after BNT162b2 vaccination in Israeli adolescents. *N Engl J Med* 2022;386:998–9.
35. Patone M, Mei XW, Handunnetthi L et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med* 2022;28:410–22.
36. Dherange P, Lang J, Qian P et al. Arrhythmias and COVID-19: a review. *JACC Clin Electrophysiol* 2020;6:1193–204.
37. Coromilas EJ, Kochav S, Goldenthal I et al. Worldwide survey of COVID-19-associated arrhythmias. *Circ Arrhythm Electrophysiol* 2021;14:e009458.
38. Flood J, Shingleton J, Bennett E et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS): prospective, national surveillance, United Kingdom and Ireland, 2020. *Lancet Reg Health Eur* 2021;3:100075.
39. Whittaker E, Bamford A, Kenny J et al. Clinical characteristics of 58 children with a Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020;324:259–69.
40. Penner J, Abdel-Mannan O, Grant K et al. 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *Lancet Child Adolesc Health* 2021;5:473–82.
41. Xie Y, Xu E, Bowe B et al. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;28:583–90.
42. Crook H, Raza S, Nowell J et al. Long covid-mechanisms, risk factors, and management. *BMJ* 2021;374:n1648.
43. Sudre CH, Murray B, Varsavsky T et al. Attributes and predictors of long COVID. *Nat Med* 2021;27:626–31.
44. Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. *Heart Rhythm* 2021;18:508–9.
45. Evans RA, McAuley H, Harrison EM et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* 2021;9:1275–87.
46. UKHSA. *The Effectiveness of Vaccination against Long COVID*, www.gov.uk, 2022
47. Chung MK, Zidar DA, Bristow MR et al. COVID-19 and cardiovascular disease: from bench to bedside. *Circ Res* 2021;128:124–36.
48. Farshidfar F, Koleini N, Ardehali H. Cardiovascular complications of COVID-19. *JCI Insight* 2021;6. https://doi.org/10.1172/jci.insight.148980.