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COVID-19 vaccination in patients with heart failure: a position paper of the Heart Failure Association of the European Society of Cardiology

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Patients with heart failure (HF) who contract SARS-CoV-2 infection are at a higher risk of cardiovascular and non-cardiovascular morbidity and mortality. Regardless of therapeutic attempts in COVID-19, vaccination remains the most promising global approach at present for controlling this disease. There are several concerns and misconceptions regarding the clinical indications, optimal mode of delivery, safety and efficacy of COVID-19 vaccines for patients with HF. This document provides guidance to all healthcare professionals regarding the implementation of a COVID-19 vaccination scheme in patients with HF. COVID-19 vaccination is indicated in all patients with HF, including those who are immunocompromised (e.g. after heart transplantation receiving immunosuppressive therapy) and with frailty syndrome. It is preferable to vaccinate against COVID-19 patients with HF in an optimal clinical state, which would include clinical stability, adequate hydration and nutrition, optimized treatment of HF and other comorbidities (including iron deficiency), but corrective measures should not be allowed to delay vaccination. Patients with HF who have been vaccinated against COVID-19 need to continue precautionary measures, including the use of facemasks, hand hygiene and social distancing. Knowledge on strategies preventing SARS-CoV-2 infection (including the COVID-19 vaccination) should be included in the comprehensive educational programmes delivered to patients with HF.

Keywords

Heart failure • SARS-CoV-2 • COVID-19 • Vaccination

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection constitutes a serious threat for patients with cardiovascular disease (CVD), particularly those with heart failure (HF).^{1–3} Patients with HF who contract SARS-CoV-2 infection are at a higher risk of cardiovascular (CV) and non-CV morbidity and mortality.^{1–3} Patients with HF represent a prime example of a patient population that accumulates numerous clinical conditions and comorbidities,^{4,5} which make them extremely vulnerable to SARS-CoV-2 infection.

Although a significant improvement in survival rates of hospitalised patients with COVID-19 has been observed with anticoagulation^{6,7} and corticosteroids,⁸ there are currently no efficacious antiviral therapies to target coronavirus disease 2019 (COVID-19), and vaccination remains the most promising global approach at present for controlling this disease.^{9,10}

There are several concerns and misconceptions regarding the clinical indications, optimal mode of delivery, safety and efficacy of COVID-19 vaccines for patients with HF.

This document is the result of a comprehensive literature search, followed by the critical analysis and discussion within an interdisciplinary group of experts, including cardiologists, specialists in HF, geriatricians, intensive care specialists, and clinical immunologists. The aim of this position paper is to provide guidance to all healthcare professionals regarding the implementation of a COVID-19 vaccination scheme in patients with HF (Table 1).

Morbidity and mortality of patients with heart failure during the COVID-19 pandemic

The COVID-19 pandemic has significantly modified the epidemiology of HF by directly and indirectly affecting morbidity and mortality.

SARS-CoV-2 infection, when occurring in patients with HF, is associated with high CV and non-CV morbidity and mortality.^{1–3} In the CARD-COVID programme, patients with confirmed

COVID-19 and a history of HF were more prone to develop acute HF (11% vs. 2%, $P < 0.001$) and had higher mortality (49% vs. 19%, $P < 0.001$).¹ The Center for Disease Control and Prevention (CDC) released a list of underlying medical conditions at increased risk for severe illness and high mortality from COVID-19.¹¹ The strongest and most consistent association with underlying conditions and COVID-19 fatality has been reported for heart conditions (including HF), cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, pregnancy, sickle cell disease, smoking, solid organ transplantation, and type 2 diabetes mellitus.^{11–13}

A systematic Cochrane review of 220 studies of COVID-19 patients demonstrated that hypertension (36%), diabetes (22%) and ischaemic heart disease (11%) were highly prevalent in people hospitalised with COVID-19.³ The incidence of CV complications was substantial, with arrhythmias (9.3%), HF (6.8%) and thrombotic complications (7.4%) being the most prevalent among hospitalised COVID-19 patients.³ Among CV complications, the presence of HF strongly predicted the risk of death (49% vs. 3%).³ Although several pathophysiological concepts have been developed to explain the processes leading to myocardial injury, circulatory and respiratory failure, and homeostasis collapse in the course of COVID-19, a unifying mechanistic theory has not been formulated.^{14–18} Insights into the pathogenic mechanisms are becoming apparent and include hyperinflammatory state (cytokine storm), coagulopathy and widespread endothelial dysfunction leading to unfavourable clinical events in patients infected with SARS-CoV-2.^{14–18} Increased levels of cardiac and inflammatory microRNAs in severely-ill ventilated COVID-19 patients (in a strong contrast to ventilated influenza patients) further point to the very specific affection of myocardium by SARS-CoV-2.¹⁹ All these mechanisms predispose to circulatory decompensation, arrhythmic and ischaemic events.²⁰ Furthermore, consistently with previous severe acute respiratory syndrome and Middle East respiratory syndrome epidemics, in patients with COVID-19, hypotension, tachycardia, bradycardia, cardiomegaly and arrhythmia are recurrent conditions recognized as predisposing to acute HF.²¹

Patients with HF are particularly vulnerable to SARS-CoV-2 infection, as they are usually elderly subjects with numerous

Table 1 Summary of all key messages and guidance statements for patients with heart failure and COVID-19

- The diagnosis of HF, particularly when present in an elderly and/or frail subject, is a strong predictor of non-lethal and lethal complications of COVID-19, which include a need for intensive non-invasive and invasive respiratory support, a need for pharmacological and mechanical circulatory support, a longer hospital stay, a longer intensive care unit stay, a high risk of severe pneumonia and respiratory failure, more common thromboembolic events, secondary myocardial damage, circulatory decompensation, neurological complications, and finally increased risk of both CV and non-CV death.
- All COVID-19 vaccine trials have recruited cohorts of subjects, including those with CVD and HF, and have confirmed the vaccines to be safe and effective in these groups. Rare cases of thromboembolism and myocarditis need to be acknowledged, but also confronted with overwhelming survival benefits due to COVID-19 vaccinations seen globally.
- COVID-19 vaccination is indicated for all patients with HF unless other contraindications exist.
- COVID-19 vaccination is indicated in all patients with HF with a compromised immune system, including patients following heart transplantation receiving immunosuppressive therapy. They are unlikely to generate a completely protective immune response after COVID-19 vaccination, and therefore need additional personal measures including facemask wearing and social distancing for added protection. The additional dose of vaccine beyond the standard scheme may increase the efficacy of vaccination in these patients.
- Patients with HF are indicated also to be vaccinated against influenza and pneumonia in order to reduce the risk of dual infections.
- It is suggested not to administer the vaccine to individuals with a known history of a severe allergic reaction (e.g. anaphylaxis) to any component of the COVID-19 vaccine. However, it should not be considered as an absolute contraindication for vaccination against COVID-19. The diagnosis of HF (or any CVD) itself does not increase the risk of anaphylactic (or any other allergic) reactions.
- Intramuscular injection required for COVID-19 vaccines can cause haematomas in patients with platelet defects, thrombocytopenia and/or on anticoagulation therapy. The benefit of COVID-19 vaccination is expected to be greater than the risks of local bleeding.
- Therapy with anticoagulants and/or antiplatelets in patients with HF is not a contraindication for vaccination against COVID-19. All approved COVID-19 vaccines must be applied intramuscularly, and subcutaneous injections are not allowed.
- COVID-19 vaccination is indicated also for frail patients with HF unless other contraindications exist.
- Vaccination against COVID-19 patients with HF is needed as early as possible, preferably in an optimal clinical state and optimized treatment of HF and other comorbidities. However, treatment optimization should not delay COVID-19 vaccination.
- Iron repletion prior to COVID-19 vaccination has the potential to optimize vaccine benefits in iron-deficient patients with HF.
- Precautionary measures, including the use of facemask, hand disinfection and social distancing, are still needed for patients with HF even after COVID-19 vaccination. Patients with HF, their close contacts (including family members and care providers) and healthcare workers still need to follow locally recommended measures designed to prevent the SARS-CoV-2 spread.
- A structured clinical follow-up of vaccinated patients with HF is preferred, but an assessment of anti-SARS-CoV-2 antibodies is not required.
- Knowledge on strategies preventing SARS-CoV-2 infection (including the COVID-19 vaccination) forms an important part of comprehensive educational programmes delivered to patients with HF.

CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure.

comorbidities^{4,5} (which are already considered as independent risk factors of COVID-19 complications—see above).^{11–13} Moreover, the majority of patients with HF demonstrate the frailty phenotype associated not only with an older average age and numerous comorbidities, but predominantly with worse functional status, markedly impaired exercise capacity, limited mobility and dependency on the others, a presence of obesity or cachexia, impaired functioning of the cardiopulmonary system leading to reduced tissue oxygenation, reduced ability of the body to respond adequately to external insults, such as inflammation and infection.^{13,22} It should be emphasised that frailty itself has been identified to be a strong risk factor for more severe COVID-19.^{12,13,23}

The diagnosis of HF, particularly when present in an elderly subject with COVID-19, is a strong predictor of non-lethal and lethal complications, which include a need for intensive non-invasive and invasive respiratory support, a need for pharmacological and mechanical circulatory support, a longer hospital stay, a longer

intensive care unit stay, a high risk of severe pneumonia and respiratory failure, more common thromboembolic events (including pulmonary embolism), secondary myocardial damage, circulatory decompensation, neurological complications (including stroke), and finally increased risk of both CV and non-CV death.^{1–3,24–26} In-hospital mortality of patients hospitalised with COVID-19 and pre-existing HF has been reported between 49–63% in different study cohorts worldwide.^{1,2,24,26} Moreover, high levels of circulating natriuretic peptides predict a complicated clinical course of infection and higher in-hospital mortality.^{2,25,26}

Patients with HF, particularly those who are highly symptomatic and at an advanced stage and/or those with circulatory decompensation, have an extremely poor prognosis when contracting SARS-CoV-2 infection.^{1,24,27} However, it is also recognised that patients with stable HF who are less symptomatic (New York Heart Association class I–II) can undergo a sudden deterioration in their clinical condition following SARS-CoV-2 infection.²⁷ This was not

helped by the fact that there were challenges associated with the initial diagnosis of SARS-CoV-2 in patients with HF. Chest radiography alone may be poor at differentiating viral lung disease from acute pulmonary oedema, but this may be overcome with the use of computed tomography and lung ultrasound which also allows the better prognostic stratification and treatment.²⁸

The COVID-19 pandemic and the lockdown measures that have followed have led to a global reduction in HF hospitalisation rates associated with an increased mortality and increased in-hospital complications as compared to the period before the pandemic, with the most striking differences noted during the first months after the COVID-19 pandemic had broken out which was observed worldwide.^{29–35} Three UK national databases during the pandemic period showed a substantial decline in admissions for HF, but an increase in deaths from HF in the community and higher 30-day post-discharge mortality.³⁶ Similar findings have been confirmed in other reports.^{33–35} Indeed, during the lockdown, psychological distress, diminished well-being, an increase in unhealthy lifestyle behaviours and an augmentation of HF symptoms were common in patients with HF and at the same time challenged the capacity for comprehensive supportive, and evidence-based care.^{37,38} Limitations in access to care were only partly counterbalanced by use of telehealth.^{37,39,40}

Fear of contracting the virus has led to substantial increases in the time from symptom onset in patients with worsening HF to seeking medical care, leading to a presentation at a more advanced stage. At the beginning there were also concerns by the medical society regarding the mechanism of action of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which were linked with SARS-CoV-2 pathophysiology, given that the ACE2 enzyme is the functional receptor for the viral spike protein. Conflicting evidence exists about the ability of these drugs to increase the enzyme expression.⁴¹ Nevertheless, since there is no clear relationship between SARS-CoV-2 infections and these therapies,^{42–44} international communities have from the beginning recommended against the interruption of these therapies.⁴⁵ The withdrawal of beta-blockers, mineralocorticoid receptor antagonists and ACEIs/ARBs in patients with HF resulted in an increase in in-hospital mortality.¹ The Italian Society of Cardiology was the first to report a 46% reduction in CV hospitalisations during the first phase of the COVID-19 pandemic.²⁹ A single centre study in England reported a 27% decrease in HF hospitalisations during the first months of the COVID-19 pandemic as compared to the immediately preceding period with an almost doubled 30-day mortality³¹ and a large European survey³² reported one third reductions in hospital CV admissions, but greater mortality among patients in the emergency departments. Patients with worsening HF were less likely to be hospitalised, but when they finally were hospitalised, they were in more severe condition, requiring more intensive therapies, greater CV and non-CV complications and higher mortality.^{29–32}

Key message and guidance statement

The diagnosis of HF, particularly when present in an elderly or/and frail subject, is a strong predictor of non-lethal and lethal complications of COVID-19, which include a need for intensive non-invasive and invasive respiratory support, a need for pharmacological and mechanical circulatory support, a longer hospital stay, a longer intensive care unit stay, a high risk of severe pneumonia and respiratory failure, more common thromboembolic events, secondary myocardial damage, circulatory decompensation, neurological complications, and finally increased risk of both CV and non-CV death.

Efficacy and safety of COVID-19 vaccination in patients with heart failure

Recently, several rapidly developed vaccines have been approved in Europe^{46–49} (Table 2). All marketed COVID-19 vaccines are effective and safe, and greatly reduce the risk of symptomatic COVID-19 requiring hospitalization and the risk of death.^{46–49} Safety and high effectiveness of COVID-19 vaccination has also been confirmed in a prospective cohort study of staff working in NHS hospitals in the UK.⁵⁰ Likewise, a mass COVID-19 vaccination programme has markedly reduced the number of COVID-19-related hospitalisations in Scotland.⁵¹ In recent months, novel SARS-CoV-2 strains have been emerging. Epidemiological reports from several countries worldwide report that the vaccinations using approved COVID-19 vaccines have been effective regarding the prevention of hospitalisations and severe COVID-19 cases.

All COVID-19 vaccine trials have recruited cohorts of subjects, including those with CVD and HF, and have confirmed the vaccines to be safe and effective in these groups.^{46–49} Patients with HF have been included in these trials, and there is no evidence suggesting that this group could differ in their benefits and risks due to COVID-19 vaccination. On the other hand, there is a need for prospective and systematic reporting of safety and efficacy of COVID-19 vaccination in individuals with high CV risk (such as patients with HF). There are suggestions that multimorbid and frail individuals (such as many patients with HF) may be to some extent immune compromised and may produce less anti-Spike antibodies. Until now, it has not been prospectively demonstrated in patients with HF.

All available COVID-19 vaccines are administered by intramuscular injection.^{46–49,52} The most common complaints in all patients include pain at the injection site, tiredness, headache, muscle pain, chills, or mild fever. These side effects occur with different timing according to the type of vaccine and are expected to be short-lived, lasting approximately 24–48 h and usually respond to paracetamol and increased fluid intake. Importantly, in patients with HF paracetamol remains the antipyretic drug of choice, and non-steroidal anti-inflammatory agents should be avoided due to their serious side-effects, including the risk of circulatory decompensation. The risk of severe

Table 2 Characteristics of available COVID-19 vaccines

Vaccine code	mRNA-1273	BNT162b2	ChAdOx1/AZD1222	JNJ-78436735/Ad26-CoV2.S	Sputnik V/Gam-Covid-Vac	NVX-CoV2373	BBIBP-CoV	Corona Vac
Company	Moderna	BioNTech/Pfizer	Oxford/AstraZeneca	Johnson & Johnson	Gamaleya (Sputnik V)	Novavax	Sinopharm	SinoVac
Key mechanism	Encapsulated mRNA vaccine (mRNA encoding for the spike protein)	Encapsulated mRNA vaccine (mRNA encoding for the spike protein)	Viral vector vaccine (dsDNA encoding for the spike protein is protected in a safe adenovirus)	Viral vector vaccine (dsDNA encoding for the spike protein is protected in a safe adenovirus)	Viral vector vaccine (dsDNA encoding for the spike protein is protected in a safe adenovirus)	Virus-like particle vaccine (nanoparticles are coated with synthetic spike proteins, adjuvant is added to boost immune response)	Inactivated virus vaccine (SARS-CoV-2 is chemically inactivated with beta-propiolactone, so it cannot replicate, but all the proteins are intact)	Inactivated virus vaccine (SARS-CoV-2 is chemically inactivated with beta-propiolactone, so it cannot replicate, but all the proteins are intact)
Dose volume	0.5 mL	0.3 mL	2	1	0.5 mL	2	2	2
No. of required doses	2	2	2	1	2	2	2	2
Time between 2 doses	28 days apart	21 days apart	12 weeks apart	–	28 days apart	21 days apart	3 weeks	3 weeks apart
Storage requirements	–20°C: 6 months +2–8°C: 30 days	–70°C: 6 months +2–8°C: 5 days	+2–8°C: 6 months	–20°C: 2 years +2–8°C: 3 months	–20°C: 2 years +2–8°C: 3 months	–20°C: 2 years +2–8°C: 3 months	+2–8°C	+2–8°C

allergic reaction (including anaphylactic reactions) is extremely low, which positions these vaccines as very safe preventive measures.⁵³

There have been reports (rare) of thromboembolism, mainly due to the Oxford-AstraZeneca and Johnson & Johnson vaccine [for details please refer to continuously updated European Medicines Agency (EMA) reports]. The pathomechanism remains unclear, but potentially could be linked with immune thrombotic thrombocytopenia. The interpretation of these findings needs to be taken with caution, particularly in the context of extremely low number of cases and not confirmed causal relationship, also taking into account huge global survival benefits due to this vaccine.⁵⁴

Recently, myocarditis (myopericarditis) has been recognized as a rare complication of COVID19 vaccinations (mainly due to Pfizer and Moderna vaccines, for details please refer to continuously updated EMA reports). Based on reported series of cases, myocarditis occurred usually in young adult and adolescent males, in those with a history of allergic diseases, was presented with chest pain, usually 2 to 3 days after a second dose of mRNA vaccination, had high circulating troponins and features of myocarditis seen at cardiac magnetic resonance. In the vast majority of cases, the course of disease was mild and resulted in a complete recovery.^{55,56} Again, the risk of myocarditis due to COVID-19 is extremely low in comparison to enormous survival benefits seen globally.

Key message and guidance statement

All COVID-19 vaccine trials have recruited cohorts of subjects, including those with CVD and HF, and have confirmed the vaccines to be safe and effective in these groups. Rare cases of thromboembolism and myocarditis need to be acknowledged, but also confronted with overwhelming survival benefits due to COVID-19 vaccinations seen globally.

COVID-19 vaccination in patients with heart failure

All patients with HF should receive the COVID-19 vaccine. The clear benefits regarding the prevention of symptomatic SARS-CoV-2 infection and related serious non-fatal and fatal complications outweigh the risk of side-effects, which are generally mild and short-lived, and severe complications, which are exceedingly rare.

Neither HF nor common CV and non-CV comorbidities constitute contraindications for this preventive procedure.

There is no evidence on comparative efficacy or safety of the available COVID-19 vaccines amongst patients with HF.

Optimally, patients with HF should be vaccinated against SARS-CoV-2 when in a stable clinical condition. There are no reported interactions between any approved vaccine and medications administered in patients with HF. It is essential that HF medications are not omitted prior to, or after, the vaccination. Patients should avoid the vaccine during febrile illness.

Key message and guidance statement

COVID-19 vaccination is indicated for all patients with HF unless other contraindications exist.

Special situations in patients with heart failure

Patients with compromised immunocompetency, including those after heart (and other organ) transplantation receiving immunosuppressive therapy

When infected with SARS-CoV-2, patients with heart transplantation can develop aggressive COVID-19, requiring prolonged intubation and respiratory support, often complicated with atypical secondary infections and associated with high in-hospital mortality (in-hospital mortality on average 30%, but amongst those requiring mechanical ventilation may exceed 80%).^{57–59}

The currently approved COVID-19 vaccines do not contain live virus and therefore there is no risk of conferring SARS-CoV-2 infection in patients with compromised immune systems, whether this is inherited, acquired or iatrogenic (immunosuppressive drugs).^{60–62} There are no safety concerns in immunocompromised patients regarding the administration of approved COVID-19 vaccines, although the efficacy of the vaccines remains uncertain in such individuals and may be lower than in the general population.^{63,64}

Immune response to SARS-CoV-2 is a combination of both innate and adaptive immune responses with the involvement of humoral and cellular mechanisms.^{60–62} Immunocompromised individuals are most likely unable to generate a fully protective immune response to COVID-19 vaccines which have been approved for use in the general population, and therefore, protection against COVID-19 may be lower as suggested by antibody studies in immunosuppressed individuals.^{63,64} These patients will have to continue to take extra precautions even after being vaccinated including facemask wearing and social distancing. It is unclear whether they may also require additional doses of COVID-19 vaccine beyond the obligatory scheme applied to the general population.^{63–65} Importantly, there are reports on a weak immune response to two doses of COVID-19 vaccine in recipients of solid-organ transplants.^{65,66} Moreover, severe COVID-19 cases have also been reported in transplant recipients who had received two doses of vaccine.⁶⁷ There is evidence that the third dose of COVID-19 vaccine can significantly enhance a protective immune response and increase the efficacy of vaccination in these patients.⁶⁸ The detailed recommendations for heart transplant recipients regarding the scheme and precautions regarding the COVID-19 vaccination are included in the International Society of Heart and Lung Transplantation document.⁶⁹

The risk–benefit ratio for immunocompromised individuals should be weighed on a case-by-case basis and timing should be personalised according to individual management plan.

Immunocompromised patients with HF (as all patients with HF) are recommended to be vaccinated against influenza and, if needed, COVID-19 vaccine may be co-administered on the same day to prevent a delay.

Key message and guidance statement

COVID-19 vaccination is indicated in all patients with HF with a compromised immune system, including patients following heart transplantation receiving immunosuppressive therapy. They are unlikely to generate a completely protective immune response after COVID-19 vaccination, and therefore need additional personal measures including facemask wearing and social distancing for added protection. The additional dose of vaccine beyond the standard scheme may increase the efficacy of vaccination in these patients.

Patients with heart failure with a recent flu and/or pneumonia vaccination

Both influenza viruses and *Streptococcus pneumoniae* constitute common causes of infections in patients with HF, which may trigger circulatory decompensation, and vaccines have shown their protective effects.^{70–72} Patients with HF should also be vaccinated against influenza and pneumonia in order to reduce the risk of dual infections.⁷² The same day administration, if needed, is advisable to prevent delay as suggested by CDC and UK National Health Service guidance.

Key message and guidance statement

Patients with HF are indicated also to be vaccinated against influenza and pneumonia in order to reduce the risk of dual infections.

Patients with heart failure and a history of anaphylactic reactions

In patients with a documented history of any anaphylactic reactions, the small risk of significant side-effects should be carefully weighed against the expected benefits. The Food and Drug Administration Emergency Use Authorization guidance is to not administer the vaccine to individuals with a known history of a severe allergic reaction (e.g. anaphylaxis) to any component of the COVID-19 vaccine.⁵³ However, it should not be considered as an absolute contraindication for vaccination against COVID-19. The diagnosis of HF (or any CVD) itself does not increase the risk of anaphylactic (or any other allergic) reactions.

The CDC additionally advises individuals with a history of an immediate allergic reaction to a vaccine or injectable or any history of anaphylaxis be observed for 30 min after COVID-19 vaccination.⁵³ As the occurrence of allergic reactions to COVID-19 vaccines is not predictable, all individuals, particularly those with a history of severe allergic reactions, should be monitored for up to 30 min afterwards.

Key message and guidance statement

It is suggested not to administer the vaccine to individuals with a known history of a severe allergic reaction (e.g. anaphylaxis) to any component of the COVID-19 vaccine. However, it should not be considered as an absolute contraindication for vaccination against COVID-19. The diagnosis of HF (or any CVD) itself does not increase the risk of anaphylactic (or any other allergic) reactions.

Patients with heart failure and haemoglobin disorders, thrombocytopaenia and/or platelet function disorders

Patients with haemoglobin disorders (sickle cell disease, thalassaemia with severe iron overload, splenectomy) are amongst patient populations most vulnerable to the complications of the SARS-CoV-2 infection.^{52,73} Therefore, those with one or more underlying comorbidities should receive the COVID-19 vaccine. There is no contraindication for COVID-19 vaccination for splenectomised patients.⁵²

In patients with pre-existing platelet disorders and/or thrombocytopaenia, a reduction of platelet count occurring during COVID-19 can aggravate the bleeding risk in these subjects.⁵² The same effect could be seen due to anticoagulant therapy.

Intramuscular injection required for COVID-19 vaccines currently available in Europe can cause haematomas in patients with platelet defects and/or thrombocytopaenia.⁵² It is commonly accepted that minimally invasive procedures (such as an intramuscular injection with COVID-19 vaccine) are not contraindicated in subjects with platelet counts higher than $30 \times 10^9/L$.^{52,74} It remains an individual decision whether to vaccinate individuals with platelets lower than this threshold when they do not have a clinically significant bleeding tendency and bleeding history. The benefit of COVID-19 vaccination is expected to be greater than the risks of local bleeding.

Key message and guidance statement

Intramuscular injection required for COVID-19 vaccines can cause haematomas in patients with platelet defects, thrombocytopaenia and/or on anticoagulation therapy. The benefit of COVID-19 vaccination is expected to be greater than the risks of local bleeding.

Patients with heart failure who require anticoagulation and/or antiplatelet therapy

Patients taking anticoagulant and/or antiplatelet drugs are at an increased risk of haematoma after an intramuscular COVID-19 vaccination.⁵² It is anticipated that the risk of bruising, swelling and tenderness around the injection site will be slightly increased in these patients. A fine needle should be used for the vaccination,

followed by firm pressure applied to the site without rubbing for a few minutes. The patient should be informed about the risk of haematoma from the injection. All approved COVID-19 vaccines must be applied intramuscularly, and subcutaneous injections are not allowed.^{46–49,52}

Key message and guidance statement

Therapy with anticoagulants and/or antiplatelets in patients with HF is not a contraindication for vaccination against COVID-19. All approved COVID-19 vaccines must be applied intramuscularly, and subcutaneous injections are not allowed.

Patients with heart failure and frailty

Frailty is a common condition in patients with HF.²² Frailty itself has been included as a medical condition at increased risk for complicated (including fatal) COVID-19.^{11–13,23} Moreover, frailty is accompanied by numerous comorbidities, which additionally may complicate the clinical course of COVID-19.²² Importantly, protection of frail populations can be achieved with effective COVID-19 vaccination, as for frail patients a benefit–risk balance is particularly favourable.⁷⁵

Therefore, frailty is not considered as a contraindication to COVID-19 vaccination. On the contrary, the presence of frailty is a strong argument for COVID-19 vaccination in patients with HF.⁷⁵ As such, there needs to be an increased awareness of assessing frailty, independent of age, in this cohort of patients who carry a disproportionately high disease burden and have the most to gain from early vaccination.²² Systems should be in place to facilitate those with limited mobility appropriate and timely access to vaccination, and if unable to attend, alternative local measures should be made available. For example, vaccination could be performed at home for frail individuals, their family members and caregivers. The frail cohorts should be prioritized during the periods of limited vaccine supply.

Key message and guidance statement

COVID-19 vaccination is indicated also for frail patients with HF unless other contraindications exist.

Interventions improving efficacy of COVID-19 vaccination in patients with heart failure

General health condition and optimal treatment of heart failure and comorbidities

The functioning of the immune system is dependent on the overall health status of an individual. Adequate hydration and nutrition, optimized treatment of comorbidities are essential for the efficient functioning of the immune system, particularly in elderly subjects.

Key message and guidance statement

Vaccination against COVID-19 in patients with HF is needed as early as possible, preferably in an optimal clinical state and optimized treatment of HF and other comorbidities. However, treatment optimization should not delay COVID-19 vaccination.

Correction of iron deficiency

Iron deficiency is a common comorbidity in patients with HF, being particularly prevalent in elderly subjects, those with severe HF and numerous comorbidities.^{76–78} Iron is involved in the functioning of the immune system, contributing to both innate and adaptive immune response,^{79–81} both of which contribute to immune reactions during the SARS-CoV-2 infection and during the vaccination exposure to specific SARS-CoV-2 antigens.^{60–62} Experimental and clinical evidence supports an important role of optimal iron status for both normal immunity and effective immunization both in children and elderly people.^{82–87} Iron deficiency impairs the development of adaptive immunity, diminishes effector and memory responses, reduces B-cell proliferation and production of antibodies to specific antigens,^{82–84} and its supplementation may improve the efficacy of vaccination.⁸⁶

Data on the efficacy of COVID-19 vaccine in the context of iron deficiency are still missing. However, it is advisable to correct iron deficiency in all patients with HF before an administration of COVID-19 vaccine.⁵² Correction of iron deficiency in patients with HF should be considered whenever possible in patients receiving COVID-19 vaccination. This should not delay vaccination in this vulnerable group and can be implemented either before or as early as possible after vaccination.

Key message and guidance statement

Iron repletion prior to COVID-19 vaccination has the potential to optimize vaccine benefits in iron-deficient patients with HF.

COVID-19 vaccination and other precautionary behaviours in patients with heart failure (e.g. use of facemask, hand disinfection and social distancing)

The COVID-19 vaccine significantly reduces disease severity in case of infection and dramatically reduces mortality.

Since no vaccine has 100% efficacy for preventing SARS-CoV-2 infection, it is expected that some patients with HF who have been vaccinated against COVID-19 will be infected. Such cases are referred as 'breakthrough' infections, indicating that the virus has been able to break through the defences created by the vaccine.⁴⁸ Patients can get infected after COVID-19 vaccination due to a number of reasons. Elderly people or those with compromised immune systems may not elicit immune response sufficient enough to prevent an infection. Also, more aggressive variants of SARS-CoV-2

can evade the protections brought on by an immunization. Some vaccinated patients may have contact with SARS-CoV-2 from subjects being close to the moment of vaccination or in the 'epidemiological window' when the vaccine is not fully protective.⁸⁸ However, the rate of infection in the vaccinated population is very low (0.13–1.19%), and the rate of positive polymerase chain reaction (PCR) tests significantly decreased in those receiving the second dose of the vaccine. In an US study, the rate of positive PCR tests is higher in the first week after the first dose and then steeply decreased at 14 days after the second dose, suggesting the importance of the fully vaccination programme.⁸⁹

Data regarding the possibility that immunised individuals can still transmit SARS-CoV-2 are still scarce, even though apparently rare may happen, especially in the first weeks after vaccination,⁸⁹ so patients with HF who have been vaccinated against COVID-19 need to remain diligent about face coverings in public places, social distancing and meticulous hand-washing.

Importantly, all measures aiming to prevent the SARS-CoV-2 spread must be taken into consideration by patients, their close contacts (including family members and care providers) and healthcare workers.

Key message and guidance statement

Precautionary measures, including the use of facemask, hand disinfection and social distancing, are still needed for patients with HF even after COVID-19 vaccination.

Patients with HF, their close contacts (including family members and care providers) and healthcare workers still need to follow locally recommended measures designed to prevent the SARS-CoV-2 spread.

Need and modes of monitoring of efficacy of COVID-19 vaccination in patients with heart failure

The assessment of titres of different protective anti-SARS-CoV-2 antibodies is being developed and several tests are currently available, but have not been standardized. They are broadly used for research purposes and have the potential to be applied to clinical practice in the near future in specific settings.^{90–93} There is ongoing extensive research in this area, but with no clear conclusions for clinical practice. Therefore, the assessment of titres of different protective anti-SARS-CoV-2 antibodies cannot be routinely recommended for clinical purposes.

Instead, patients with HF who have been vaccinated against COVID-19 should be followed up clinically in a structured manner, with the careful monitoring of the following events: the occurrence of short-term and long-term side-effects, the occurrence of COVID-19 along with its clinical course and complications, CV and non-CV urgent hospitalisation rates, CV and non-CV mortality.

Key message and guidance statement

A structured clinical follow-up of vaccinated patients with HF is preferred, but an assessment of anti-SARS-CoV-2 antibodies is not required.

Need for increasing awareness and education on COVID-19 vaccination in patients with heart failure

Educational programmes covering information on the aim of COVID-19 vaccinations, benefits and risks, mode of administration and follow-up should be designed and provided to patients with HF, their family members and care providers. This educational campaign should be implemented into the comprehensive programme of interdisciplinary management of patients with HF led by HF nurses and other healthcare professionals (Table 3). The Heart Failure Association has actively guided patients on the informational website 'heart failure matters' to improve their self-care during the pandemic and to vaccinate.⁹⁴

Key message and guidance statement

Knowledge on strategies preventing SARS-CoV-2 infection (including the COVID-19 vaccination) forms an important part of comprehensive educational programmes delivered to patients with HF.

Table 3 Instructions for healthcare providers regarding the management of patients with heart failure during lockdown periods

- Establishment of distant contact with the patient (e.g. phone calls, e-mail messages). Encouragement of the patient to use this communication pathway in case of uncertainty regarding treatment or in case of clinical deterioration.
- Enforcement of education regarding the signs/symptoms of decompensation and other urgent health- and life-threatening conditions. Emphasis on early presentation to healthcare assessment by the patient in case of clinical deterioration.
- Re-assurance about the efficacy and safety of COVID-19 vaccination as the preventive measure against non-lethal and lethal COVID-19 complications.
- Enforcement of education regarding the importance of lifestyle interventions, the optimized life-saving treatment and its up-titration, the role of symptomatic treatment and optimal treatment of comorbidities, considered also as non-specific preventive measures against non-lethal and lethal COVID-19 complications.

Conclusions

The diagnosis of HF, particularly when present in an elderly and/or frail subject, is a strong predictor of non-lethal and lethal complications of COVID-19. All COVID-19 vaccine trials have recruited cohorts of subjects, including those with CVD and HF, and have confirmed the vaccines to be safe and effective in these groups. Rare cases of thromboembolism and myocarditis need to be acknowledged.

COVID-19 vaccination is indicated for all patients with HF unless other contraindications exist, including those who are immunocompromised (e.g. after heart transplantation receiving immunosuppressive therapy) and with frailty syndrome. Therapy with anticoagulants and/or antiplatelets in patients with HF should not be considered as a contraindication for vaccination against COVID-19. Patients with HF are indicated also to be vaccinated against influenza and pneumonia in order to reduce the risk of dual infections. Vaccination against COVID-19 patients with HF is needed as early as possible, preferably in an optimal clinical state and optimized treatment of HF and other comorbidities (including the correction of potential iron deficiency). However, treatment optimization should not delay COVID-19 vaccination.

Knowledge on strategies preventing SARS-CoV-2 infection (including the COVID-19 vaccination) forms an important part of comprehensive educational programmes delivered to patients with HF.

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References

- Rey JR, Caro-Codón J, Rosillo SO, Iniesta ÁM, Castrejón-Castrejón S, Marco-Clement I, Martín-Polo L, Merino-Argos C, Rodríguez-Sotelo L, García-Vecas JM, Martínez-Marín LA, Martínez-Cossiani M, Buño A, Gonzalez-Valle L, Herrero A, López-Sendón JL, Merino JL; CARD-COVID Investigators. Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. *Eur J Heart Fail* 2020;**22**:2205–2215.
- Dalia T, Lahan S, Ranka S, Acharya P, Gautam A, Goyal A, Mastoris I, Sauer A, Shah Z. Impact of congestive heart failure and role of cardiac biomarkers in COVID-19 patients: a systematic review and meta-analysis. *Indian Heart J* 2021;**73**:91–98.
- Pellicori P, Doolub G, Wong CM, Lee KS, Mangion K, Ahmad M, Berry C, Squire I, Lambiase PD, Lyon A, McConnachie A, Taylor RS, Cleland JG. COVID-19 and its cardiovascular effects: a systematic review of prevalence studies. *Cochrane Database Syst Rev* 2021;**3**:CD013879.
- Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen S, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B, O'Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2014;**64**:2281–2293.
- Tripodikiadis F, Giamouzis G, Parissis J, Starling RC, Boudoulas H, Skoularigis J, Butler J, Filippatos G. Reframing the association and significance of co-morbidities in heart failure. *Eur J Heart Fail* 2016;**18**:744–758.
- ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators; Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, Gong MN, Carrier M, Rosenson RS, Reynolds HR, Turgeon AF, Escobedo J, Huang DT, Bradbury CA, Houston BL, Kornblith LZ, Kumar A, Kahn SR, Cushman M, McQuilten Z, Slutsky AS, Kim KS, Gordon AC, Kirwan BA, Brooks MM, Higgins AM, Lewis RJ, Lorenzi E, Berry SM, Berry LR, Aday AW, Al-Beidh F, Annane D, Arabi YM, Aryal D, Baumann Kreuziger L, Beane A, Bhimani Z, Bihari S, Billett HH, Bond L, Bonten M, Brunkhorst F, Buxton M, Buzgau A, Castellucci LA, Chekuri S, Chen JT, Cheng AC, Chkhikvadze T, Coiffard B, Costantini TW, de Brouwer S, Derde LPG, Detry MA, Duggal A, Dzavik V, Effron MB, Estcourt LJ, Everett BM, Fergusson DA, Fitzgerald M, Fowler RA, Galanaud JP, Galen BT, Gandotra S, García-Madróna S, Girard TD, Godoy LC, Goodman AL, Goossens H, Green C, Greenstein YY, Gross PL, Hamburg NM, Haniffa R, Hanna G, Hanna N, Hegde SM, Hendrickson CM, Hite RD, Hindenburg AA, Hope AA, Horowitz JM, Horvat CM, Hudock K, Hunt BJ, Husain M, Hyzy RC, Iyer VN, Jacobson JR, Jayakumar D, Keller NM, Khan A, Kim Y, Kindzelski AL, King AJ, Knudson MM, Kornblith AE, Krishnan V, Kutcher ME, Laffan MA, Lamontagne F, Le Gal G, Leeper CM, Leifer ES, Lim G, Lima FG, Linstrum K, Litton E, Lopez-Sendon J, Lopez-Sendon Moreno JL, Lother SA, Malhotra S, Marcos M, Saud Marinez A, Marshall JC, Marten N, Matthay MA, McAuley DF, McDonald EG, McGlothlin A, McGuinness SP, Middeldorp S, Montgomery SK, Moore SC, Morillo Guerrero R, Mouncey PR, Murthy S, Nair GB, Nair R, Nichol AD, Nunez-Garcia B, Pandey A, Park PK, Parke RL, Parker JC, Parnia S, Paul JD, Pérez González YS, Pompilio M, Prekker ME, Quigley JG, Rost NS, Rowan K, Santos FO, Santos M, Olombrada Santos M, Satterwhite L, Saunders CT, Schutgens REG, Seymour CW, Siegal DM, Silva DG Jr, Shankar-Hari M, Sheehan JP, Singhal AB, Solvason D, Stanworth SJ, Tritschler T, Turner AM, van Bentum-Puijk W, van de Veerdonk FL, van Diepen S, Vazquez-Grande G, Wahid L, Wareham V, Wells BJ, Widmer RJ, Wilson JG, Yuriditsky E, Zampieri FG, Angus DC, McArthur CJ, Webb SA, Farkouh ME, Hochman JS, Zarychanski R. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med* 2021;**385**:790–802.
- Kamel AM, Sobhy M, Magdy N, Sabry N, Farid S. Anticoagulation outcomes in hospitalized Covid-19 patients: a systematic review and meta-analysis of case-control and cohort studies. *Rev Med Virol* 2021;**31**:e2180.
- Li H, Yan B, Gao R, Ren J, Yang J. Effectiveness of corticosteroids to treat severe COVID-19: a systematic review and meta-analysis of prospective studies. *Int Immunopharmacol* 2021;**100**:108121.
- Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect Dis* 2021;**21**:e26–e35.
- Majid S, Khan MS, Rashid S, Niyaz A, Farooq R, Bhat SA, Wani HA, Qureshi W. COVID-19: diagnostics, therapeutic advances, and vaccine development. *Curr Clin Microbiol Rep* 2021 Feb 15. <https://doi.org/10.1007/s40588-021-00157-9> [Epub ahead of print].
- Centers for Disease Control and Prevention. People with Certain Medical Conditions. Published online on 23 December 2020. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html> (11 March 2021).
- Izurieta HS, Graham DJ, Jiao Y, Hu M, Lu Y, Wu Y, Chillarige Y, Werneck M, Menis M, Pratt D, Kelman J, Forshee R. Natural history of coronavirus disease 2019: risk factors for hospitalizations and deaths among >26 million US Medicare beneficiaries. *J Infect Dis* 2021;**223**:945–956.
- Centers for Disease Control and Prevention. Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. Published online on 22 November 2020. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html> (22 March 2021).
- Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol* 2020;**5**: 831–840.
- Kipshidze N, Dangas G, White CJ, Kipshidze N, Siddiqui F, Lattimer CR, Carter CA, Fareed J. Viral coagulopathy in patients with COVID-19: treatment and care. *Clin Appl Thromb Hemost* 2020;**26**:1076029620936776.
- Canzano P, Brambilla M, Porro B, Cosentino N, Tortorici E, Vicini S, Poggio P, Cascella A, Pengo MF, Veglia F, Fiorelli S, Bonomi A, Cavalca V, Trabattini D, Andreini D, Omodeo Salé E, Parati G, Tremoli E, Camera M. Platelet and endothelial activation as potential mechanisms behind the thrombotic complications of COVID-19 patients. *JACC Basic Transl Sci* 2021;**6**:202–218.
- England JT, Abdulla A, Biggs CM, Lee AYY, Hay KA, Hoiland RL, Wellington CL, Sekhon M, Jamal S, Shojania K, Chen LYC. Weathering the COVID-19 storm: lessons from hematologic cytokine syndromes. *Blood Rev* 2021;**45**:100707.
- Chang WT, Toh HS, Liao CT, Yu WL. Cardiac involvement of COVID-19: a comprehensive review. *Am J Med Sci* 2021;**361**:14–22.
- Garg A, Seeliger B, Derda AA, Xiao K, Gietz A, Scherf K, Sonnenschein K, Pink I, Hoepfer MM, Welte T, Bauersachs J, David S, Bär C, Thum T. Circulating cardiovascular microRNAs in critically ill COVID-19 patients. *Eur J Heart Fail* 2021;**23**:468–475.
- Mehra MR, Ruschitzka F. COVID-19 illness and heart failure: a missing link? *JACC Heart Fail* 2020;**8**:512–514.
- Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis* 2016;**49**:129–133.
- Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, Lainscak M, Jaarsma T, Ponikowski P, Rosano GMC, Seferovic P, Coats AJ. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail* 2019;**21**:1299–1305.
- Knights H, Mayor N, Millar K, Cox M, Bunova E, Hughes M, Baker J, Mathew S, Russell-Jones D, Kotwica A. Characteristics and outcomes of patients with COVID-19 at a district general hospital in Surrey, UK. *Clin Med (Lond)* 2020;**20**:e148–e153.

24. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbriatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in northern Italy. *Eur Heart J* 2020;**41**: 1821–1829.
25. Gao L, Jiang D, Wen XS, Cheng XC, Sun M, He B, You LN, Lei P, Tan XW, Qin S, Cai GQ, Zhang DY. Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res* 2020;**21**:83.
26. Belarte-Tornero LC, Valdivielso-Moré S, Vicente Elcano M, Solé-González E, Ruiz-Bustillo S, Calvo-Fernández A, Subinara I, Cabero P, Soler C, Cubero-Gallego H, Vaquerizo B, Farré N. Prognostic implications of chronic heart failure and utility of NT-proBNP levels in heart failure patients with SARS-CoV-2 infection. *J Clin Med* 2021;**10**:323.
27. Driggin E, Maddox TM, Ferdinand KC, Kirkpatrick JN, Ky B, Morris AA, Mullen JB, Parikh SA, Philbin DM Jr, Vaduganathan M. ACC health policy statement on cardiovascular disease considerations for COVID-19 vaccine prioritization: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2021;**77**:1938–1948.
28. Zhu Z, Tang J, Chai X, Fang Z, Liu Q, Hu X, Xu D, He J, Tang L, Tai S, Wu Y, Zhou S. How to differentiate COVID-19 pneumonia from heart failure with computed tomography at initial medical contact during epidemic period. *medRxiv* March 6, 2020. <https://doi.org/10.1101/2020.03.04.20031047>.
29. Spaccarotella CAM, De Rosa S, Indolfi C. The effects of COVID-19 on general cardiology in Italy. *Eur Heart J* 2020;**41**:4298–4300.
30. Cox ZL, Lai P, Lindenfeld J. Decreases in acute heart failure hospitalizations during COVID-19. *Eur J Heart Fail* 2020;**22**:1045–1046.
31. Doolub G, Wong C, Hewitson L, Mohamed A, Todd F, Gogola L, Skyrme-Jones A, Aziz S, Sammut E, Dastidar A. Impact of COVID-19 on inpatient referral of acute heart failure: a single-centre experience from the South-West of the UK. *ESC Heart Fail* 2021;**8**:1691–1695.
32. Sokolski M, Gajewski P, Zymliński R, Biegus J, Berg JMT, Bor W, Braunschweig F, Caldeira D, Cuculi F, D'Elia E, Edes IF, Garus M, Greenwood JP, Halfwerk FR, Hindricks G, Knuuti J, Kristensen SD, Landmesser U, Lund LH, Lyon A, Mebazaa A, Merkely B, Nawrocka-Milward S, Pinto FJ, Ruschitzka F, Semedo E, Senni M, Sepelhi Shamloo A, Sorensen J, Stengaard C, Thiele H, Toggweiler S, Tukiendorf A, Verhorst P, Wright DJ, Zamorano P, Zuber M, Narula J, Bax JJ, Ponikowski P. Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments across Europe. *Am J Med* 2021;**134**:482–489.
33. König S, Hohenstein S, Meier-Hellmann A, Kühlen R, Hindricks G, Bollmann A; Helios Hospitals, Germany. In-hospital care in acute heart failure during the COVID-19 pandemic: insights from the German-wide Helios hospital network. *Eur J Heart Fail* 2020;**22**:2190–2201.
34. Cannata A, Bromage DI, Rind IA, Gregorio C, Bannister C, Albarjas M, Piper S, Shah AM, McDonagh TA. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail* 2020;**22**:2219–2224.
35. Bromage DI, Cannata A, Rind IA, Gregorio C, Piper S, Shah AM, McDonagh TA. 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**:978–984.
36. Shoaib A, Van Spall HGC, Wu J, Cleland JGF, McDonagh TA, Rashid M, Mohamed MO, Ahmed FZ, Deanfield J, de Belder M, Gale CP, Mamas MA. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:378–387.
37. Chagué F, Boulon M, Eicher JC, Bichat F, Saint Jalmes M, Cransac-Miet A, Soudry-Faure A, Danchin N, Cottin Y, Zeller M. Impact of lockdown on patients with congestive heart failure during the coronavirus disease 2019 pandemic. *ESC Heart Fail* 2020;**7**:4420–4423.
38. Hill L, Lambrinou E, Moser DK, Beattie JM. The COVID-19 pandemic: challenges in providing supportive care to those with cardiovascular disease in a time of plague. *Curr Opin Support Palliat Care* 2021;**15**:147–153.
39. Taskforce of the Hellenic Heart Failure Clinics Network. Distribution, infrastructure, and expertise of heart failure and cardio-oncology clinics in a developing network: temporal evolution and challenges during the coronavirus disease 2019 pandemic. *ESC Heart Fail* 2020;**7**:3408–3413.
40. Farmakis D, Mehra MR, Parissis J, Filippatos G. Heart failure in the course of a pandemic. *Eur J Heart Fail* 2020;**22**:1755–1758.
41. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhardt D, Kumaraiah D, Rabbani L, Schwartz A, Uriel N. COVID-19 and cardiovascular disease. *Circulation* 2020;**141**:1648–1655.
42. Savarese G, Benson L, Sundström J, Lund LH. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. *Eur J Heart Fail* 2021;**23**:476–485.
43. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Dos Santos TM, Mazza L, Feldman A, D'Andréa Saba Arruda G, de Albuquerque DC, Camiletti AS, de Sousa AS, de Paula TC, Giusti KGD, Domiciano RAM, Noya-Rabelo MM, Hamilton AM, Loures VA, Dionísio RM, Furquim TAB, De Luca FA, Dos Santos Sousa IB, Bandeira BS, Zukowski CN, de Oliveira RGG, Ribeiro NB, de Moraes JL, Petriz JLF, Pimentel AM, Miranda JS, de Jesus Abufaiad BE, Gibson CM, Granger CB, Alexander JH, de Souza OF; BRACE CORONA Investigators. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA* 2021;**325**:254–264.
44. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, Rodriguez-Mori JE, Renna N, Chang TI, Corrales-Medina V, Andrade-Villanueva JF, Barbagelata A, Cristodulo-Cortez R, Diaz-Cucho OA, Spaak J, Alfonso CE, Valdivia-Vega R, Villavicencio-Carranza M, Ayala-García RJ, Castro-Callirgos CA, González-Hernández LA, Bernal-Salas EF, Coacalla-Guerra JC, Salinas-Herrera CD, Nicolosi L, Basconcel M, Byrd JB, Sharkoski T, Bendezu-Huasquishe LE, Chittams J, Edmonston DL, Vasquez CR, Chirinos JA. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med* 2021;**9**:275–284.
45. European Society of Cardiology. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. 13 March 2020. [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang) (4 October 2021).
46. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, Voysey M, Aley PK, Angus B, Babbage G, Belij-Rammerstorfer S, Berry L, Bibi S, Bittaye M, Cathie K, Chappell H, Charlton S, Cicconi P, Clutterbuck EA, Colin-Jones R, Dold C, Emary KRW, Fedosyuk S, Fuskova M, Gbesemete D, Green C, Hallis B, Hou MM, Jenkin D, Joe CCD, Kelly EJ, Kerridge S, Lawrie AM, Lelliott A, Lwin MN, Makinson R, Marchevsky NG, Mujadidi Y, Munro APS, Pacurar M, Plested E, Rand J, Rawlinson T, Rhead S, Robinson H, Ritchie AJ, Ross-Russell AL, Saich S, Singh N, Smith CC, Snape MD, Song R, Tarrant R, Themistocleous Y, Thomas KM, Villafana TL, Warren SC, Watson MEE, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Faust SN, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2021;**396**:1979–1993.
47. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, Bibi S, Briner C, Cicconi P, Collins AM, Colin-Jones R, Cutland CL, Darton TC, Dheda K, Duncan CJ, Emary KRW, Ewer KJ, Fairlie L, Faust SN, Feng S, Ferreira DM, Finn A, Goodman AL, Green CM, Green CA, Heath PT, Hill C, Hill H, Hirsch I, Hodgson SHC, Izu A, Jackson S, Jenkin D, Joe CCD, Kerridge S, Koen A, Kwatra G, Lazarus R, Lawrie AM, Lelliott A, Libri V, Lillie PJ, Mallory R, Mendes AVA, Milan EP, Minassian AM, McGregor A, Morrison H, Mujadidi YF, Nana A, O'Reilly PJ, Padayachee SD, Pittella A, Plested E, Pollock KM, Ramasamy MN, Rhead S, Schwarzbold AV, Singh N, Smith A, Song R, Snape MD, Sprinz E, Sutherland RK, Tarrant R, Thomson EC, Tröör M, Toshner M, Turner DPJ, Vekemans J, Villafana TL, Watson MEE, Williams CJ, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;**397**:99–111.
48. Polack FP, Thomas SJ, Kitchen N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;**383**: 2603–2615.
49. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;**384**:403–416.
50. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, Wellington E, Stowe J, Gillson N, Atti A, Islam J, Karagiannis I, Munro K, Khawam J, Chand MA, Brown

- CS, Ramsay M, Lopez-Bernal J, Hopkins S; SIREN Study Group. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet* 2021;**397**:1725–1735.
51. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, Bedston S, Beggs J, Bradley D, Chuter A, de Lusignan S, Docherty AB, Ford D, Hobbs FR, Joy M, Katikireddi SV, Marple J, McCowan C, McGagh D, McMenamin J, Moore E, Murray JL, Pan J, Ritchie L, Shah SA, Stock S, Torabi F, Tsang RS, Wood R, Woolhouse M, Robertson C, Sheikh A. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021;**397**:1646–1657.
 52. European Hematology Association. Expert opinions for COVID-19 vaccination in patients with non-malignant hematologic diseases. Published online on 12 February 2021. <https://ehaweb.org/covid-19/eha-statement-on-covid-19-vaccines/recommendations-for-covid-19-vaccination-in-patients-with-non-malignant-hematologic-diseases> (16 May 2021).
 53. Banerji A, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, Wolfson AR, Williams P, Khan DA, Phillips E, Blumenthal KG. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract* 2021;**9**:1423–1437.
 54. Perera R, Fletcher J. Thromboembolism and the Oxford-AstraZeneca vaccine. *BMJ* 2021;**373**:n1159.
 55. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation* 2021;**144**:471–484.
 56. Kim HW, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, Darty SN, Parker MA, Kim RJ. Patients with acute myocarditis following mRNA COVID-19 vaccination. *JAMA Cardiol* 2021;**6**:1196–1201.
 57. Bottio T, Bagozzi L, Fiocco A, Nadali M, Caraffa R, Bifulco O, Ponzone M, Lombardi CM, Metra M, Russo CF, Frigerio M, Masciocco G, Potena L, Loforte A, Pacini D, Faggian G, Onorati F, Sponga S, Livi U, Iacovoni A, Terzi A, Senni M, Rinaldi M, Boffini M, Marro M, Jorgji V, Carrozzini M, Gerosa G. COVID-19 in heart transplant recipients: a multicenter analysis of the northern Italian outbreak. *JACC Heart Fail* 2021;**9**:52–61.
 58. Rivinius R, Kaya Z, Schramm R, Boeken U, Provaznik Z, Heim C, Knosalla C, Schoenrath F, Rieth A, Berchtold-Herz M, Barten MJ, Rauschnig D, Mücke VT, Heyl S, Pistulli R, Grininger C, Hagl C, Gummert JF, Warnecke G, Schulze PC, Katus HA, Kreusser MM, Raake PW. COVID-19 among heart transplant recipients in Germany: a multicenter survey. *Clin Res Cardiol* 2020;**109**:1531–1539.
 59. Latif F, Farr MA, Clerkin KJ, Habal MV, Takeda K, Naka Y, Restaino S, Sayer G, Uriel N. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. *JAMA Cardiol* 2020;**5**:1165–1169.
 60. Jeyanthan M, Afkhami S, Smail F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. *Nat Rev Immunol* 2020;**20**:615–632.
 61. Chowdhury MA, Hossain N, Kashem MA, Shahid MA, Alam A. Immune response in COVID-19: a review. *J Infect Public Health* 2020;**13**:1619–1629.
 62. Tregoning JS, Brown ES, Cheeseman HM, Flight KE, Higham SL, Lemm NM, Pierce BF, Stirling DC, Wang Z, Pollock KM. Vaccines for COVID-19. *Clin Exp Immunol* 2020;**202**:162–192.
 63. Aslam S, Goldstein DR, Vos R, Gelman AE, Kittleson MM, Wolfe C, Danziger-Isakov L. COVID-19 vaccination in our transplant recipients: the time is now. *J Heart Lung Transplant* 2021;**40**:169–171.
 64. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, Pertzov B, Eliakim-Raz N, Abed G, Abuhazira M, Barac YD, Mats I, Kramer MR, Aravot D, Kornowski R, Ben-Gal T. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients – a prospective cohort study. *Eur J Heart Fail* 2021;**23**:1555–1559.
 65. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA* 2021;**325**:2204–2206.
 66. Marion O, Del Bello A, Abravanel F, Couat C, Faguer S, Esposito L, Hebrat AL, Izopet J, Kamar N. Safety and immunogenicity of anti-SARS-CoV-2 messenger RNA vaccines in recipients of solid organ transplants. *Ann Intern Med* 2021;**174**:1336–1338.
 67. Wade HM, Gonwa TA, Leoni JC, Shah SZ, Aslam N, Speicher LL. COVID-19 infection in solid organ transplant recipients after SARS-CoV-2 vaccination. *Am J Transplant* 2021;**21**:3496–3499.
 68. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med* 2021;**385**:661–662.
 69. International Society of Heart and Lung Transplantation. SARS-CoV-2 Vaccination in Heart and Lung Transplantation, MCS and PH. Recommendations from the ISHLT COVID-19 Task Force. May 21, 2021. https://ishlt.org/ishlt/media/documents/COVID19_Vaccine-Recommendations_5-21-2021.pdf (4 October 2021).
 70. Behrouzi B, Araujo Campoverde MV, Liang K, Talbot HK, Bogoch II, McGeer A, Fröbert O, Loeb M, Vardeny O, Solomon SD, Udell JA. Influenza vaccination to reduce cardiovascular morbidity and mortality in patients with COVID-19: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**76**:1777–1794.
 71. Rodrigues BS, David C, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Influenza vaccination in patients with heart failure: a systematic review and meta-analysis of observational studies. *Heart* 2020;**106**:350–357.
 72. Gotsman I, Shuvy M, Tahiroglu I, Zwas DR, Keren A. Influenza vaccination and outcome in heart failure. *Am J Cardiol* 2020;**128**:134–139.
 73. Thalassaemia International Federation Position Statement: COVID-19 Vaccines & Haemoglobin Disorders. 30 December 2020. https://thalassaemia.org.cy/wp-content/uploads/2020/12/TIF-Position-Statement_COVID-19-Vaccines_201230.pdf (4 October 2021).
 74. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol* 2003;**120**:574–596.
 75. Centers for Disease Control and Prevention. Benefits of getting a COVID-19 vaccine. Published online on 5 January 2021. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/vaccine-benefits.html> (19 March 2021).
 76. Rocha BML, Cunha GJL, Menezes Falcão LF. The burden of iron deficiency in heart failure: therapeutic approach. *J Am Coll Cardiol* 2018;**71**:782–793.
 77. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013;**165**:575–582.e3.
 78. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, von Haehling S, Macdougall IC, Weiss G, McMurray JJ, Anker SD, Gheorghiade M, Ponikowski P. Iron status in patients with chronic heart failure. *Eur Heart J* 2013;**34**:827–834.
 79. Nairz M, Weiss G. Iron in infection and immunity. *Mol Aspects Med* 2020;**75**:100864.
 80. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients* 2020;**12**:236.
 81. Cherayil BJ. Iron and immunity: immunological consequences of iron deficiency and overload. *Arch Immunol Ther Exp (Warsz)* 2010;**58**:407–415.
 82. Frost JN, Tan TK, Abbas M, Wideman SK, Bonadonna M, Stoffel NU, Wray K, Kronsteiner B, Smits G, Campagna DR, Duarte TL, Lopes JM, Shah A, Armitage AE, Arezes J, Lim PJ, Preston AE, Ahern D, Teh M, Naylor C, Salio M, Gileadi U, Andrews SC, Dunachie SJ, Zimmermann MB, van der Klis FRM, Cerundolo V, Bannard O, Draper SJ, Townsend ARM, Galy B, Fleming MD, Lewis MC, Drakesmith H. Hepcidin-mediated hypoferrremia disrupts immune responses to vaccination and infection. *Med (NY)* 2021;**2**:164–179.e12.
 83. Jiang Y, Li C, Wu Q, An P, Huang L, Wang J, Chen C, Chen X, Zhang F, Ma L, Liu S, He H, Xie S, Sun Y, Liu H, Zhan Y, Tao Y, Liu Z, Sun X, Hu Y, Wang Q, Ye D, Zhang J, Zou S, Wang Y, Wei G, Liu Y, Shi Y, Eugene Chin Y, Hao Y, Wang F, Zhang X. Iron-dependent histone 3 lysine 9 demethylation controls B cell proliferation and humoral immune responses. *Nat Commun* 2019;**10**:2935.
 84. Bundi CK, Nalwoga A, Lubyayi L, Muriuki JM, Mogire RM, Opi H, Mentzer AJ, Mugenyi CK, Mwacharo J, Webb EL, Bejon P, Williams TN, Gikunju JK, Beeson JG, Elliott AM, Ndungu FM, Atkinson SH. Iron deficiency is associated with reduced levels of plasmodium falciparum-specific antibodies in African children. *Clin Infect Dis* 2020;**73**:43–49.
 85. MacDougall LG, Jacobs MR. The immune response in iron-deficient children. Isohaemagglutinin titres and antibody response to immunization. *S Afr Med J* 1978;**53**:405–407.
 86. Stoffel NU, Uyoga MA, Mutuku FM, Frost JN, Mwasi E, Paganini D, van der Klis FRM, Malhotra IJ, LaBeaud AD, Ricci C, Karanja S, Drakesmith H, King CH, Zimmermann MB. Iron deficiency anemia at time of vaccination predicts decreased vaccine response and iron supplementation at time of vaccination increases humoral vaccine response: a birth cohort study and a randomized trial follow-up study in Kenyan infants. *Front Immunol* 2020;**11**:1313.
 87. Fülöp T Jr, Wagner JR, Khalil A, Weber J, Trotter L, Payette H. Relationship between the response to influenza vaccination and the nutritional status in institutionalized elderly subjects. *J Gerontol A Biol Sci Med Sci* 1999;**54**:M59–M64.
 88. Tang L, Hijano DR, Gaur AH, Geiger TL, Neufeld EJ, Hoffman JM, Hayden RT. Asymptomatic and symptomatic SARS-CoV-2 infections after BNT162b2 vaccination in a routinely screened workforce. *JAMA* 2021;**325**:2500–2502.

89. Keehner J, Horton LE, Pfeffer MA, Longhurst CA, Schooley RT, Currier JS, Abeles SR, Torriani FJ. SARS-CoV-2 infection after vaccination in health care workers in California. *N Engl J Med* 2021;**384**:1774–1775.
90. Assadiasl S, Fatahi Y, Zavvar M, Nicknam MH. COVID-19: significance of antibodies. *Hum Antibodies* 2020;**28**:287–297.
91. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Mulligan MJ, Bailey R, Swanson KA, Li P, Koury K, Kalina VV, Cooper D, Fontes-Garfias C, Shi PY, Türeci Ö, Tompkins KR, Lyke KE, Raabe V, Dormitzer PR, Jansen KU, Şahin U, Gruber WC. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020;**383**:2439–2450.
92. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, Bellamy D, Bibi S, Bittaye M, Clutterbuck EA, Dold C, Faust SN, Finn A, Flaxman AL, Hallis B, Heath P, Jenkin D, Lazarus R, Makinson R, Minassian AM, Pollock KM, Ramasamy M, Robinson H, Snape M, Tarrant R, Voysey M, Green C, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020;**396**:467–478.
93. Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, Schäfer A, Reidy JX, Trivette A, Nargi RS, Sutton RE, Suryadevara N, Martinez DR, Williamson LE, Chen EC, Jones T, Day S, Myers L, Hassan AO, Kafai NM, Winkler ES, Fox JM, Shrihari S, Mueller BK, Meiler J, Chandrashekar A, Mercado NB, Steinhart JJ, Ren K, Loo YM, Kallewaard NL, McCune BT, Keeler SP, Holtzman MJ, Barouch DH, Gralinski LE, Baric RS, Thackray LB, Diamond MS, Carnahan RH, Crowe JE Jr. Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature* 2020;**584**:443–449.
94. Neubeck L, Hansen T, Jaarsma T, Klompstra L, Gallagher R. Delivering healthcare remotely to cardiovascular patients during COVID-19: a rapid review of the evidence. *Eur J Cardiovasc Nurs* 2020;**19**:486–494.