ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 1806–1818
doi:10.1002/ejhf.2356

POSITION PAPER

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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Received 19 June 2021; revised 8 September 2021; accepted 28 September 2021

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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, thrombocytopaenia 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 mortality[31] and a large European survey[32] 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-CorV	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			0.5 mL			
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 in 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 30×10^9/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.

Conflict of interest: M.A. reports speaker's honoraria from Bayer, AstraZeneca, Novartis, Boehringer Ingelheim. S.D.A. reports receiving fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma. A.B.G. reports grants and/or personal fees from AstraZeneca, Abbott, Vifor, Boehringer Ingelheim, Novartis, Roche Diagnostics and Critical Diagnostics. M.B. declares a support from the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Servier, Medtronic, Vifor, Novartis and Daiichi Sankyo. D.F. reports speaker honoraria and/or consultation fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Leo, Novartis and Orion Pharma. G.F. reports lecture fees and/or committee member of trials/registries sponsored by Boehringer Ingelheim, Bayer, Vifor, Novartis, Medtronic, Servier, Amgen and research grants from European Union. F.G. reports being an advisor for Pfizer, Alnylam, Abbott, Pharmacosmos, Boehringer Ingelheim, Inonis, Bayer, and a speaker for AstraZeneca, Novartis. E.A.J. reports grants and personal fees from Vifor Pharma, personal fees from Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Takeda, Gedeon Richter, outside the submitted work. L.L. reports personal fees from Merck, Bayer, Pharmacosmos, Abbott, Medscape, Myokardia, Sanofi, Lexicon, Radcliffe cardiology, grants and personal fees from Vifor-Fresenius, AstraZeneca, Boehringer Ingelheim, Novartis, grants from Boston Scientific, outside the submitted work. M.M. reports personal fees from Actelion, Amgen,

AstraZeneca, Abbott Vascular, Bayer, Servier, Edwards Therapeutics, Livanova, Vifor pharma, WindTree Therapeutics, as member of Trials' Committees or for speeches at sponsored meetings. A.R. reports grants and personal fees from European Union H2020 program, grants and personal fees from Ministry of Education and Science, Republic of Serbia, personal fees from Pfizer, MSD, Actavis, Hemofarm Stada, GSK, Novartis, Boehringer Ingelheim, AstraZeneca, Arena, Abbott Laboratories, Richter Gedeon, Mylan, Takeda, Janssen, outside the submitted work. G.S. reports grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, Roche, Servier, GENESIS, Cytokinetics, Medtronic, grants and personal fees from AstraZeneca, grants from Novartis, Boston Scientific, PHARMACOSMOS, Merck, outside the submitted work. M.S. reports consultancy for Novartis, Bayer, Abbott, Merck, Vifor, Astrazeneca, Boehringer. T.T. is founder and shareholder of Cardior Pharmaceuticals, and received lecture fees from Boehringer Ingelheim, Takeda, Sanofi-Genzyme, Amicus Therapeutics, outside the submitted work. C.G.T. has received funding from Amgen and personal fees from Vivalyfe, outside of the submitted work, and is listed as an inventor on two heart failure patent. R.R. reports personal fees from Vifor and PHARMACOSMOS. All other authors have nothing to disclose.

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