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POSITION PAPE

Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology

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The coronavirus disease 2019 (COVID-19) pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is causing considerable morbidity and mortality worldwide. Multiple reports have suggested that patients with heart failure (HF) are at a higher risk of severe disease and mortality with COVID-19. Moreover, evaluating and treating HF patients with comorbid COVID-19 represents a

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formidable clinical challenge as symptoms of both conditions may overlap and they may potentiate each other. Limited data exist regarding comprehensive management of HF patients with concomitant COVID-19. Since these issues pose serious new challenges for clinicians worldwide, HF specialists must develop a structured approach to the care of patients with COVID-19 and be included early in the care of these patients. Therefore, the Heart Failure Association of the European Society of Cardiology and the Chinese Heart Failure Association & National Heart Failure Committee conducted web-based meetings to discuss these unique clinical challenges and reach a consensus opinion to help providers worldwide deliver better patient care. The main objective of this position paper is to outline the management of HF patients with concomitant COVID-19 based on the available data and personal experiences of physicians from Asia, Europe and the United States.

Keywords Heart failure • Coronavirus • COVID-19 • Management • SARS-CoV-2 • Diagnosis

Introduction and epidemiology

The coronavirus disease 2019 (COVID-19) pandemic has caused considerable morbidity and mortality worldwide. Epidemiological data from China show that 20% or more of COVID-19 patients have concomitant cardiovascular disease and these patients are more likely to develop life-threatening complications from the infection.[1–10] The risk of complications may be higher in patients with heart failure (HF) not only because they are older and have more comorbidities,[1–8] but also due to the specific characteristics of this syndrome. It has also been suggested that COVID-19 may cause or precipitate myocardial injury and worsen HF due to a cytokine storm-related hyper-inflammation syndrome.[11]

To date, most studies have only reported the prevalence of cardiovascular disease,[2–4,10] without details about the prevalence of HF. The prevalence of HF was 4% in the study by Shi *et al.*,[12] with similar percentages for cardiomyopathy in the study by Guo *et al.*[13] These values are likely higher in the COVID-19 patients in Europe or the United States because of their older age.[9,14–18] In the study by Zhou *et al.*[5] from the Wuhan area in China, including 191 COVID-19 inpatients, 23% of the patients developed HF, and the prevalence of HF in those who died was markedly higher (52%) than that among those who survived (12%). Similar data were reported in other series.[18,19]

Evaluating and treating HF patients with COVID-19 presents a clinical dilemma, as symptoms from both conditions overlap and the two conditions can beget and potentiate each other. To worsen matters, limited data exist regarding the management of HF patients with concomitant COVID-19. These issues pose formidable challenges for clinicians worldwide in delivering optimal care to patients. Therefore, the Heart Failure Association of the European Society of Cardiology and Chinese Heart Failure Association & National Heart Failure Committee conducted web-based meetings to discuss these unique clinical challenges and form a consensus opinion to help health care providers worldwide deliver better patient care. The main objective of this expert position paper is to outline the management of HF patients with concomitant COVID-19 based on the available data and personal experiences of physicians from Asia and Europe.

Prevention of COVID-19 in ambulatory heart failure patients

It is critical that all necessary steps are taken to ensure prevention of COVID-19 in ambulatory HF patients. Patients who do not have any urgent requirements should avoid routine, non-urgent outpatient visits at hospitals or clinics in these challenging times. Instead, physicians should move elective routine care to virtual visits and attempt to contact HF patients using telephone or before their clinic appointments to assess whether they need to see a doctor urgently or require any change in management plan. These calls may also be important to reassure patients and reduce their anxiety during these difficult times. Medical staff should also consider converting office into virtual visits whenever possible, particularly with the help of video links. Heart rate and rhythm and blood pressure may be assessed by patients, if appropriate equipment is available or given to them.

Implementing remote monitoring of vitals through use of simple devices, or data captured by pacemakers/implantable cardioverter-defibrillators should be encouraged.[20] Moreover, if no urgent reason for a visit is found, drugs may be mailed to the patients' home address using dedicated couriers to ensure that HF patients do not run out of their medications. This may be especially important as patients may be reluctant to leave their homes/go to the pharmacy during the COVID-19 pandemic, especially in certain regions. In regions where physical visits are not possible at all due to local situations and regulations, options regarding home visits for urgent blood checks should be communicated to patients, if available. Practice outlined above may be conducted by the HF team located centrally in the hospital. However, primary care physicians may play a central role taking directly care of the telephone calls and tele-monitoring of the patients and then referring to the HF unit in the hospital.

If HF specialists are seeing patients in their clinic, visits should be arranged in such a way so that patient waiting times and patient-to-patient exposure are minimized by spreading visits over the day. This may imply reserving longer times to each visit (e.g.

1 h) and discouraging that the patient be accompanied by any person when coming to the hospital. Such visits may be, however, forbidden, if not urgent, by local authorities when COVID-19 is spreading.

Since health care professionals involved in the care of patients with COVID-19 may also be vectors of coronavirus unknowingly, they should consider undergoing testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to assure the safety of all patients. Health care professionals with symptoms of COVID-19, or a significant exposure risk with contacts, should self-isolate until they test negative for the infection, and they should strictly adhere to local regulations. Importantly, health care professionals and patients should be diligently trained on the appropriate use of wearing personal protective equipment (PPE) during clinic visits to minimize transmission risk. Between each patient visit, rooms and materials should also be properly cleaned to avoid spreading infection to other staff and patients. It is of utmost importance that such preventive measures be undertaken to reduce the spread of the infection.

The facility should perform a triage to assess patients' and caregivers' risk. In the triage, temperature and symptoms or risk factors of COVID-19 infection within 14 days before evaluation (travel or residence history in high-risk regions or countries, history of contact with COVID-19 case) should be assessed. After the triage, suspected patients should be managed in a dedicated ambulatory setting with health care PPE including: disposable surgical cap, medical protection mask (N95/FFP2 or FFP3), infection, work uniform, disposable medical protective uniform, disposable latex gloves and goggles, and the non-suspected COVID-19 patients should be managed in a separate ambulatory setting with PPE including: disposable surgical cap, disposable surgical mask, work uniform, disposable latex gloves and/or disposable isolation clothing. Every patient and caregiver should use a surgical mask.

It is also important to stress that in some areas HF specialists have been assigned to more general roles in acute or medical wards to take care of a huge number of patients with suspected or confirmed COVID-19. Also, many HF nurses and doctors have been infected with COVID-19. All of this has negatively impacted the ability of local HF services in some areas to give the necessary level of medical attention to HF patients. Therefore, it is critical that adequate treatment and resources are provided to HF patients, whilst preserving the safety of both patients and medical personnel. To help achieve this, a risk stratification strategy may be employed to identify HF patients who require closer attention (i.e. those with substantially elevated natriuretic peptide levels or requiring high doses of loop diuretics) compared with patients who are lower risk. Patients at lower risk may not require specific care by HF specialists and may be managed on an ad-hoc basis by a primary care physician or community HF nurse with telephone support from an expert HF service. The criteria to stratify severity of HF patients may be used in this scenario of patients with concomitant COVID-19 as well. Criteria of HF severity are outlined in guidelines and position statements.[21,22]

Evaluation of patients with concomitant heart failure and COVID-19

Symptoms and signs

Symptoms of COVID-19 may be confused with those of HF (*Table 1*). Hence, it is important that COVID-19 be considered as a cause of worsening symptoms in a patient with HF, and all admitted HF patients should be tested for SARS-CoV-2, whenever possible, and above all in times of breakthrough of the infection (*Figure 1*). Admission to specific COVID units should be established according to clinical and laboratory screening results (*Figure 1*). In addition, pneumonia and pulmonary oedema may coexist.[23] Therefore, differentiation of COVID-19 pneumonia from pulmonary congestion based on clinical signs alone is challenging and often impossible. While fever, dry cough and anosmia are more specific for COVID-19, pulmonary rales or crackles are common in patients with COVID-19 pneumonia and may be confused with pulmonary rales caused by lung congestion. It is important to emphasize that fever is not very sensitive of a COVID-19 diagnosis, for example Guan *et al.*[4] found that only 44% of patients presented with fever on admission, although fever developed in 89% of patients during hospitalization. COVID-19 may cause, by itself, profound fatigue and breathlessness. Tachycardia may be present in COVID-19 patients because of fever and hypoxaemia, but is also present in patients with acute HF. Some patients, especially if with COVID-19-related myocarditis or takotsubo syndrome, may present with chest pain suggestive of angina.[24] COVID-19 mandates that this infection is looked for by appropriate diagnostic tests in all patients with HF who show worsening symptoms of breathlessness and/or fatigue and/or who develop clinical signs such as fever, pulmonary crackles, or tachycardia (*Figure 1*). Most patients with severe COVID-19 develop dyspnoea and/or hypoxaemia from 5 to 10 days after onset of infection, which then rapidly progress to acute respiratory distress syndrome (ARDS) and aggravation of patients' pre-existing organ dysfunction towards multiple organ failure.[10,16,25]

Electrocardiography

Among hospitalized COVID-19 patients, 17% have concomitant arrhythmia,[1] and electrocardiographic abnormalities may occur in those with myocardial injury, such as myocardial ischaemia, even in the absence of significant epicardial coronary stenosis due to impaired microcirculatory function, myocarditis, or as side effect of COVID-19 treatment. Approximately 75% of the COVID-19 patients have an abnormal electrocardiogram (ECG) with 41% having ST-T changes and 13% QTc prolongation.[26]

In HF patients, an ECG on admission is always required regardless of a suspected COVID-19 diagnosis. Serial ECGs must be performed in hospitalized patients with increased troponin levels and in those at higher risk receiving drugs with pro-arrhythmic effects, including chloroquine or hydroxychloroquine, either with or without concomitant azithromycin.[27–32] Specific protocols for ECG monitoring have been developed.[27,29]

Table 1 Differential diagnosis between heart failure and COVID-19

	Heart failure	COVID-19
History		
Cardiovascular disease	Likely present	May be. Elderly patients with heart failure history are more likely to develop severe COVID-19.
Contact with COVID-19 subjects	Maybe	Maybe (as many COVID-19 patients are asymptomatic)
Fever	Unlikely	Likely
Symptoms and signs		
Dry cough	Rare	Yes
Anosmia, ageusia	No	Yes
Exertional dyspnoea	Yes	Yes
Fatigue	Yes	Yes
Muscle pain	No	Usually yes
Diarrhoea and other gastrointestinal symptoms	No	May be present
Third heart sound	Yes	No
Rales at lung bases	May be present	May be present
Rales changes after cough	No	May be present
Jugular vein distention/hepatic jugular vein reflux	Yes	No
Lower limb oedema	Yes	No
Leg cramps or pain	May be present	May be present
Diagnostic evaluation		
Chest X-ray	Interstitial thickening and alveolar oedema with preferential distribution to lung bases. Frequent cardiac shadow enlargement	Diffuse interstitial and alveolar lung oedema without a preferential distribution to lung bases in COVID-19 pneumonia. Normal chest X-ray may be seen as well
Lung CT	Predominantly central and basal lung congestion. Basal pleural effusions, larger at the right lung bases. Cardiac enlargement	Bilateral, predominantly peripheral, diffuse ground-glass opacities, reticular patterns, air bronchograms, bilateral consolidation areas, lobular interstitial thickening. Normal heart
Electrocardiogram	Tachycardia, arrhythmia (e.g. atrial fibrillation) aspecific ST-segment changes	Sinus tachycardia, malignant arrhythmia when in critical condition
Laboratory exams		
White blood cell count	No abnormality	Lymphopoenia, decreased lymphocyte/white blood cell count ratio
Natriuretic peptides	Always increased	Increased in some critically ill patients
Troponin	Often increased	Increased in critically ill patients
CK, LDH	Usually normal	Increased in critically ill patients
D-dimer	Normal, unless thrombosis	Increased in critically ill patients

CK, creatinine kinase; LDH, lactate dehydrogenase; CT, computed tomography.

Chest X-ray and computed tomography

Differential diagnosis between HF and COVID-19 is of utmost importance. On chest X-ray, COVID-19 pneumonia causes diffuse interstitial and alveolar lung oedema without a preferential distribution to the lung bases such as in HF alone (*Table 1*). Lung computed tomography (CT) has high sensitivity and specificity to diagnose COVID-19-related pulmonary disease.[1–3,5–7,13,33–35]

Chest X-ray is recommended in all HF patients with suspected or confirmed COVID-19. Chest X-ray may be repeated during hospitalization depending on the clinical course to monitor COVID-19 and HF and to rule out superimposed bacterial infections.

Laboratory exams

Blood cell count

In the early stage of COVID-19, the white blood cell count may be normal or decreased, while lymphocyte count is decreased. Both absolute lymphocyte counts and lymphocyte/white blood cell count ratio are decreased. The severity of COVID-19 is inversely correlated with lymphocyte count with a decreased lymphocyte count associated with increased mortality.[4,5,8,10,36] Given that repletion of lymphocytes has been hypothesized to be key to the recovery from COVID-19,[37] lymphocyte count should be checked daily and closely monitored. A lack of increase or a decrease in lymphocyte count and the lymphocyte/white blood

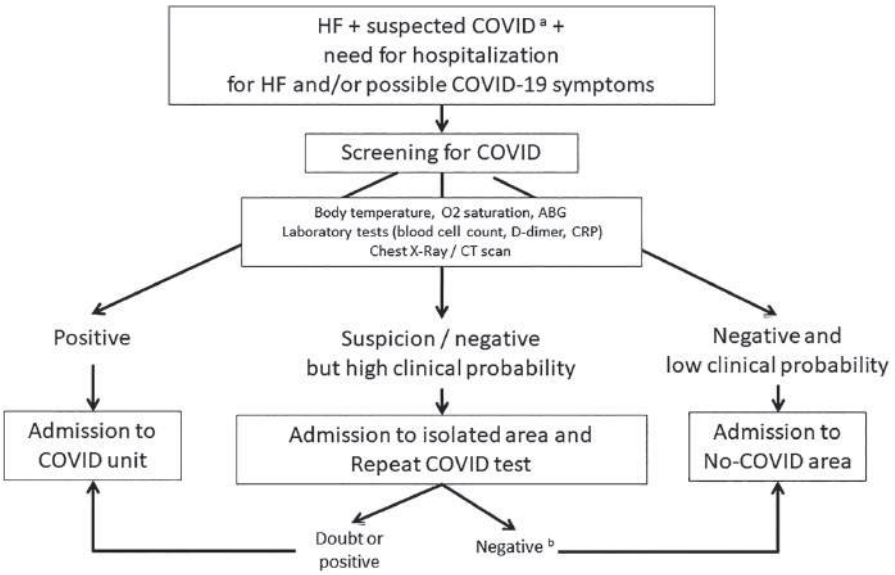

Figure 1 Management of patients with heart failure (HF) and suspected COVID-19 who need hospitalization. In all patients with suspected COVID-19 who need hospitalization for HF and/or possible COVID-19 symptoms, screening by naso-pharyngeal swab and other specific investigations (i.e. body temperature, oxygen saturation, chest X-ray, blood cell count, arterial blood gas) are recommended. This allows identifying patients who need admission to a COVID unit, an isolated area, or a non-COVID unit.

cell ratio is associated with high mortality.[8,36] Lymphocyte count is relevant also for patients on extracorporeal membrane oxygenation (ECMO), as ECMO can significantly decrease the number and function of lymphocytes by itself and this may have an impact on outcomes.[38] Increases in white blood cell count and inflammatory markers during hospitalization may suggest superimposed bacterial infection.

Brain natriuretic peptides

Increased levels of brain natriuretic peptide or N-terminal pro brain natriuretic peptide may be found in COVID-19 patients and may suggest concomitant impairment of cardiac function and poorer clinical course. However, they are not specific for a diagnosis of concomitant HF in COVID-19. In contrast, low values of brain natriuretic peptides have a high negative predictive value and may exclude concomitant cardiac dysfunction.

Troponin

Myocardial injury is observed in more than 20% of hospitalized patients with COVID-19. Patients with elevated troponin levels have higher rates of major complications, including cardiac arrhythmias, acute kidney injury, ARDS, need for mechanical ventilation, and death.[12,13] The prognostic value of increased troponin levels for mortality persisted at multivariable Cox regression analysis, independent of a history of cardiovascular disease.[12] These data are confirmed in more recent studies.[18,19,39,40]

Markers of inflammation and thrombogenicity

Most patients have elevated C-reactive protein, erythrocyte sedimentation rate and other indexes of inflammation and thrombogenicity, such as ferritin, interleukin-6, lactate dehydrogenase, fibrinogen, and D-dimer. An increase in these markers is associated with high mortality.[1,2,4,5,8,12,13] Zhou *et al.*[5] showed elevated D-dimer, interleukin-6, serum ferritin, high-sensitivity troponin, and lactate dehydrogenase, and reduced lymphocyte count in patients not surviving COVID-19 infection. These parameters tended to be higher during the first days of hospitalization and continued to increase in non-survivors while remaining low and stable in surviving patients, consistent with a major role for the inflammatory response in the poor outcomes of COVID-19 patients.

Monitoring of inflammatory markers should be considered in patients with unstable clinical course and worsening respiratory symptoms. In addition, procalcitonin must be measured when bacterial superinfection is suspected.

COVID-19 is associated with a marked prevalence of peripheral venous thrombosis and pulmonary embolism.[41] Inflammatory activation in COVID-19 leads to frequent abnormalities in the coagulation system and these may be estimated by laboratory exams, especially D-dimer plasma levels.[41–43] The increase of Th17 and high cytotoxicity of CD8 T cells in COVID-19 patients suggest that the body might suffer from widespread damage to the immune system, and that some patients may respond to COVID-19 with an exuberant hyper-inflammatory response and cytokine release storm.[23,44,45]

For risk stratification purposes and, namely, to identify patients at increased risk of thromboembolic disease, markers of inflammation and thrombotic risk should be measured at baseline and repeated every 2–3 days if abnormal and whenever clinical deterioration is suspected.

Biomarkers of organ damage

End-organ damage, caused by respiratory and, possibly, circulatory failure, is often the final common pathway of patients not surviving COVID-19. The Sequential Organ Failure Assessment (SOFA) score, including laboratory and clinical parameters, was reported as a predictor of poor prognosis in COVID-19 patients.[5] In addition to the increase in serum troponin, COVID-19 may be associated with an increase in serum transaminases and bilirubin, as markers of liver damage, myoglobin and creatine kinase, as markers of skeletal muscle injury, and serum creatinine, as a marker of renal impairment. In patients hospitalized for COVID-19 and HF, markers of organ damage should be measured at the time of hospitalization and during the clinical course when indicated by worsening patients' clinical conditions or concomitant treatment with possible untoward effects.

Transthoracic echocardiography

COVID-19 patients with a history of HF may often show worsening of cardiac function throughout the course of the disease, likely because of myocardial injury caused by the infection.[11] In addition, some patients with no history of cardiac disease may develop myocarditis with myocardial thickening and oedema and reduced left ventricular systolic function.[24,46] In these cases, strain analysis may also be useful since global longitudinal strain analysis allows the early detection of systolic dysfunction and correlates with cardiac inflammation; however, further investigations are needed.[47,48] Echocardiography must be considered in all patients with HF and suspected or confirmed COVID to assess cardiac function and to detect concomitant causes of HF, either pre-existing (e.g. valve disease) or COVID-19-related (e.g. right ventricular dysfunction secondary to pulmonary embolism).

Lung ultrasound

Lung ultrasound (LUS) may be useful to detect and semi-quantitatively estimate pulmonary congestion and lung infiltrates.[49–51] LUS images tend to be substantially abnormal, and it is difficult to differentiate between HF and COVID-19.[52] Bilateral B-lines are common to both HF and COVID-19. Distinguishing features for COVID-19 may be thickening of pleural line and consolidations. However, detection of these alterations require greater skills than the standard LUS approach. Thus, LUS could be of use just to rule out substantial pulmonary involvement in patients with suspected COVID-19 infection and HF.

Coronary angiography and interventions, computed tomography scan, cardiac magnetic resonance imaging

Patients with COVID-19 and HF may have concomitant coronary artery disease. Indications for coronary angiography and interventional procedures for coronary artery disease are outlined below.

In patients with suspected myocarditis, coronary angiography is recommended to rule out acute coronary syndrome. Coronary CT angiography may be considered to complement thoracic CT scan routinely performed in patients with severe respiratory involvement, if the patient may tolerate the contrast load.

Cardiac magnetic resonance imaging is a method of choice for the diagnosis of acute myocarditis and may show a pattern of diffuse myocardial oedema and thickening.[24] It is also useful for prognostic stratification. Cardiac magnetic resonance imaging may be considered in COVID-19 patients who are suspected to have cardiac involvement (i.e. myocarditis), according to local availability. Endomyocardial biopsy may be limited to cases of severe or refractory HF where histological diagnosis may affect therapeutic decisions.[21,53]

Differential diagnosis

Differences between new-onset HF and COVID-19 clinical presentations are shown in *Table 1*. It is important that symptoms of dyspnoea, cough and fatigue are correctly differentiated between the two conditions. Patients with epidemiological contact, fever and respiratory symptoms, chest X-ray and/or CT imaging characteristics of COVID-19, normal or decreased white blood cell count in the early stage, decreased lymphocyte count, positive to virus nucleic acid or gene sequencing test, should be considered for COVID-19. COVID-19 complicated by myocardial injury or underlying cardiovascular disease can be comprehensively identified through symptoms, signs, biomarkers as well as structural and functional cardiac impairment by echocardiography. It should also be differentiated from other pulmonary diseases, pulmonary embolism, pericardial diseases, severe anaemia and other conditions.

Severity assessment

According to the seventh edition of the consensus protocol for the diagnosis and treatment of COVID-19 published by the Chinese National Health Commission, severe adult COVID-19 patients are those who meet any of the following criteria: tachypnoea with respiratory rate $\geq$30 breaths/min, oxygen saturation (SpO_2) $\leq$93% at rest, arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio $\leq$300 mmHg, or pulmonary imaging showing $\geq$50% progression of lesions within 24–48 h, and they should be managed as critically ill cases. Critically ill patients are those who meet any of the following criteria: respiratory failure in need for mechanical ventilation, shock and other organ failure require intensive care unit (ICU) care.[54–56] The World Health Organization recently stated that COVID-19 patients with severe illness (fever or suspected respiratory infection and respiratory rate >30 breaths/min and/or SpO_2 $\leq$93% in room air and/or severe respiratory distress) require rapid care treatment and admission to designated hospital wards or ICUs.[25] These criteria apply also to the patients with concomitant HF. An algorithm regarding the management of HF patients with suspected COVID-19 who need to be hospitalized due to pneumonia or worsening of HF is reported in *Figure 2*.

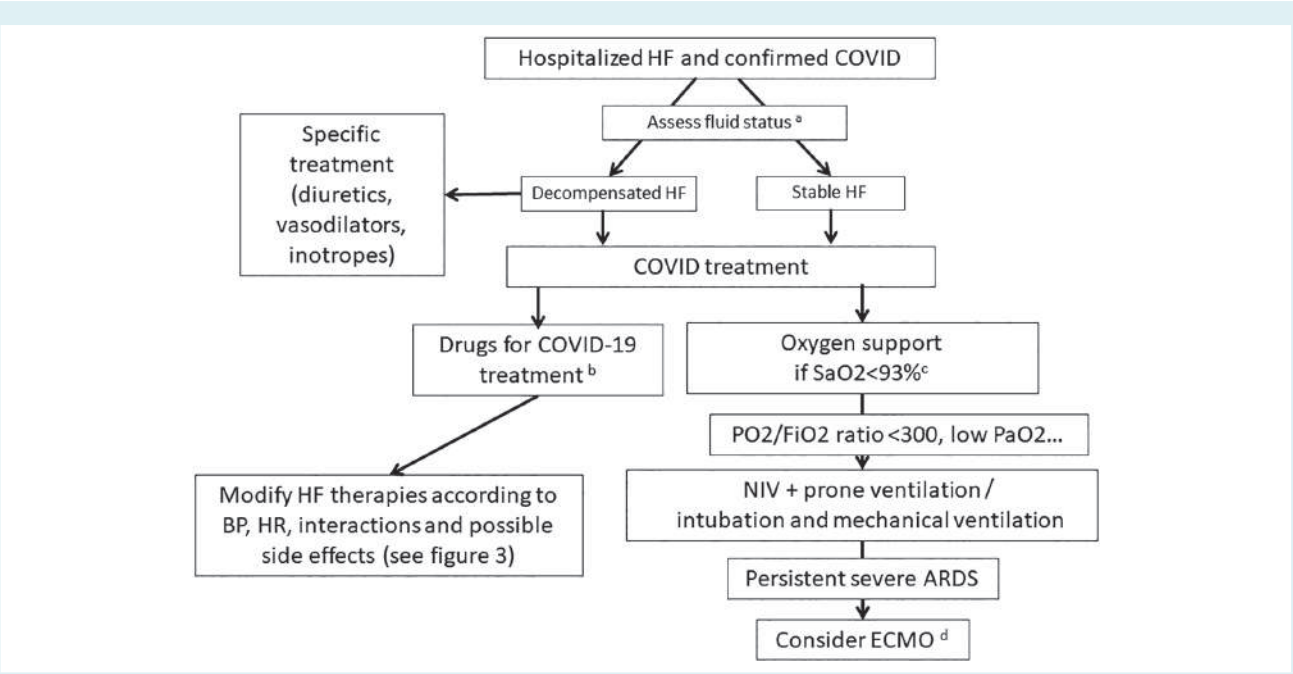

Figure 2 Management of hospitalized patients with heart failure (HF) and confirmed COVID-19. In patients with HF and confirmed COVID-19, assessment of fluid status is recommended in order to evaluate the need for additional pharmacological therapies (i.e. diuretics, inotropes, nitrates). All patients should receive COVID-19 treatment including drugs and oxygen support. HF treatment should be adjusted according to haemodynamics, interactions and side effects. ARDS, acute respiratory distress syndrome; BP, blood pressure; ECMO, extracorporeal membrane oxygenation; HR, heart rate; LV, left ventricular; NIV, non-invasive ventilation; PaO_2, arterial partial pressure of oxygen; PO_2/FiO_2, partial pressure of oxygen to fraction of inspired oxygen ratio; SaO_2, arterial oxygen saturation; V-A, veno-arterial; V-V, veno-venous.

Treatment of heart failure in patients with concomitant COVID-19

Acute and chronic heart failure

Patients with HF are at higher risk of major complications, including severe hypotension, ARDS and death, when they become affected by COVID-19.[5,15] End-of-life treatment should be considered in patients in whom intubation is contraindicated and/or when COVID-19 has worsened HF to such an extent that it has progressed to end-stage HF.[57] These decisions should be discussed in the context of age, severity of HF, number of comorbidities, severity of respiratory failure and the survival probability after intubation and mechanical ventilation.[14,58]

The high frequency of pulmonary complications and the high rate of transition to hypoxic respiratory failure in COVID-19 suggest that HF may predispose to pulmonary complications of COVID-19 possible through the increase in left ventricular filling pressures and lung congestion.[59] COVID-19 is therefore an indication for hospitalization of symptomatic patients with HF. However, shortage of ICUs and, generally, hospital beds may occur during the COVID-19 pandemic and patients in stable clinical conditions may be asked to remain at home.[14] These patients with COVID-19 infection and HF who remain at home should be monitored with extreme care, possibly using tele-monitoring tools, in order to detect any change in their clinical conditions as soon as possible.

Medications should be initiated and continued as per current HF guidelines and their updates .[21,60–62] Special considerations for each of the classes of drugs in HF patients with comorbid COVID-19 are outlined below. For patients who are on mechanical ventilation, oral HF medications should be restarted before ICU discharge. Algorithms for the management of patients with HF and COVID-19 are reported in *Figures 2* and *3*. Fluid status may be assessed using imaging methods such as repeated measures of inferior vena cava diameter and collapsibility by echocardiography.[48] A meaningful decrease from baseline of, for instance, >20%, accompanied by signs of hypoperfusion, must prompt intravenous fluid supplementation and temporary withdrawal or dose reduction of diuretics and angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) or angiotensin receptor–neprilysin inhibitors (ARNI). Invasive haemodynamic monitoring may be considered in selected patients admitted to ICU when signs of active infection have subsided.

Diuretics

Every effort has to be made to restore or maintain euvolaemia. In patients with COVID-19 pneumonia, intravascular volume may be decreased by the shift of fluids from the intravascular into the extravascular space and lung exudate. Increased respiratory rate

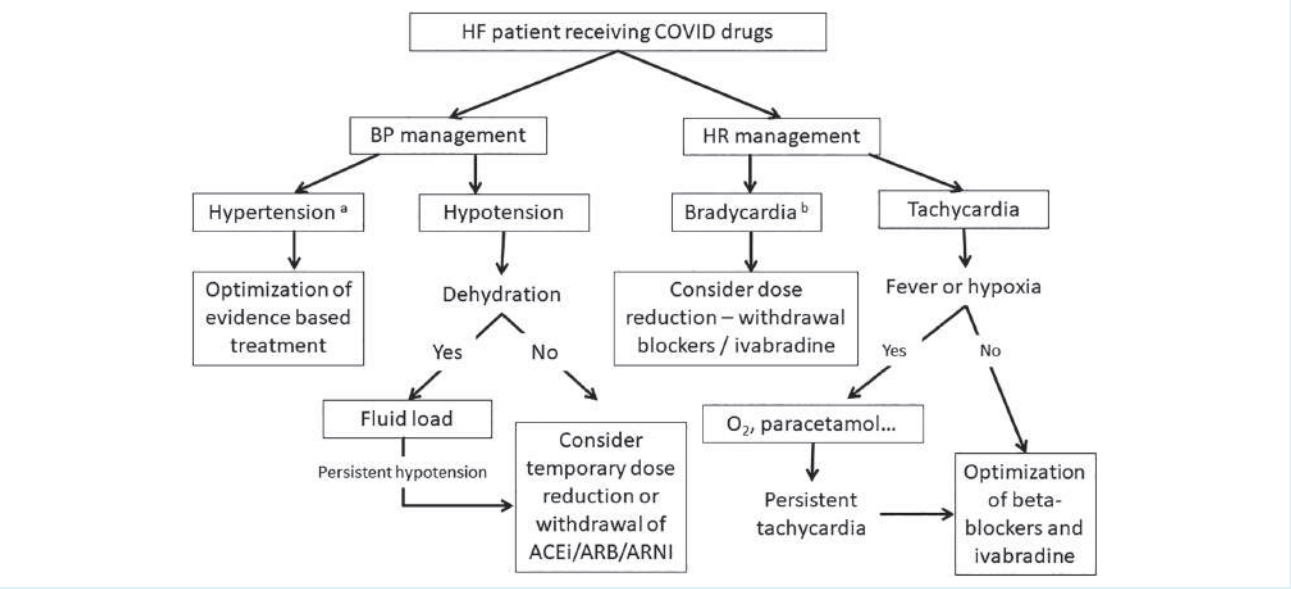

Figure 3 Management of patients with heart failure (HF) receiving COVID-19 drugs. HF therapies need to be adjusted in case of concomitant COVID-19 drugs taking into consideration heart rate (HR) and blood pressure (BP). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor.

may also increase fluid loss while anorexia and fasting may decrease fluid intake. Other causes of hypoperfusion, in addition to low cardiac output, may include other COVID-19 complications such as septic shock and gastrointestinal bleeding.

Diuretic doses must be carefully adjusted considering both the risks of dehydration, hypovolaemia and/or COVID-19-related hypotension and, vice versa, possible COVID-19-induced haemodynamic deterioration and increased lung congestion.[5,16]

Other concomitant treatments often used in COVID-19 may affect fluid balance and renal function. These include non-steroidal anti-inflammatory agents, administered to abrogate constitutional disease symptoms, such as fever and headache, and insulin and other antidiabetic agents, as glycaemia is often elevated in the stress of acute illness in these patients.

Lastly, it should be considered that excessive diuresis may cause difficulties for sputum examination before discharge.

Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers or angiotensin receptor–neprilysin inhibitors

SARS-CoV-2 invades the lung cells through binding of its spike protein S to angiotensin-converting enzyme 2 (ACE2) of lung cells, decreases ACE2 levels and may influence angiotensin tissue levels.[63] It is debated whether ongoing treatment with ACEi/ARBs may affect susceptibility to COVID-19 infection through an up-regulation of ACE2. One experimental study suggested this but there is lack of epidemiological data confirming this hypothesis.[64] In contrast, increased angiotensin II tissue levels may have a role in lung inflammation and damage caused by COVID-19 and ACEi/ARBs might actually be protective at a later stage of COVID-19 infection. In one study, there was no difference in the rate of ACEi/ARB use between survivors and non-survivors among 112 patients with cardiovascular disease complicated with COVID-19.[6] Also, ACEi/ARBs did not increase the mortality of patients with COVID-19 complicated with cardiovascular disease.[10] Large series in patients with hypertension or cardiovascular disease and COVID-19 have now confirmed the lack of relation between ongoing treatment with ACEi/ARB and the severity of the clinical course of the infection.[65–67] Thus, there is no indication to withdraw ongoing ACEi/ARB/ARNI treatment to reduce the likelihood or severity of COVID-19.[68–71] However, patients with COVID-19 may have a decrease in blood pressure related to the infection itself and/or to concomitant antiviral treatment.[16] Therefore, while there is little rationale to stop ACEi in asymptomatic carrier state or very early COVID-19 illness without lung complications, hypotension may require dose reduction if not withdrawal of concomitant ACEi/ARB/ARNI treatment (*Figure 3*).

Beta-blockers

Patients with COVID-19 generally have tachycardia due to infection and fever, and hypoxia. Whether to up-titrate the dose of beta-blockers should be comprehensively determined according to clinical status. Some of the severe patients with COVID-19 have tachyarrhythmias such as atrial fibrillation, which could be treated with beta-receptor blockers. Beta-receptor blockers can also be used appropriately in patients with HF combined with acute coronary syndrome or stress cardiomyopathy; however, they should be used with caution in case of haemodynamic instability. Patients with early COVID-19 infection are sometimes empirically treated with antiviral agents such as lopinavir/ritonavir or darunavir.

These agents may decrease heart rate and cause hypotension and temporary reduction in beta-blocker dose or withdrawal should be considered. At present, although there is no evidence for a preference between any of the four approved beta-blockers for HF (metoprolol, bisoprolol, carvedilol, or nebivolol), experimental studies have suggested that carvedilol might offer additional unique anti-cytokine properties.[72]

Ivabradine

If beta-receptor blockers cannot be continued or up-titrated due to hypotension, hyper-responsiveness of the respiratory tract or haemodynamic instability, ivabradine, alone or in combination with beta-receptor blockers, may be used to control heart rate in patients in sinus rhythm whose increase in heart rate is not due to adaptive mechanisms (fever, hypoxia, anxiety) (*Figure 3*).

Other drugs

Other drugs, including traditional Chinese herb medicine, may be provided according to local guidelines. Any other HF treatment should be initiated or continued according to HF guidelines. However, acute COVID-19 infection may require a delay in the start of a new treatment, including interventional procedures and device implantation, because of its severity.

Treatment of COVID-19 in patients with heart failure

COVID-19 can cause a unique set of clinical problems that need careful management.[15] Only topics which may have an impact on HF treatment are listed in this document.

COVID-19 drugs in patients with heart failure

Multiple agents including natural products are currently being investigated to control COVID-19. Online supplementary *Table SS1* shows a select list of current ongoing trials for treating COVID-19. *Tables 2* and *3* show the commonly used dosages, side effects, mechanisms of action and drug interactions with HF medications of agents routinely administered for COVID-19 in clinical practice. Hydroxychloroquine had favourable effects on viral load reduction in a small non-randomized clinical trial.[73] Recent data did not show its safety. A randomized trial showed that high dosage of hydroxychloroquine (600 mg twice daily) was associated with higher mortality in COVID-19 patients compared to lower dosage (450 mg twice daily).[74] The investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial announced on June 5, 2020 that there is no beneficial effect of hydroxychloroquine in patients hospitalized for COVID-19. A total of 1542 patients were randomized to hydroxychloroquine and compared with 3132 patients on usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; HR 1.11; 95% CI 0.98–1.26.[75] In an observational study involving 1446 consecutive patients hospitalized with COVID-19 in a large medical center in New York City, hydroxychloroquine administration was not associated with either a lower or increased risk of the composite endpoint of intubation or death.[32] In addition, proarrhythmic and cardiotoxic effects of chloroquine or hydroxychloroquine have been shown as well as their interactions with cardiovascular medications, including digoxin, antiarrhythmic drugs and even ivabradine, with the potential to cause HF, QT prolongation and cardiac arrhythmias.[28,30,31,76] Specific strategies and ECG monitoring are needed in patients at risk.[27,29]

Remdesivir, which was originally developed to treat Ebola, has also shown potential efficacy against SARS-CoV-2 in small preclinical studies.[77] QT prolongation, especially with electrolyte abnormalities, needs to be carefully monitored in patients taking remdesivir or chloroquine. Remdesivir is not known, yet, to interact with any of the HF medications. The Adaptive COVID-19 Treatment Trial sponsored by the National Institute of Allergy and Infectious Diseases will give us further insight about the safety and efficacy of remdesivir (ClinicalTrials.gov NCT04280705). Various other antiviral drugs such as darunavir/cobicistat and lopinavir/ritonavir are also commonly used against COVID-19. Lopinavir/ritonavir was not effective in a small randomized trial although it was administered relatively late during the course of the infection (median interval time between symptom onset and randomization of 13 days).[78]

Antiviral drugs have major effects on the pharmacokinetics of many cardiovascular drugs, including antiplatelet agents, eplerenone, ivabradine, calcium channel blockers, digoxin, sacubitril/valsartan and amiodarone (*Table 3*), possibly increasing the risk of toxicities and arrhythmias. Favipiravir, which was recently approved for influenza in China, has also shown potential action against SARS-CoV-2. In a preliminary study of 80 patients, favipiravir was found to have more potent antiviral action with fewer adverse effects than lopinavir/ritonavir.[79] Lastly, corticosteroid administration may be considered to treat severe COVID-19 pneumonia, a complication possibly related with an exaggerated inflammatory response.[35,44] In the RECOVERY trial, dexamethasone reduced deaths by one-third in ventilated patients (HR 0.65; 95% CI 0.51 to 0.82) and by one fifth in the patients receiving oxygen only (HR, 0.80; 95%CI, 0.70 to 0.92) and had no effects in those patients who did not require respiratory support.[80] Adverse effects of this treatment are associated with dose and duration of administration and patient's individual susceptibility.

Respiratory management

Respiratory management is mainly under the responsibility of specialized personnel including ICU specialists and anaesthetists. Attention should be paid to finger oxygen saturation during oxygen therapy. Target SpO_2 is above 95% (with chronic obstructive pulmonary disease SpO_2 >90%). When standard oxygen therapy cannot improve hypoxia, Venturi mask or mask with reservoir bag are used and chosen according to SpO_2 and PaO_2/FiO_2 ratio. When respiratory distress and/or hypoxaemia cannot be relieved by high-flow oxygen, non-invasive ventilation and prone positioning may be considered.[55,56] If the condition does not improve or worsen within a short time (1–2 h), endo-tracheal intubation and invasive mechanical ventilation should be promptly carried out. Mechanical ventilation of patients with COVID-19

Table 2 Common drugs used for COVID-19 and their side effects

Agent	Mechanism	Dosing	Side effects	Approved/target diseases
Arbidol	Inhibits viral entry	Oral: 200 mg tid for up to 10 days	Bradycardia Sinus node impairment	Not approved
Darunavir + cobicistat	Antiretroviral, protease inhibitor	800/150 mg daily	Interacts with many CV drugs	Approved for AIDS
Favipiravir	RNA-dependent RNA polymerase inhibitor	600 mg tid for no more than 14 days	Limited data	Approved for influenza
Hydroxychloroquine	Prevents binding to ACE2, prevents transport in endosome	Oral: 400 mg bid in 2 doses, then 200 mg bid for 5 days	No benefit in registries and trials QT prolongation Cardiotoxicity Interacts with digoxin and amiodarone	Approved for autoimmune disease
Interferon alpha	Immuno-modulatory	5 million U 2 times a day (vapor inhalation)	Depression Flu-like symptoms No major CV effect	Approved for hepatitis
Lopinavir/ritonavir	3CLpro (viral protease) inhibitor	Oral: 400/100 mg bid for up to 10 days	Increase lipid levels PR prolongation Interacts with many CV drugs	Approved/AIDS
Methylprednisolone	Steroid hormone	40 mg Q12 for 5 days	Adverse effects are associated with dose and duration of administration	Approved for various indications
Remdesivir	RNA-dependent RNA polymerase inhibitor	200 mg IV, then 100 mg IV daily, up to 10 days	QT prolongation	Experimental/Ebola and wide array of RNA viruses
Ribavirin[a]	Nucleoside inhibitor	IV: 500 mg 2–3 times a day for up to 10 days	Dose-related anaemia Interacts with warfarin	Approved for hepatitis
Tocilizumab	Monoclonal antibody to IL-6 receptor	Unknown	No known CV side effect	Investigational/ rheumatoid arthritis

ACE, angiotensin-converting enzyme; AIDS, acquired immunodeficiency syndrome; CV, cardiovascular; IL, interleukin; IV, intravenous.
[a]Ribavirin is taken in combination with interferon or lopinavir/ritonavir.

requires lung protective ventilation strategy, that is low tidal volume (6–8 mL/kg ideal body weight) and low-level airway platform pressure $\leq$30 cmH_2O to reduce ventilator-associated lung injury.

Mechanical circulatory support

When respiratory failure and hypoxaemia do not respond to standard therapy, veno-venous ECMO (VV-ECMO), for which the primary focus is gas exchange, may be used when cardiac function is only slightly impaired. In the Paris region, 4.7% of the critically ill COVID-19 patients had VV-ECMO (Mebazaa A., personal communication) following the recently published indications.[81] The indication for veno-arterial ECMO (VA-ECMO) is cardiogenic shock, defined by decreased cardiac output and myocardial contractility resulting in tissue hypoperfusion. The femoral vein and femoral artery are generally chosen as vascular accesses and specific approaches refer to the corresponding guidelines.[21,22] Also, a hybrid ECMO (VV combined with VA-ECMO) configuration may be used in patients who require both respiratory and circulatory support (*Figure 2*).

The ECMO has been used in critically ill COVID-19 patients, though with still high mortality rates.[5,10] Caution has been suggested because of the potential reduction of the number and function of some classes of lymphocytes and further inflammatory activation by ECMO in COVID-19 patients.[38]

Under the current epidemic conditions, intra-aortic balloon pump is relatively simple and applicable, when oxygenation is stable. Micro-axial flow pump systems like Impella might have additional advantages by generating a significant cardiac output and reducing cardiac inflammation by unloading.[82]

Renal replacement therapy

COVID-19 patients admitted to ICU have a roughly 30% prevalence of acute kidney injury and they may need renal replacement therapy. Ultrafiltration may be considered to treat HF complicated by diuretic resistance.[17,60] Haemofiltration therapy may also effectively reduce circulating inflammatory factors, inhibit inflammatory response, and relieve tissue injury caused by inflammatory reaction.[83]

Table 3 Interaction between heart failure medications and COVID-19 medications

HF Medications	COVID-19 Medications				
	HCLQ	DRV/C	Favipiravir	REM	LPV/r
ACEi[a]	↔	↔	↔	↔	↔
ARBs[b]	↔	↔	↔	↔	↔
Spironolactone	↔	↔	↔	↔	↔
Eplerenone	↔	↑	↔	↔	↑
Beta Blockers[c]	↔	↑	↔	↔	↑
Torsemide	↔	↔	↔	↔	↓
Indapamide	↔	↑	↔	↔	↑
Furosemide	↔	↔	↔	↔	↔
Metolazone	↔	↔	↔	↔	↔
Digoxin	↑	↑	↔	↔	↑
Hydralazine	↔	↔	↔	↔	↔
ISDN	↔	↑	↔	↔	↑
Sacubitril	↔	↑	↔	↔	↑
SGLT-2i[d]	↔	↔	↔	↔	↔
Ivabradine	↔	↑	↔	↔	↑
Sodium Nitroprusside	↔	↔	↔	↔	↔
CCB[e]	↔	↑	↔	↔	↑

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DRV/C, darunavir/cobicistat; HCQ, hydroxychloroquine; ISDN, isosorbide dinitrate; LPV/r, lopinavir/ritonavir; REM, remdesivir; SGLT2i, sodium–glucose co-transporter 2 inhibitor.
[a]Fosinopril levels go up with LPV/r, otherwise no interaction with any other drugs in the class.
[b]Valsartan levels are increased with LPV/r and DRV/c while losartan levels go down with LPV/r, otherwise no interaction with any other drugs in class.
[c]QT prolongation is a major side effect with LPV/r and HCLQ.
[d]Canagliflozin levels are lowered with LPV/r, otherwise no other drug interactions in the class.
[e]QT prolongation with LPV/r, verapamil increases the concentration of chloroquine.

Complications and comorbidities

Arrhythmias

An analysis of the clinical characteristics of patients with COVID-19 shows that 16.7% of 138 patients with COVID-19 had arrhythmias.[1] According to a study of cardiovascular complications in patients with SARS, 72% of 121 patients had persistent tachycardia, and 15% had transient bradycardia.[18] In the presence of haemodynamic instability, emergent electrical cardioversion is recommended.

Thromboembolism

Heart failure is associated with an increased risk of thromboembolic events also in patients with sinus rhythm. A marked activation of the coagulation cascade may occur in patients with COVID-19, as shown by the prolongation of the prothrombin time and D-dimer increase.[3,5,41] Coronavirus infection causes endothelial damage, inflammation and thrombosis. Continuous positive airway pressure ventilation may also favour thromboembolic events. On the other hand, gastrointestinal bleeding may occur during COVID-19 and focal haemorrhagic areas in the lungs have been described.[84] Thus, in general, increased attention to the higher likelihood of thrombotic or bleeding events must be taken.

In patients on chronic therapy with new oral anticoagulants requiring COVID-19 drugs, switch to heparin or unfractionated or low molecular weight heparin (LMWH) should be considered because of potential drug interactions (increase in anticoagulant effect). Prophylactic doses of LMWH may be considered in all COVID-19 patients who do not have haemorrhagic risk. Full anticoagulation with LMWH may be considered in patients with atrial fibrillation or with increased thromboembolic risk as shown by high D-dimer levels or signs of sepsis-induced coagulopathy.[85]

Coronary heart disease

Acute coronary syndrome should be treated according to guidelines also in patients with concomitant COVID-19 infection. Optimal treatment, however, will depend on the resources and expertise available and the impact of COVID-19 pandemic on health care resources. The cardiac catheterization laboratory should be prepared to manage patients with acute coronary syndrome and concomitant suspected or confirmed COVID-19.[86,87] However, in case of logistical difficulties or delays in transportation to a regional

Table 4 Key messages for daily handling of heart failure patients in light of the COVID-19 pandemic

- Patients with HF are at increased risk of COVID-19 and have poorer outcomes once infected
- Tele-monitoring must be implemented for COVID-19 prevention and screening and HF patients' follow-up
- All hospitalized HF patients should be screened for COVID-19, whenever possible, at the time of hospital admission
- At the time of hospital admission, HF patients with suspected or confirmed COVID-19 must undergo measurement of body temperature, RR and SpO_2, in addition to HR and BP. ECG, chest X-ray and laboratory exams including blood cell count, markers of inflammation and thrombotic risk (CRP, fibrinogen, D-dimer) and markers of organ damage (troponin) must be obtained in addition to routine procedures
- Blood cell count and laboratory exams of inflammation and thrombotic risk (CRP, D-dimer, etc.), cardiac function (BNP, NT-proBNP) and organ damage (troponin) must be repeated during hospitalization in case of clinical deterioration or when complications are suspected
- Echocardiography must be considered during hospitalization to assess cardiac function and detect concomitant causes of HF, either pre-existing or COVID-19-related
- Careful assessment of fluid status, in addition to clinical signs of HF, is mandatory during hospitalization. Repeated measures of inferior vena cava diameter and collapsibility by echocardiography may be used to assess fluid status
- Invasive haemodynamic monitoring may be considered in selected patients admitted to ICU when signs of active infection have subsided
- Guideline-directed HF medical therapy (including beta-blocker, ACEi, ARB or ARNI and mineralocorticoid receptor antagonist) should be continued in chronic HF patients whenever BP and haemodynamic conditions permit and considering drug interaction with COVID-19-related therapies and side effect profile
- Invasive ventilation and, less frequently, MCS or renal replacement therapy may become necessary in severely ill patients. Resource availability may need to be taken into account in critical cases

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BNP, brain natriuretic peptide; BP, blood pressure; CRP, C-reactive protein; ECG, electrocardiogram; HF, heart failure; HR, heart rate; ICU, intensive care unit; MCS, mechanical circulatory support; NT-proBNP, N-terminal pro brain natriuretic peptide; RR, respiratory rate; SpO_2, arterial oxygen saturation.

centre (time from first medical contact to percutaneous revascularization >120 min), thrombolysis may be considered.[88]

Confirmed or suspected COVID-19 patients with acute coronary syndromes and ongoing ischaemic symptoms and/or haemodynamic compromise should be taken to the cardiac catheterization laboratory for angiography and primary percutaneous coronary intervention, if indicated. Appropriate PPE should be used by the entire cardiac catheterization laboratory team. It is reasonable to postpone elective procedures in stable patients with structural heart disease, coronary artery disease, and peripheral vascular disease, in order to preserve hospital bed capacity because of the COVID-19 inpatient service burden during the COVID-19 pandemic.

Interaction between antiviral treatment and antiplatelet agents must also be considered. Prasugrel seems not to be affected by antiviral agents whereas clopidogrel effects may be reduced and ticagrelor effects may be enhanced by them.[89,90]

Hypertension

It has been reported that 15% to more than 30% of COVID-19 cases have hypertension.[1,17] Hypertension treatment should continue according to guidelines.[21] There is no evidence that ACEi or ARB should be discontinued in patients suffering from COVID-19.[68,70]

Myocardial injury and myocarditis

COVID-19 may cause acute myocardial injury, which is shown by an increase in troponin levels possibly with new ECG and echocardiographic abnormalities.[1,2,4,12,13] Acute myocarditis, HF and sudden death may occur in patients with no prior history of cardiac disease after COVID-19 infection.[3,24,91] Few cases of acute myocardial injury, sometimes with the clinical presentation of acute HF and cardiogenic shock, are described.[53,92–96] However, a demonstration of acute myocarditis was shown only in sporadic cases and histology findings were mostly of low grade inflammation with non-specific myocardial changes and low or absent myocyte necrosis.[53,94,96–99]

Indeed, elevated biomarkers of cardiac injury were associated with generalized myocardial oedema without late gadolinium enhancement at cardiac magnetic resonance imaging, despite a normal echocardiogram, during COVID-19.[100,101] In the absence of epicardial coronary artery stenosis, sub-clinical myocardial dysfunction in COVID-19 may therefore be a consequence of an impairment of microcirculatory endothelial function, observed during the early stages of the systemic inflammatory response to infection, especially in patients with pre-existing cardiovascular disease and impaired microcirculatory endothelial function. Importantly, direct COVID-19-mediated infection of endothelial cells as well as a host immune response might further worsen pre-existing endothelial function in patients with cardiovascular risk and/or HF and further contribute to cardiac injury.[102]

Left ventricular assist device and heart transplantation

Since patients with left ventricular assist device (LVAD) are particularly vulnerable to infections, extensive safety precautions should be employed against COVID-19. As these patients, who are on

anticoagulation, may have fluctuant international normalized ratio (INR) due to concomitant COVID-19, anticoagulation laboratory exams should be carefully monitored with appropriate safety measures. To check the function of LVAD, tele-remote programming may be considered. Precautionary measures of social distancing, sanitization and general hygiene are crucial to ensure that heart transplant recipients experience a low rate of COVID-19 illness. Also, LVAD patients may be at a higher risk of right ventricular failure due to hypoxia and probable high output syndrome.

Many heart transplant recipients already have haematological changes of lymphopenia due to the effects of immunosuppressive therapy which may be worsened by COVID-19 infection. Pharmacotherapy targeted against the virus holds the greatest promise when applied early in the course of the illness, but its usefulness in advanced stages may be doubtful. Also, antiviral therapy may have considerable interaction with cyclosporine. Use of anti-inflammatory therapy applied too early may not be necessary and could even favour viral replication such as in the case of corticosteroids.

Anxiety and depression

During the pandemic of the novel coronavirus, patients with HF are more likely to develop emotional disorders, such as hypochondria, anxiety, and emotional stress reaction. Psychological and emotional assessment and counselling may be appropriate and psychological disease-related drug treatment may be needed. It is important to emphasize that many patients may not seek medical attention during these challenging times due to the fear of getting exposed to COVID-19 which may aggravate issues.

Conclusion

The COVID-19 outbreak poses serious challenges to clinicians worldwide. HF patients are particularly prone to developing the infection, thus, it is imperative that strict preventive measures are taken by ambulatory HF patients to reduce the risk of exposure. Moreover, HF patients are also at higher risk of serious complications once they acquire the infection. It is critical to rule out COVID-19 in any HF patient who is hospitalized as symptoms may significantly overlap. As COVID-19 is a worldwide outbreak of a new infectious disease with limited data regarding concomitant HF, this position paper will be helpful for clinicians worldwide taking care of HF patients with concomitant suspected or overt COVID-19 as well as with patients at risk of this infection (*Table 4*). It is important to emphasize that these expert recommendations are mainly based on the current pandemic situation and may need to be updated according to its changes across the world.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Select list of current ongoing trials against COVID-19.

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