ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2-care pathways, treatment, and follow-up

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SPECIAL ARTICLE

ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up

The Task Force for the management of COVID-19 of the European Society of Cardiology

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Aims Since its emergence in early 2020, the novel severe acute respiratory syndrome coronavirus 2 causing coronavirus disease 2019 (COVID-19) has reached pandemic levels, and there have been repeated outbreaks across the globe. The aim of this two part series is to provide practical knowledge and guidance to aid clinicians in the diagnosis and management of cardiovascular (CV) disease in association with COVID-19.

Methods and results A narrative literature review of the available evidence has been performed, and the resulting information has been organized into two parts. The first, which was reported previously, focused on the epidemiology, pathophysiology, and diagnosis of CV conditions that may be manifest in patients with COVID-19. This second part addresses the topics of: care pathways and triage systems and management and treatment pathways, both of the most commonly encountered CV conditions and of COVID-19; and information that may be considered useful to help patients with CV disease (CVD) to avoid exposure to COVID-19.

Conclusion This comprehensive review is not a formal guideline but rather a document that provides a summary of current knowledge and guidance to practicing clinicians managing patients with CVD and COVID-19. The recommendations are mainly the result of observations and personal experience from healthcare providers. Therefore, the information provided here may be subject to change with increasing knowledge, evidence from prospective studies, and changes in the pandemic. Likewise, the guidance provided in the document should not interfere with recommendations provided by local and national healthcare authorities.

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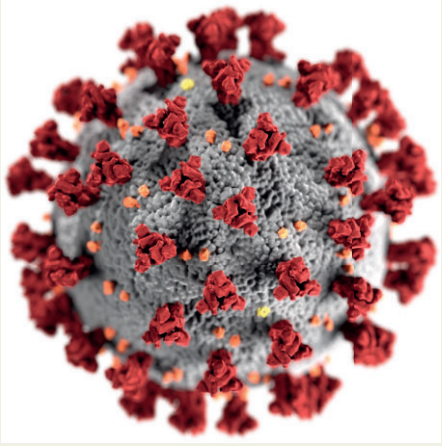
Graphical Abstract

ESC Guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic
Part 2 – Care pathways, treatment and follow-up



- Protective measures for healthcare personnel and patients in cardiology and triage systems
- Risk categorization of invasive procedures
- Management/treatment pathways
- Treatment of SARS-CoV-2 infection
- Patient information

ESC

Keywords ACE2 • Acute coronary syndromes • Arrhythmias • Biomarkers • Cardiogenic shock • COVID-19 • Heart failure • Myocarditis • Venous thromboembolism • Pulmonary embolism • Thrombosis

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) reached pandemic levels in March 2020 and has caused repeated waves of outbreaks across the globe. COVID-19 shares many manifestations of a systemic disease and has major implications for the cardiovascular (CV) system, which are summarized in a two part review entitled European Society of Cardiology (ESC) Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic.

The second part of the document addresses the topics of protection measures, triage systems, risk categorization of procedures, management and treatment pathways, therapeutic strategies for SARS-CoV-2 infections, and patient information. Owing to the highly contagious nature of the SARS-CoV-2 virus, appropriate protection of healthcare professionals (HCP) and patients in different encounters, such as ambulatory care setting, hospital wards, emergency room visits, and intermediate and intensive care units, is of pivotal importance. Depending on the extent of pandemic involvement in various regions, prioritization of specialized procedures according to degree of urgency gains prominence, and this document provides guidance on how invasive procedures for coronary artery disease (CAD), valvular heart disease (VHD), acute and chronic heart failure (HF), and arrhythmic heart disease may be categorized. Management and treatment pathways for the most important CV disease (CVD) manifestations that may affect COVID-19 patients are summarized in detail in Section Management/treatment pathways, including acute coronary syndrome (ACS) and chronic coronary syndrome (CCS), acute and chronic HF, VHD, hypertension, pulmonary embolism, and arrhythmias. This is followed by an overview of various therapeutic agents under evaluation to treat SARS-CoV-2 infections highlighting the important issue of drug–drug interactions, particularly as it relates to proarrhythmic properties, such as QTc (corrected QT interval) prolongation. Useful information for patients and updates on vaccinations are summarized in the final chapter.

While the document is comprehensive, it is *not a guideline* but rather *a guidance* document. The recommendations are the result of observations and personal experience from healthcare providers. The present publication provides a summary of the guidance until March 2021. Therefore, the information provided here may be subject to change with increasing knowledge, evidence from prospective studies, and changes in the pandemic. Likewise, the guidance provided in the document should in no way interfere with recommendations provided by local and national healthcare authorities.

Management/treatment pathways

This section provides guidance on the specialist management of patients with CV conditions, while general guidance on protective measures and care pathways for healthcare personnel and patients in cardiology is provided as Supplementary material online.

Cardiogenic shock

Key points

- Management of cardiogenic shock (CS) and out-of-hospital cardiac arrest (OHCA) is critically time-dependent, requiring a dedicated network and multidisciplinary expertise.
- Resource allocation should still try to deliver a standardized team-based approach including availability and feasibility of mechanical circulatory support (MCS).
- Invasive coronary angiography (ICA) remains the mainstay of treatment. However, special considerations need to be taken into account to minimize the risk of widespread nosocomial infections.
- In patients with concomitant COVID-19, escalation to MCS should be carefully weighed against the development of coagulopathy associated with COVID-19 and the need for specific treatment (prone position) required for acute lung injury.
- In case of requirement for MCS, extracorporeal membrane oxygenation should be the preferred temporary MCS because of the oxygenation capabilities.
- In case of acute renal failure, continuous renal replacement should be used restrictively according to established criteria.
- Daily sequential organ failure assessment and therapeutic intervention scoring system scores should be assessed for most critical patients, to improve decision-making.
- The safety of HCP is of predominant importance to avoid any HCP infections
- SARS-Cov-2 infection should be excluded throughout two negative tests performed using a reverse transcriptase-polymerase chain reaction (RT-PCR). For intubated patients, a tracheal aspirate would additionally be required (see Supplementary material online, *Section 1* and Supplementary material online, *Section 2*).
- When the patient cannot be placed in the supine position, it may be reasonable to provide cardiopulmonary resuscitation with the patient in the prone position, particularly in patients with advanced airway and circulatory support.[1,2]

CS and OHCA are time-dependent diseases in need of relevant resources, trained systems, and dedicated networks for optimal outcome. In general, treatment of CS and OHCA should follow current guidelines and current evidence.[3–9] However, it should be considered that in an overwhelmed critical care system stressed by the pandemic COVID-19, it will not be possible for all patients to receive intensive care unit (ICU) treatment due to limited resources. This leads to difficult situations based also on the four widely recognized principles of medical ethics (beneficence, non-maleficence, respect for autonomy, and equity), which are also crucial under conditions of resource scarcity. If resources available are insufficient to enable all patients to receive the ideally required treatment, then fundamental principles should be applied in accordance with the following rules of precedence:

(1) Equity: Available resources are to be allocated without discrimination (i.e. without unequal treatment on grounds of age, sex, residence, nationality, religious affiliation, social or insurance status, or chronic disability). The allocation procedure must be fair, objectively justified, and transparent. With a fair allocation procedure, arbitrary decisions, in particular, can be avoided.
(2) Preserving as many lives as possible: Under conditions of acute scarcity, all measures are guided by the aim of minimizing the number of deaths. Decisions should be made in such a way as to ensure that as few people as possible become severely ill or die.
(3) Protection of the professionals involved: Therefore, triage protocols are needed to maximize benefits and relieve HCP from improvising decisions about whom to treat or making those decisions in isolation.

Triage strategies, based on current evidence and a previously established critical care triage protocol developed by working groups for use during a worldwide influenza pandemic,[10] are summarized in *Table 1*. Specific recommendations are provided for patients with and without concomitant infection in *Figure 1*. Two scenarios will be considered:

(1) Non-infected patients and
(2) Possibly infected/COVID-19-positive patients.

The infection should be suspected according to recently defined epidemiological and clinical criteria.[11]

ST-segment elevation myocardial infarction

The COVID-19 pandemic should not compromise timely reperfusion of ST-segment elevation MI (STEMI) patients.[12–14] In line with current guidelines, reperfusion therapy remains indicated in patients with symptoms of ischaemia of <12 h duration and persistent ST-segment elevation in at least two contiguous electrocardiogram (ECG) leads.[5] Concurrently, the safety of HCP should be ensured.[15] To that purpose, and in the absence of previous SARS-CoV-2 testing, all STEMI patients should be managed as if they are COVID-19 positive. The main principles of STEMI management in the COVID-19 pandemic are the following (*Figure 2*):

(1) The maximum delay from STEMI diagnosis to the reperfusion of 120 min should remain the goal for reperfusion therapy under the following considerations:
   a. Primary percutaneous coronary intervention (PCI) remains the reperfusion therapy of choice, if feasible within this time frame and performed in facilities approved for the treatment of COVID-19 patients in a safe manner for healthcare providers and other patients.
   b. Primary PCI pathways may be delayed during the pandemic (up to 60 min in some networks experience) due to delays in the delivery of care and the implementation of protective measures.
   c. If the target time cannot be met and it is not contraindicated, fibrinolysis should be performed in accordance with ESC guidelines recommendations.[5]

Table 1 Detailed inclusion and exclusion criteria for triage in intensive care unit upon admission

Inclusion criteria:

- Requirement for invasive ventilator support.
- Requirement for hemodynamic support with vasoactive agents (noradrenaline-equivalent dose >0.1 μg/kg/min) or mechanical support.
- Requirement for renal replacement therapy.

If at least one criterion is fulfilled, check for exclusion criteria.

Exclusion criteria:

- Patients' end of life decision preferences.
- Unwitnessed cardiac arrest, witnessed cardiac arrest, not responsive to electrical therapy, recurrent cardiac arrest.
- Metastatic malignant disease.
- End-stage neurodegenerative disease.
- Severe and irreversible neurological event or condition.
- Chronic condition:
  - GOLD group D COPD,
  - Cystic fibrosis or pulmonary fibrosis with baseline PaO_2 <55 mmHg, and
  - Cirrhosis, Child-Pugh score >7.
- End-stage kidney disease on dialysis with refractory symptoms despite active medical management treatment.
- Severe dementia.
- Estimated survival <12 months.

If not even one criterion is met and ICU beds are not available, check for additional exclusion criteria.

Additional exclusion criteria to be checked if no ICU beds are available:

- Severe trauma.
- Severe cerebral deficits after stroke.
- Moderate dementia (confirmed).
- Estimated survival <24 months.
- Chronic condition:
  - home oxygen therapy and
  - Cirrhosis with refractory ascites or encephalopathy > stage I.
- Age >80 years.
- Age >75 years and at least one criterion:
  - Cirrhosis,
  - Stage III chronic kidney disease KDIGO, and
  - NYHA Class >II heart failure.

If neither of these criteria is fulfilled, consider to withdraw ICU support from patients who arrived earlier to save those with better prognoses.

Criteria for little or no likelihood of benefit with ICU treatment (occurrence of at least one criterion):

- Occurrence of two new significant organ failures not present on admission.
- No improvement in respiratory or hemodynamic status.
- Advanced multiple organ failure defined by an increase in SOFA score (≥25% compared to admission values after at least 10 days of treatment) associated with accumulated TISS ≥500.

COPD, chronic obstructive pulmonary disease; FEV, forced expiratory volume in 1 s; FIO, fraction of inspired oxygen; GOLD, global Initiative for chronic obstructive lung disease; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; NYHA, New York Heart Association; PaO_2, partial pressure of arterial oxygen; SOFA, Sequential Organ Failure Assessment; SpO_2, oxygen saturation measured by pulse oximetry; TISS, therapeutic intervention scoring system; TLC, total lung capacity; VC, vital capacity.

(2) As SARS-CoV-2 test results are not immediately available in STEMI patients, any STEMI patient should be considered potentially infected.
(3) All STEMI patients should undergo testing for SARS-CoV-2 as soon as possible following first medical contact irrespective of reperfusion strategy, at the latest upon admission to the ICU post primary PCI. Until the result of the test is known, all precautionary measures should be taken to avoid potential infection of other patients and HCP.
(4) Consider immediate complete revascularization if indicated and appropriate to avoid staged procedures and reduce hospital stay.
(5) All physicians involved in the management of patients with STEMI should be familiar with indications, contraindications, and dosage of fibrinolysis and adhere to established administration protocols.[5]

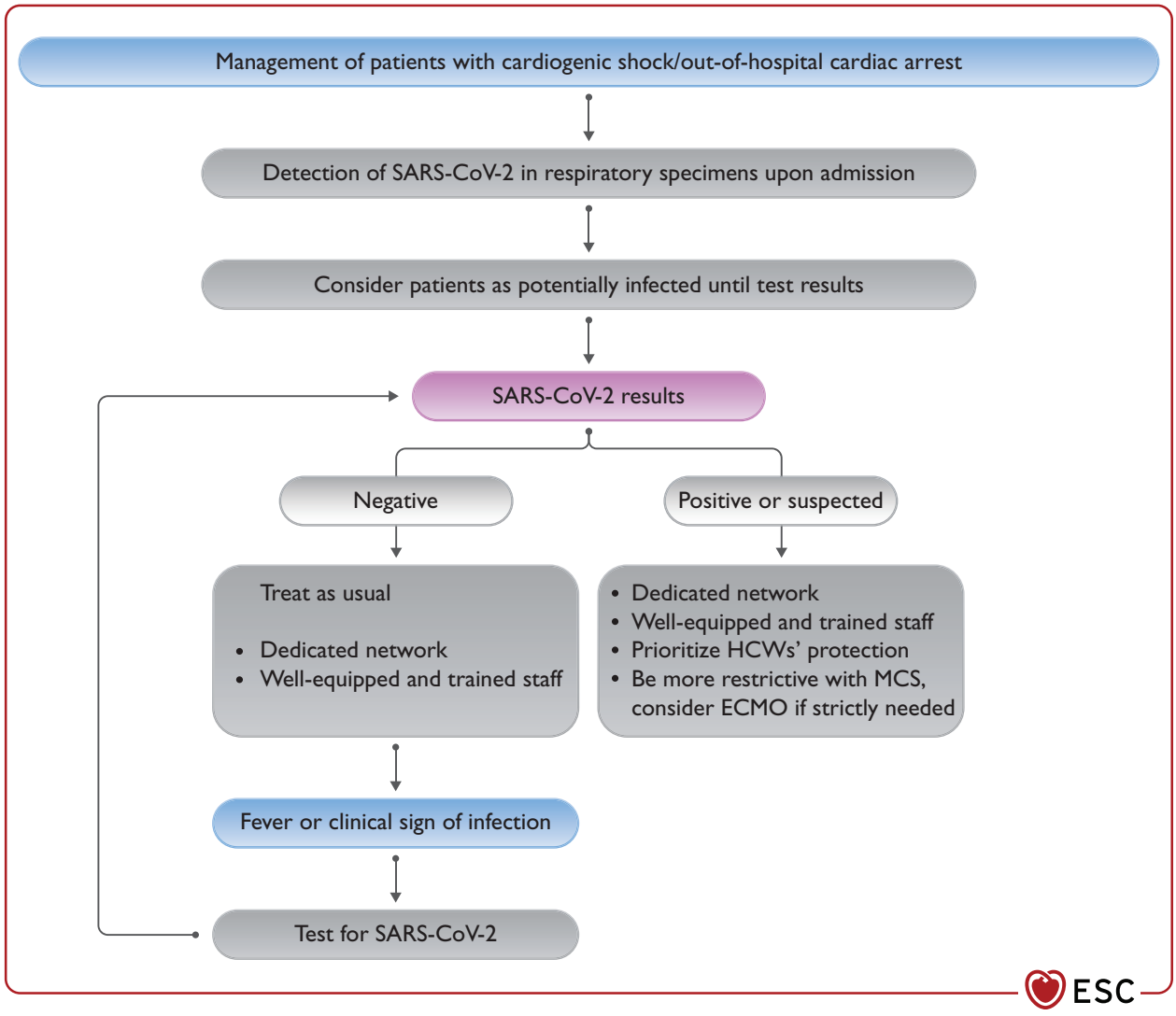


Figure 1 Management of patients with cardiogenic shock/out-of-hospital cardiac arrest during COVID-19 pandemic. COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HCW, healthcare worker; MCS, mechanical circulatory support; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Left ventriculography should be considered during catheterization if echocardiography has not been performed before catheterization laboratory admission or is not feasible soon after the procedure.

The treatment of the non-culprit lesions should be managed according to patients' clinical stability as well as angiographic features of those lesions. In the presence of persistent symptomatic evidence of ischaemia, subocclusive stenoses, and/or angiographically unstable non-culprit lesions, PCI during the same hospitalization should be considered. Treatment of other lesions should be delayed, planning a new hospitalization after the peak of the outbreak.[5]

Non-ST-segment elevation acute coronary syndromes

The management of patients with non-ST-segment elevation ACS should be guided by the risk stratification and intensity of involvement in the epidemics.[16] In geographic territories with significant pandemic involvement, testing for SARS-CoV-2 should be performed as soon as possible following first medical contact, irrespective of treatment strategy, to allow HCP to implement adequate protective measures and management pathways (see Supplementary material online, *Section 1*). Patients should be categorized into four risk groups (i.e. very high risk, high risk, intermediate risk, and low risk) and managed accordingly (*Figure 3*).

For patients at high risk, medical strategy aims at stabilization while planning an early (<24 h) invasive strategy. The time of the invasive strategy may, however, be longer than 24 h according to the timing of testing results.

Patients at intermediate risk should be carefully evaluated taking into consideration alternative diagnoses to Type I myocardial infarction (MI), such as Type II MI, myocarditis, or myocardial injury due to respiratory

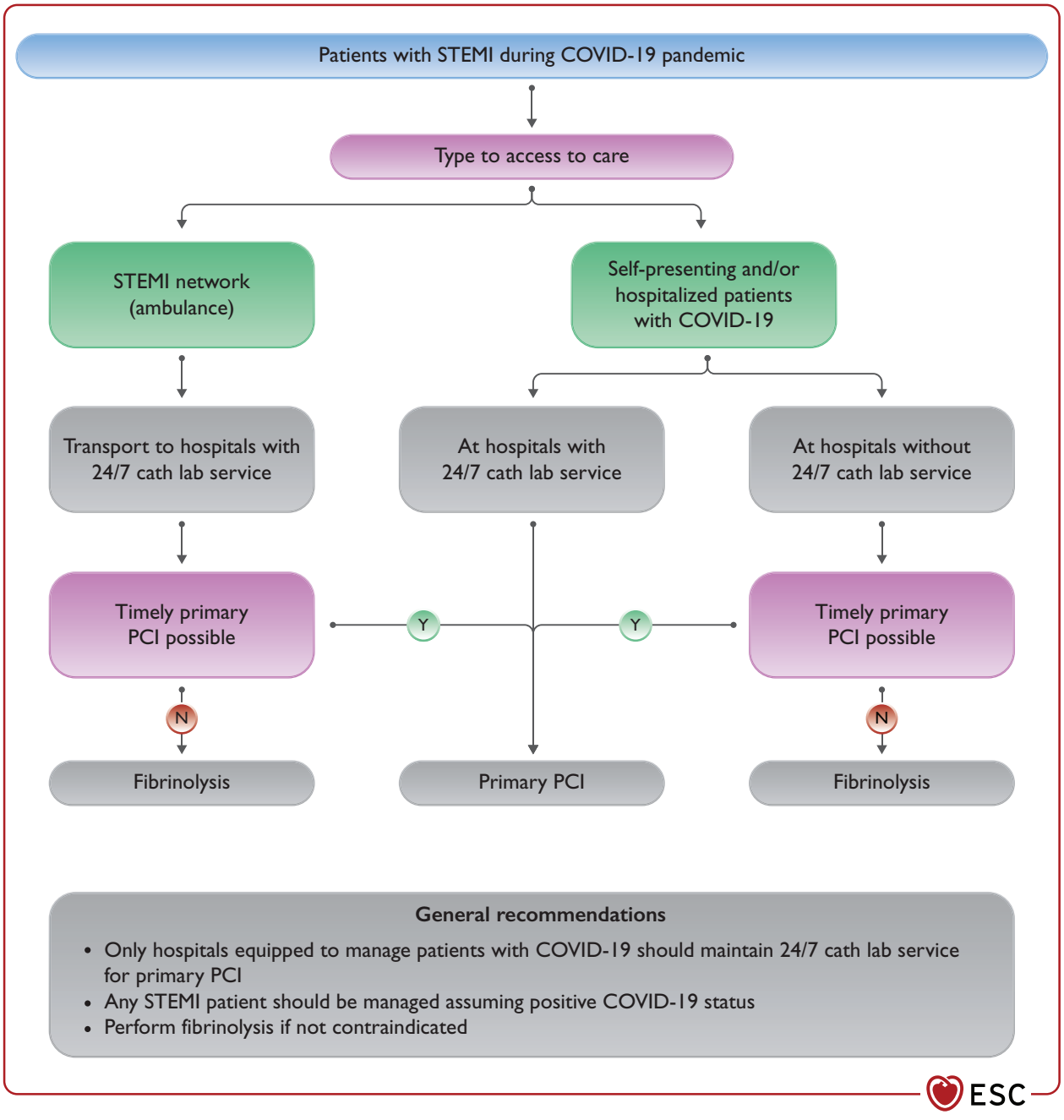


Figure 2 Management of patients with STEMI during COVID-19 pandemic. COVID-19, coronavirus disease 2019; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

distress or multiorgan failure or Takotsubo. In the event any of the differential diagnoses seem plausible, a non-invasive strategy should be considered and coronary computed tomography angiography (CCTA) should be favoured, if equipment and expertise are available.

When there is a positive SARS-CoV-2 test, patients should be transferred for invasive management to a COVID-19 hospital equipped to manage COVID-19-positive patients. At times of high demand on the infrastructure and reduced availability of catheterization laboratories or operators, non-invasive conservative management might be considered with early discharge from the hospital and planned clinical follow-up.

Patients with troponin rise and no acute clinical signs of instability (ECG changes, recurrence of pain) might be managed with a primarily conservative approach.[17,18] Non-invasive imaging using CCTA may speed up the risk stratification and avoid an invasive approach allowing for early discharge.[19,20]

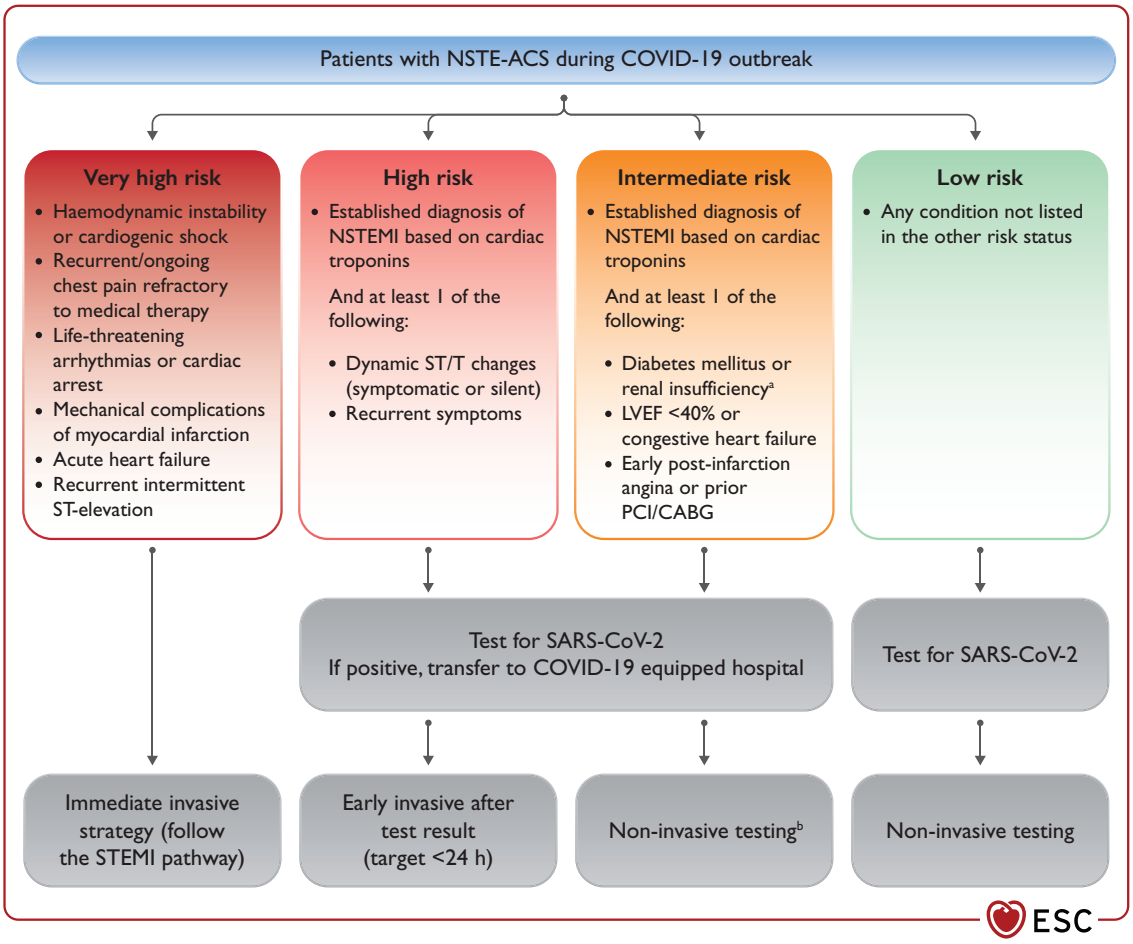


Figure 3 Recommendations for the management of patients with NSTE-ACS in the context of COVID-19 outbreak. CABG, coronary artery bypass graft; COVID-19, coronavirus disease 2019; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation MI; PCI, percutaneous coronary intervention; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. [a]Estimated glomerular filtration rate <60 mL/min/1.73 m^2. [b]Coronary computed tomography angiography should be favoured, if equipment and expertise are available. In low-risk patients, other non-invasive testing might be favoured in order to shorten hospital stay. It is suggested to perform left ventriculography during catheterization if echocardiography not performed before catheterization laboratory admission.

Chronic coronary syndromes

HCP managing patients with CCS in geographical areas heavily affected by the COVID-19 pandemic should consider the following main points:

- CCS patients are generally at low risk for CV events allowing the deferment of diagnostic and/or interventional procedures, in most cases.
- Medical therapy should be optimized and/or intensified depending on the clinical status.
- Remote clinical follow-up should be warranted to reassure patients and capture possible changes in clinical status that might require hospital admission in selected high-risk profile patients.

Practical considerations of medical therapy

Nonsteroidal anti-inflammatory drugs have been identified as a potential risk factor for serious clinical presentation of SARS-CoV-2 infection.[21] Potential impact of chronic aspirin therapy has been questioned. However, at the low dose administered in CCS, aspirin has very limited anti-inflammatory effect. Therefore, CCS patients should not withdraw aspirin for secondary prevention.

Statin therapy has been variably associated with favourable outcomes in patients admitted with influenza or pneumonia.[22,23] On the other hand, patients with COVID-19 have been reported to develop severe rhabdomyolysis or increased liver enzymes.[24] In these latter cases, it may be prudent to temporarily withhold statin therapy.

For CCS patients treated with antihypertensive drugs please refer to Section Hypertension.

Non-invasive testing

Non-invasive testing in patients with CCS is tailored upon different clinical presentations.[25] In regions with a high rate of SARS-CoV-2 infection, evaluation of asymptomatic CCS patients with non-invasive

testing should be postponed in order not to expose these patients to an unnecessary risk of infection or overload the healthcare systems.

For symptomatic patients with suspected CAD and a pre-test probability of 5–15%, functional imaging for the detection of myocardial ischaemia or CCTA is normally recommended as initial tests to diagnose CAD. In regions experiencing a critical situation and medical systems overloaded by the COVID-19 pandemic, CAD screening, even in symptomatic patients, should probably be postponed in the majority of patients. Yet, if necessary, depending upon local availability and expertise, CTA should be preferred (see Guidance Part 1).

However, the increased workload of computed tomography (CT) departments should be acknowledged; they have been heavily disrupted by the high request of pulmonary CT for patients with COVID-19. In addition, feasibility/accuracy of CCTA might be hampered in patients with COVID-19 for the common occurrence of tachycardia and, at times, severe renal dysfunction. In case CCTA is not suitable (e.g. inability of heart rate control) or available, non-invasive testing should be postponed. Alternative imaging modalities should be discouraged during the acute pandemic phase unless severe ischaemia is suspected, to minimize the access of the patients to healthcare system (single photon emission computed tomography/Positron emission tomography) or to prevent close contact between patients and personnel (stress echocardiography).

For known CCS patients, clinical follow-up should be done mostly via tele-health (a dedicated telephone line should be made available to patients). Physicians could therefore address most of the patients' concerns related to continuation or changes in medical therapy. Possible onset/recurrence of unstable symptoms should be estimated within the clinical history of the patient to weigh the need for hospitalization and diagnostic testing.

Table 2 Management of chronic coronary syndromes during COVID-19 pandemic

Continuation of medications in CCS patients is recommended during COVID-19 pandemic
Follow-up of CCS patients via tele-health is recommended
Revascularization of CCS patients must be postponed in low- to intermediate-risk patients
Postponing of non-invasive testing of CCS patients should be considered during COVID-19 pandemic
CT angiography should be preferred to non-invasive functional testing during COVID-19 pandemic
Screening for SARS-CoV-2 infection should be considered before cardiac surgery with nasopharyngeal swab and CT scan
Revascularization of high-risk[a] CCS patients may be considered during COVID-19 pandemic
PCI may be considered over CABG in selected patients during COVID-19 pandemic[b]
Identification of COVID-19-free hospitals may be considered as 'Hub' for cardiac surgery
Invasive management of CCS in SARS-CoV-2-positive patients should be deferred until the patient has recovered, whenever possible

CABG, coronary artery bypass graft; CCS, chronic coronary syndrome; COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; PCI, percutaneous coronary intervention; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Patients with high-risk symptoms and/or coronary anatomy and/or large ischaemia as assessed by Heart team.
[b]To shorten hospital stay and keep ICU beds available for patients with COVID-19.

Invasive assessment and revascularization

Symptomatic patients with very high clinical likelihood of obstructive CAD are generally referred to ICA without prior non-invasive diagnostic testing.[25] However, medical treatment should be attempted first to reserve ICA with possible ad hoc revascularization only in case of clinical instability, especially in regions where healthcare systems are heavily overloaded by patients with COVID-19.[26] Revascularization, either by PCI or by coronary artery bypass graft (CABG), can be postponed in most CCS patients. Healthcare systems might identify COVID-19-free hospitals serving as hubs for selected CCS patients in whom invasive and surgical procedures cannot be postponed. In selected patients, hybrid revascularization CABG/PCI or even full-PCI can be considered by the heart team based on the patient's clinical condition and local situation (see *Table 2*).

Heart failure: acute, myocarditis, chronic, left ventricular assist device, and transplantation

Patients with CV comorbidities, namely HF, are at increased risk of the more severe presentation and complications of COVID-19. Chronic HF is associated with a greater risk of hospitalization, requirement of mechanical ventilation, and mortality. Acute HF may occur as a major complication in patients hospitalized for COVID-19.

Acute heart failure

Key points

- Acute HF may complicate the clinical course of COVID-19, particularly in severe cases.
- Underlying mechanisms of acute HF in COVID-19 may include the following: acute myocardial injury due to ischaemia, infarction or inflammation (myocarditis), acute respiratory distress syndrome (ARDS), acute kidney injury and hypervolemia, stress-induced cardiomyopathy, and tachyarrhythmia. Acute myocarditis with direct demonstration of SARS-CoV-2, inflammatory infiltrate, and myocardial necrosis is, however, rare.[27,28]
- COVID-19 pneumonia may lead to the worsening haemodynamic status due to hypoxaemia, dehydration, and hypoperfusion.
- Since symptoms of COVID-19 and acute/worsening chronic HF can be similar, distinguishing these two entities is challenging. In addition, the two conditions may coexist. Clinical presentation, pre-existing CV comorbidities, and chest imaging findings suggestive of HF (e.g. cardiomegaly and/or bilateral pleural effusion) are of utmost importance. Significantly elevated B-type natriuretic peptide (BNP)/N-terminal B-type natriuretic peptide (NT-proBNP) levels also suggest acute HF, although increased levels of natriuretic peptides may also be found in COVID-19

patients in the absence of HF or left ventricular (LV) systolic dysfunction. Prudent use of bedside point-of-care or transthoracic echocardiography should be considered, keeping in mind the prevention of contamination of personnel and/or equipment.[29]
- The treatment of acute HF in patients with SARS-CoV-2 infection should be equivalent to those without COVID-19, and attention should be given to early detection and treatment of complications, including the need for non-invasive or invasive ventilation, bleeding events, and cardiac arrhythmias.[29,30]

Data on acute HF in COVID-19 are still scarce. In an earlier report from China, 23% of all hospitalized patients developed HF, while HF prevalence was significantly higher in fatal cases compared with survivors (52% vs. 12%, $P < 0.0001$).[31] In a cohort of 21 patients from the USA admitted to an intensive care unit, 7 (33.3%) patients developed dilated cardiomyopathy, characterized by globally decreased LV systolic function, clinical signs of CS, elevated creatine kinase, or troponin I levels, or hypoxaemia, without a history of systolic dysfunction.[32] An analysis of mortality causes in COVID-19 patients (150 hospitalized/68 dead) revealed that myocardial damage/HF and combined respiratory failure/myocardial damage/HF were responsible for 7% and 33% of fatal cases, respectively.[33] These early reports require cautious interpretation, because small sample size and inclusion of the more severe cases may have resulted in an overestimation.

Recently, a meta-analysis of 30 studies (6389 patients) published between February and April 2020 including a broader spectrum of COVID-19 patients demonstrated that acute myocardial injury and overt HF occur in 15.7% and 11.5% of patients, respectively.[34] In a cohort of 3080 confirmed cases in Spain, acute HF developed more frequently in those with a history of chronic HF; however, 2.5% developed incident HF during SARS-CoV-2 infection.[30] Similar results were reported in an Italian multicentre study.[35] In addition to chronic HF, advancing age, atrial tachyarrhythmias, and chronic obstructive pulmonary disease (COPD) were identified as independent predictors of acute HF. Patients developing HF have significantly higher 30-day mortality rates compared to those without HF (46.8% vs. 19.7%, $P < 0.001$), and withdrawal of standard HF medications increased in-hospital mortality.[30] Recent studies show that COVID-19 also confers greater risk of right ventricular dysfunction and dilation, which are predictors of poorer outcome.[36] In a cohort of 510 COVID-19 in-patients undergoing echocardiographic examinations, right ventricular remodelling was associated with a more than two-fold increase in mortality risk after adjustment for clinical variables and biomarkers.[37,38]

There are several, not mutually exclusive, mechanisms of acute HF in COVID-19, such as:

acute myocardial injury (defined as serum high-sensitivity troponin I elevation >99th percentile of the upper normal limit or new abnormalities in electrocardiography or echocardiography) occurs in 8–15% of COVID-19 patients.[39] It may be caused by ischaemia, infarction, or inflammation (myocarditis). In patients with severe infection, evidence of acute myocardial injury is present in 22.2–31%.[31,40,41] A meta-analysis of four studies ($n = 341$) suggested that in patients with severe infection, high-sensitivity troponin I was significantly higher at admission (mean standardized difference 25.6 ng/L) compared to those with non-severe course.[42] In addition, troponin levels remained high in non-survivors throughout the clinical course and increased with illness deterioration.[31] A history of HF was more frequently noted in patients with, compared to those without, acute myocardial injury (14.6% vs. 1.5%).[43] Acute myocardial injury was also more frequently associated with significantly elevated NT-proBNP levels (median 1689 pg/mL).[43] In a Spanish registry of 245 patients hospitalized for COVID-19, elevated troponin I levels were observed in 17.1%.[44] On multivariate analysis, elevated troponin I was associated with higher mortality [odds ratio (OR), 4.93; 95% confidence interval (CI), 1.24–19.52; $P = 0.023$], HF (OR, 4.28; 95% CI, 1.30–14.07; $P = 0.017$) and the combined outcome of mortality or HF in patients without a history of heart disease (OR, 7.09; 95% CI, 2.28–22.03; $P = 0.001$), but not in patients with previous heart disease ($P = 0.561$, $P = 0.337$ and $P = 0.992$, respectively).[44]

ARDS, hypoxaemia, acute kidney injury, hypervolemia, increased adrenergic drive, stress-induced cardiomyopathy, fever, and a profound systemic inflammatory activation ('cytokine storm'), characteristic of severe infection and multiorgan dysfunction, could also contribute to acute HF or exacerbation of chronic HF in COVID-19.[45]

Sustained/repetitive cardiac arrhythmia may also lead to deterioration in cardiac function. Apparently, cardiac arrhythmias have been described in 16.7% of all hospitalized COVID-19 patients and in 44.4% of those requiring intensive care admission,[41] and atrial tachyarrhythmias have been identified as a predictor of acute HF development.[30] An ECG on admission should always be performed and serial ECGs are required in patients with myocardial injury and those receiving pro-arrhythmic drugs.

Management of heart failure in individuals without COVID-19 during the COVID-19 outbreak

Internationally, several reports have suggested a decline in hospitalization rates for acute HF in individuals without SARS-CoV-2 infection during the peak of the COVID-19 pandemic compared with 2019.[46–48] Despite similar disposition and management, patients admitted for acute HF in 2020 had more severe symptoms (e.g. New York Heart Association class III–IV in 96% vs. 77%, $P = 0.03$)[49] and higher in-hospital mortality (7.3% vs. 6.1%, $P = 0.03$) compared with 2019.[50] Also, a decline in the emergency department (ED) visits and an increase in out-of-hospital CV mortality have been reported.[51,52] These findings call for further research into the causes and long-term prognostic implications to inform strategic plans for the management of chronic CV disorders during the COVID-19 crisis.

Myocarditis

Key points

- Acute myocarditis as traditionally defined by viral presence, inflammatory infiltrates, and myocardial injury is seldom demonstrated in COVID-19 patients with increased interstitial myocardial macrophages shown in most of the cases.[53]

- Accumulating clinical experience indicates that myocarditis can occur in SARS-CoV-2-infected individuals, even without pulmonary involvement, with various clinical presentations, including fulminant myocarditis.[53]
- COVID-19 myocarditis should be suspected in patients with acute-onset chest pain, ST-segment changes and/or T wave inversion, cardiac arrhythmias, acute HF, and haemodynamic instability. Mild/moderate LV dilatation, global/multi-segmental LV hypocontractility, increased LV wall thickness (suggestive of oedema), moderately elevated cardiac troponin, and increased NT-proBNP, without significant coronary artery disease, are also suggestive of myocarditis. In particular, suspicion of COVID-19 myocarditis should be raised in patients with rapidly worsening acute HF/CS, without pre-existing CV disorders and acute coronary syndrome.
- Cardiac magnetic resonance, if available, is the preferred method for the diagnosis of acute myocarditis.
- Endomyocardial biopsy is not recommended for the routine assessment of patients suspected of having COVID-19 myocarditis and should be limited to cases of severe or refractory HF where histological findings may guide therapeutic choices.
- No clear recommendation could be given regarding the treatment of patients with COVID-19 myocarditis. MCS, inotropes and/or vasopressors, and mechanical ventilation may be needed in severe cases. There is no compelling evidence to support the use of immunomodulatory therapy, including corticosteroids and intravenous immunoglobulins. However, corticosteroids are indicated when there is respiratory involvement and have been administered to patients who then had favourable clinical outcomes.[53–56] Tocilizumab and favipiravir are currently being tested in a randomized trial.[57]

Incidence, underlying mechanisms and risk factors of COVID-19 myocarditis are currently unclear. Endomyocardial biopsies have shown cardiotropism, including direct cardiomyocyte infection by SARS-CoV-2, a high degree of interstitial macrophages in a majority of the cases, and multifocal lymphocytic myocarditis in a minority.[27,58] However, the mechanisms responsible for myocardial injury and dysfunction remain insufficiently understood. The clinical features vary. Some patients present with fever, dyspnoea, and acute-onset chest pain but without haemodynamic instability. Deterioration to acute HF, hypotension, and CS may also occur.[53] In the most severe cases, fulminant myocarditis with CS has been described.[59,60]

Chronic heart failure

Key points

- The risk of COVID-19 may be higher in chronic HF patients due to the advanced age and presence of several comorbidities.
- Chronic HF patients with COVID-19 have a significantly higher risk of adverse outcomes.
- In HF patients suspected of COVID-19, routine clinical assessment, temperature measurement, ECG (arrhythmias, ST-T wave changes), chest X-ray (cardiomegaly, COVID-19 pneumonia), and laboratory findings (elevated sedimentation rate, fibrinogen and C-reactive protein, and lymphocytopenia) can provide a diagnostic clue. Transthoracic echocardiography and chest CT scan can be used for further assessment, as indicated. In all instances, attention should be given to the prevention of viral transmission to healthcare providers and contamination of the equipment.
- Patients with chronic HF should closely follow protective measures to prevent infection.
- Ambulatory HF patients (with no cardiac emergencies) should refrain from hospital visits.
- Guideline-directed medical therapy [including angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists, and other guideline-directed medications) should be continued in chronic HF patients, irrespective of COVID-19.
- Telemedicine should be considered whenever possible to provide medical advice and follow-up of ambulatory HF patients.

Prevention of SARS-CoV-2 infection

During the COVID-19 outbreak, patients with chronic HF should be advised to closely follow protective measures aimed at preventing disease transmission (e.g. self-isolation, social distancing, frequent hand washing, use of hand sanitisers, and wearing a face mask in public spaces). HF outpatients should avoid routine, non-urgent hospital visits. Implementing remote monitoring may be an alternative.

Diagnostic hints

Routine clinical methods, ECG (arrhythmias, myocardial injury, myocarditis), and chest X-ray (cardiomegaly, COVID-19 pneumonia) can provide a diagnostic clue. Due to the relatively low sensitivity of chest X-ray to detect COVID-19 pneumonia, patients with a high degree of clinical suspicion (tachypnoea, hypoxaemia), but with ambiguous chest X-ray findings, should be referred to chest CT,[61] which has high sensitivity and specificity to diagnose COVID-19-related pulmonary disease. Laboratory findings, such as increased erythrocyte sedimentation rate, fibrinogen and C-reactive protein, and lymphocytopenia, may suggest COVID-19 pneumonia. Transthoracic echocardiography is useful, not only to evaluate the pre-existing LV dysfunction in HF but also to assess patients suspected of having SARS-CoV-2-associated worsening cardiac function and/or myocarditis.[62] Prudent use of bedside point-of-care or transthoracic echocardiography should be considered when the result of an examination is expected to provide a diagnosis and modify therapy.

Chronic heart failure treatment

SARS-CoV-2 utilizes the angiotensin-converting enzyme-2 (ACE2) receptors for cell entry and some data indicate that ACEIs and ARBs may up-regulate ACE2,[63] thus hypothetically increasing susceptibility to the infection.

However, there is no clinical evidence of an association between ACEI/ARB treatment and the susceptibility to infection, or the clinical course. A recent study of 111 hospitalized patients with COVID-19 in France treated with ACEI/ARB for CV disorders (9% with HF) has demonstrated no association between exposure to ACEI/ARB and the rate of complications or mortality in a propensity score-adjusted analysis.[64] Similarly, in a cohort of 965 patients with COVID-19 from Spain (21.8% on ACEI/ARB), treatment with ACEI/ARB had a neutral effect on mortality (OR, 0.62; 95% CI, 0.17–2.26; $P = 0.486$), HF (OR,

1.37; 95% CI, 0.39–4.77; $P = 0.622$), and other complications.[44] Furthermore, available data do not support discontinuation of ACEI/ARB in HF patients with COVID-19, as this may increase the risk of death.[30] Hence, it could be recommended that HF patients continue all prescribed guideline-directed medications (including ACEI, ARB, or sacubitril/valsartan), irrespective of COVID-19.[65]

COVID-19 patients may become hypotensive due to dehydration, septic shock, and haemodynamic deterioration; hence adjustment of HF medication doses should be considered.

Chronic heart failure and outcomes in COVID-19

Worse clinical outcomes have been reported among COVID-19 patients with a history of chronic HF. Along with an older age, arrhythmias, dementia, ischaemic heart disease, diabetes, obesity, and hypertension, chronic HF has been associated with a higher risk of hospitalization [hazard ratio (HR), 1.6, 95% CI, 1.2–2.1] and mortality (HR, 2.3, 95% CI, 1.6–3.2) among 2653 COVID-19 patients in Italy.[66] Similarly, in 9148 COVID-19 patients from South Korea, a history of chronic HF conferred a 3.17 higher odds ratio (95% CI, 1.88–5.34) for mortality.[67] Among 692 patients admitted for COVID-19 in 13 Italian cardiology centres, a history of HF has been associated with an increased risk of death (adjusted HR, 2.25, 95% CI, 1.26–4.02), and in-hospital complications, including acute HF (33.3% vs. 5.1%, $P < 0.001$), acute renal failure (28.1% vs. 12.9%, $P < 0.001$), sepsis (18.4% vs. 8.9%, $P = 0.006$), and multiorgan failure (15.9% vs. 5.8%, $P = 0.004$). [35] In a cohort of 6439 hospitalized COVID-19 patients from the USA, a history of HF conferred a 3.66 higher odds ratio (95% CI, 2.56–5.16, $P < 0.001$) for mechanical ventilation and a 1.88 higher odds ratio (95% CI, 1.27–2.78, $P = 0.02$) for death, regardless of LV ejection fraction or the use of ACEI.[68]

Telemedicine and home drug delivery

Given the restraints to the usual care and high morbidity and mortality among HF patients contracting COVID-19, the more widespread use of telemedicine should be encouraged to minimize the risk of infection, and to ensure continuity of care and timely optimisation of medical treatment. Successful use of this technology has been reported in providing medical advice, treatment adjustment, and follow-up of ambulatory HF patients during the COVID-19 outbreak.[69,70] If feasible (and necessary), home delivery and mailing of standard HF drugs may be a viable option, if permitted by local regulations/laws.

Left ventricular assist device and heart transplantation

Key points

- Due to the nature of the device, left ventricular assist device (LVAD) patients have greater susceptibility to the infection, and strict preventive measure should be applied to avoid it.
- Owing to the state of iatrogenic immunosuppression, heart transplant recipients may be at a higher risk of severe COVID-19 disease or prolonged viral shedding; hence, tight adherence to preventive measures should be advised to avoid infection.
- Limited data suggest that heart transplant recipients may have a similar presentation as immunocompetent individuals and a favourable clinical course of COVID-19. However, variable clinical outcomes in solid organ recipients in earlier coronavirus outbreaks [SARS and Middle East respiratory syndrome (MERS)][71,72] suggest that hospitalization, close monitoring, and appropriate treatment of COVID-19 heart transplant patients should be recommended.

LVAD patients are fragile, and every measure should be used to prevent viral transmission. Cautious monitoring and management of anticoagulation therapy is advised because both COVID-19 and antiviral medications can affect anticoagulant dosing. If technically feasible, assessment of LVAD function by telemonitoring is preferable. General recommendations for all LVAD patients should also be applied, regardless of COVID-19.

Data on the susceptibility to infection and the clinical course of COVID-19 in heart transplant recipients are sparse. According to a systematic review of four studies (one from China[73] and three from the USA[74–76]) on COVID-19-positive heart transplant recipients ($n = 33$), the presenting symptoms were similar to those of immunocompetent individuals, including fever (81.8%), cough (94.8%), dyspnoea (75.8%), and gastrointestinal complaints (48.5%).[77] The majority of patients (81.8%) were hospitalized, while 24.2% required mechanical ventilation. The treatment included modification of maintenance immunosuppressive therapy (75.8%) and variable approaches with high-dose glucocorticoids, immunoglobulins, fluroquinolone antibiotics, tocilizumab, hydroxychloroquine, and antiviral medications. Of note, the overall mortality rate was 24.2%, while the recovered patients remained rejection free.[77] Yet another report of 87 heart transplant recipients from China indicated that high-degree adherence to preventive measures (see above) resulted in a low rate of infection and transition to manifest illness.[78]

Valvular heart disease

Key points

- Patients with VHD (particularly those with associated left or right ventricular impairment, or pulmonary hypertension) may be at particular risk during the COVID-19 pandemic
- Coordinated allocation of resources at hospital and regional level is essential to sustain ICU capacity
- Maintained function of the Heart Team is paramount, even if face-to-face meetings are not feasible.

VHD mainly affects the elderly and the symptoms of disease progression (mainly dyspnoea) may mimic those of lung infection or infiltration. In addition, VHD may aggravate the course of COVID-19 and complicate haemodynamic management of the systemic inflammatory response (cytokine storm),[79] ARDS, and any superimposed bacterial septicaemia (observed in up to one third of ICU patients).[40] In early COVID-19 case series, up to 40% of patients admitted to the ICU had pre-existing congestive HF.[32] Excess mortality was reported in patients with VHD who were contaminated with COVID-19. Among 136 elderly patients (mean age 80 years) with severe VHD [54% with aortic stenosis (AS)], 84.6% were treated conservatively and mortality at 30 days was as high as 41.8%.[80]

Elective surgical and transcatheter interventions for VHD consume significant healthcare resources and many, or all, depending on circumstances, may be inappropriate during the pandemic given the immense pressure on acute and intensive care facilities. During the first pandemic peak in England, a drastic reduction in valve surgery was observed, ranging from 73–76% for surgical aortic valve replacement (SAVR) to 84–85% for surgical mitral valve replacement. Transcatheter aortic valve implantation (TAVI) was less affected with a reduction of 35% and 18% during the months of April and May 2020, respectively.[81]

Patients with severe VHD must remain under close telephone surveillance and be encouraged to report progressive symptoms. Concentration of resources on the treatment of pandemic victims guides decisions with the overall aim of avoiding shortages of ICU beds and ventilators. Prioritization of valve interventions should therefore balance the immediate and short-term prognosis of individual patients against available resources and the risk to patients and HCP of acquiring in-hospital infection. In this respect, use of less-invasive procedures (particularly TAVI via transfemoral approach performed under conscious sedation and/or local anaesthesia), may present an opportunity to minimize the need for healthcare resources, including ICU and hospital stays. The need for clinical decision-making by Heart Teams remains of paramount importance and the use of telemedicine or other means of virtual communication is essential if face-to-face meetings are difficult, or impossible, during the acute phase of the pandemic.

Management of aortic stenosis

Key points

- Priority should be given to patients with syncope and HF, and those with high (or very high) transvalvular gradients and/or impaired LV function.
- Non-urgent procedures should be deferred based on objective criteria assessed by the Heart Team.
- Greater use of transfemoral TAVI (as judged appropriate by the Heart Team) may allow optimal utilization of healthcare resources.

The prognosis of patients with severe AS depends on several factors, including age, symptomatic status, peak aortic jet velocity/mean transvalvular gradient,[82,83] left ventricular ejection fraction, pulmonary hypertension,[84] and elevated biomarkers (natriuretic peptides or troponin).[85–87] Mortality of patients with severe symptomatic AS who are treated conservatively is high, reaching 50% at 1 year and 70–80% at 2 years.[88] Deferring SAVR or TAVI was associated with an increased risk of hospitalization for valve-related symptoms or worsening HF (19.6% within the first month).[89] In another study, 10% of patients awaiting an intervention died or required urgent TAVI.[90]

In the context of the COVID-19 pandemic, the Heart Team should undertake systematic individual risk assessment based on objective criteria that determine disease progression. Priority should be given to patients with syncope or HF [New York Heart Association (NYHA) Class III/IV], high or very high transvalvular gradients, and those with reduced LV function (See Guidance Part 1), whereas a watchful waiting strategy is more appropriate in those with minimal or no symptoms, provided close follow-up is organized using telemedicine and face-to-face consultation in case of worsening symptoms. TAVI (or balloon aortic valvuloplasty[91]) may be considered in haemodynamically unstable patients (COVID-19 positive/negative).[92] However, the potential benefits of valve intervention in a critically ill COVID-19-positive patient should be carefully weighed against the likelihood of futility given the >60% mortality of COVID-19-positive patients admitted to ICU.[93]

All cases should be discussed by the Heart Team and indications for TAVI extended to intermediate[94,95] and selected low-risk patients.[96,97] Increased use of transfemoral TAVI, when feasible, may allow optimal utilization of resources by avoiding general anaesthesia and intubation, shortening or preventing an ICU stay, and accelerating hospital discharge and recovery.[98]

Management of mitral regurgitation

Key points

- The majority of patients with mitral regurgitation (MR) is stable and surgical or transcatheter intervention can be deferred.
- Priority should be given to the treatment of patients with acute MR complicating, e.g. acute myocardial infarction (AMI) or infective endocarditis (IE), and those with severe symptomatic primary MR or secondary MR (SMR) that is not responsive to guideline-directed medical and device treatment and seems likely to require hospital admission. The choice of intervention should be guided by the Heart Team.

The management of MR differs according to its aetiology and presentation. Chronic primary MR (e.g. flail leaflet and Barlow disease) is usually stable and well tolerated. In contrast, SMR is a more variable entity and while many patients remain stable under guideline-directed medical and device treatment (including sacubitril/valsartan and cardiac resynchronization therapy when indicated),[99] others may develop unstable HF syndromes that are refractory to medical treatment, particularly in the context of acute infection.[100]

In the context of the COVID-19 pandemic, priority should be given to the treatment of patients with acute primary MR complicating, e.g. AMI or IE, and those with severe primary or SMR who remain symptomatic despite guideline-directed medical and device treatment and seem likely to require hospital admission. All other patients should be managed conservatively.[99–102]

Transcatheter mitral edge-to-edge repair may be considered in anatomically suitable high-risk or inoperable patients with acute MR (excluding those with IE) or highly selected patients with highly symptomatic (NYHA III–IV or congestive HF) primary MR or SMR refractory to guideline-directed medical and device treatment. Despite a low risk of complications requiring ICU admission,[103] the procedure requires general anaesthesia (in distinction to transfemoral TAVI) and prolonged transoesophageal echocardiographic guidance, thereby exposing echocardiographers and anaesthetists to the risk of COVID-19 transmission. Use of temporary circulatory support (intra-aortic balloon pump or Impella) should be restricted to patients with a good prospect of recovery in the context of available ICU resources.

Hypertension

Key points

- The early reports of an association between hypertension and risk of severe complications or death from COVID-19 were confounded by the lack of adjustment for age and high-risk comorbidities such as obesity and diabetes that commonly co-segregate with hypertension. There is currently no evidence to suggest that hypertension, per se, is an independent risk factor for severe complications or death from COVID-19.
- Despite much early speculation of a link between use of ACEIs or ARBs and increased risk from COVID-19, evidence from a series of observational cohort studies from across the world published in major journals has shown that prior or current treatment with ACEIs or ARBs does not increase the risk of COVID-19, or the risk of developing severe complications or death from COVID-19, when compared to the risk in patients taking other antihypertensive drugs.
- Two randomized controlled trials have been published (REPLACE COVID) (BRACE-CORONA), both addressing whether ACEIs or ARBS should be continued or withdrawn in patients admitted to hospital with COVID-19. In both studies, there was no difference in major outcomes from COVID-19 whether or not the patients were randomized to continue or discontinue their treatment with ACEIs or ARBs.
- Treatment of hypertension should follow existing recommendations in the ESC-European Society of Hypertension (ESH) Guidelines. No change to these treatment recommendations is necessary during the COVID-19 pandemic.
- Self-isolated patients with treated hypertension should not need to attend hospital for routine review visits during this pandemic. Patients could make use of periodic home blood pressure (BP) monitoring, with videoconference or phone consultations only if needed (*Figure 4*).
- Hypertensive patients may be at increased risk of cardiac arrhythmias due to underlying cardiac disease, or the reported higher frequency of hypokalaemia in patients with severe COVID-19.
- Antihypertensive therapy may need to be temporarily withdrawn in acutely ill patients in hospital who develop hypotension or acute kidney injury secondary to severe COVID-19.
- In patients previously treated for hypertension who require invasive ventilation, parenteral antihypertensive medication is only indicated for those developing persistent severe hypertension.

Hypertension and COVID-19

Initial reports from China noted that hypertension was one of the most common co-morbidities (20–30% of cases) associated with the need for ventilatory support due to severe respiratory complications of COVID-19.[40,41,104–106] These analyses did not adjust for age, which is important because hypertension is very common in older people (~50% in people over 60 are hypertensive) and hypertension prevalence increases sharply in the very old. Older age is by far the most important risk factor for severe complications and death due to COVID-19; thus, a high frequency of hypertension would be expected in older patients with severe infection. Moreover, obesity and diabetes are significant risk factors for poorer outcomes in patients with COVID-19 and hypertension commonly co-segregates with these comorbidities. New evidence from a very large study involving over 20 million people and 10 000 COVID-19 deaths showed no independent association between hypertension and risk of death from COVID-19.[107]

It now seems likely that the reported association between hypertension and risk of severe complications or death from COVID-19 is substantially confounded by the lack of adjustment for age and other unmeasured confounders.[108] There is currently no evidence to suggest that hypertension, per se, is an independent risk factor for severe complications or death from COVID-19.

Antihypertensive treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

Renin–angiotensin system (RAS) blockade with ACEIs or ARBs is the foundation of antihypertensive therapy in the current ESC–ESH Guidelines for the management of arterial hypertension (2018).[109] The recommended treatment of hypertension for most patients is a combination of an ACEI or ARB with a calcium channel blocker (CCB) or thiazide/thiazide-like diuretic.[109]

Early in the pandemic, concern had been expressed that treatment with ACEIs or ARBs might increase the risk of infection, or of developing the severe consequences of infection with COVID-19.[110–112] This concern originated from a hypothesis linking the observations that COVID-19 invades cells by binding to the enzyme ACE2, which is ubiquitous and expressed on the surface of alveolar cells in the lung.[113–115] In some animal studies, but not all, ACEIs or ARBs have been shown to increase ACE2 levels, mainly in cardiac tissue.[116–118]

There are no studies showing that RAS-blocking drugs increase ACE2 levels in human tissues and no studies in animals or humans showing that RAS-blocking drugs increase ACE2 levels in the lung, or that the level of ACE2 expression in the lung is rate limiting for COVID-19. A recent study of human tissues indicates that neither hypertension nor antihypertensive treatment (including ACEI or ARBs) altered the expression of ACE2 in the human kidney but did show that ACE2 expression was increased in both lungs and kidneys with ageing, which may be relevant to the striking increased risk of Covid-19 with ageing in SARS-CoV-2 infection.[119]

Series of observational cohort studies have been published in major journals which consistently show that treatment with RAS blockers does not increase the risk of COVID-19 or increase the risk of severe complications or death from COVID-19.[120–125] In one study, there was even a substantial reduction in the risk of severe complications or death from COVID-19 in patients with diabetes mellitus.[121]

Two randomized controlled trials addressing concerns about ACEI and ARBs in patients hospitalized with COVID-19 have now been published. The first study (BRACE CORONA) showed that in 659 patients from 29 sites in Brazil admitted to hospital with COVID-19 and currently treated with ACEIs or ARBs, there was no difference in outcomes (days alive and out of hospital at 30 days), whether or not the patients were randomized to continue or discontinue their treatment with ACEIs or ARBs.[126] In the second randomized controlled trial (REPLACE COVID), 152 participants were randomly

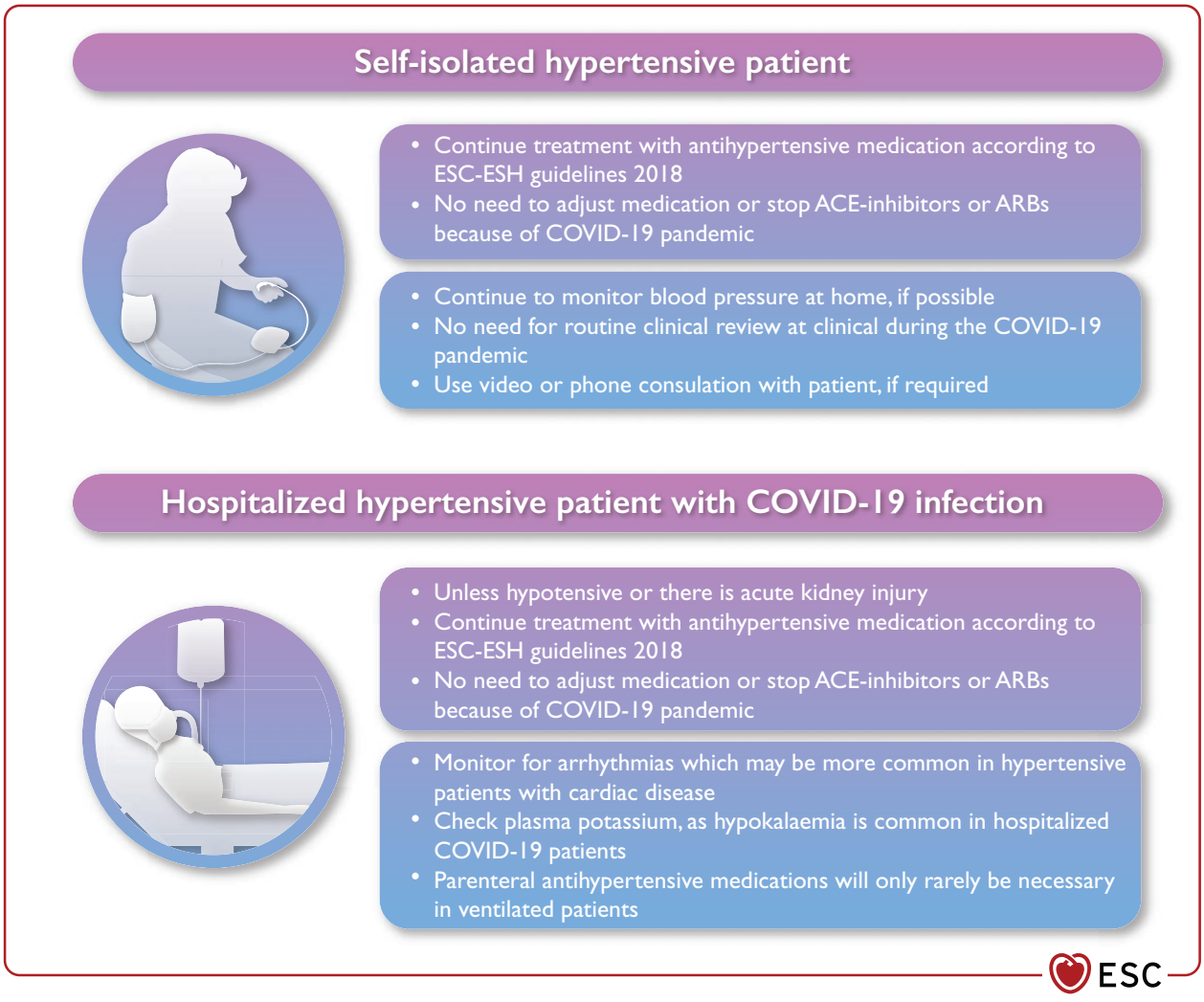


Figure 4 Hypertension management in the COVID-19 context. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COVID-19, coronavirus disease 2019.

assigned to either continue or discontinue renin–angiotensin system inhibitor therapy and, irrespective of randomized group, there was no difference in a global rank score of major outcomes.[127]

This series of large-scale observational studies and the first randomized controlled trials provide a consistent message and re-assurance to patients and their doctors that the prior speculation about the safety of RAS blockers in the context of COVID-19 has not been proven.[128]

Indeed, studies in animal models of infection with influenza or coronaviruses have suggested that ACE2 is important in protecting the lung against severe injury and that RAS-blocking drugs are also protective against severe lung injury due to these viruses.[129–131] Human studies of RAS blockade or recombinant ACE2 to prevent respiratory decompensation in COVID-19-infected patients have been suggested, planned, or are ongoing.[132,133]

In summary, there is currently no evidence to suggest that ACEIs or ARBs increase the risk associated with COVID-19 and there is no reason why these drugs should be discontinued due to concern about COVID-19. Treatment of hypertension, when indicated, should continue to follow the existing ESC–ESH guideline recommendations.[134]

Remote management of hypertension in the patient isolated at home

Most patients with hypertension require only infrequent visits to the clinic to manage their hypertension. Many patients with treated hypertension will be in self isolation to reduce the risk of COVID-19 and unable to attend their usual routine clinical review. When possible, patients should monitor their own BP as frequently as they usually would, using a validated home BP monitor.[109]

Videoconference or telephone consultation with patients, when required, may facilitate urgent physician follow-up until normal clinic attendance resumes.

Hypertension and the hospitalized patient with COVID-19

Most patients who are hospitalized will have more severe infection and be hospitalized for respiratory support. They are likely to be older with comorbidities, such as hypertension, diabetes, and chronic kidney disease. Patients with severe disease may also develop multi-organ complications in severe disease.

Hypertensive patients may also have LV hypertrophy or heart disease and be at increased risk of developing arrhythmias, particularly when hypoxic.[135] Plasma potassium levels should be monitored because arrhythmias may be exacerbated by the frequent occurrence of low plasma potassium levels, which appears to be more prominent in hospitalized COVID-19-infected patients with more severe disease.[136] This is thought to be due to increased urinary loss of potassium, which may be exacerbated by diuretic therapy.

If patients are acutely unwell and become hypotensive or develop acute kidney injury due to their severe disease, antihypertensive therapy may need to be withdrawn. Conversely, parenteral antihypertensive drugs are rarely needed for hypertensive patients who are ventilated and have sustained any significant increases in BP after withdrawal of their usual treatment (i.e. grade 2 hypertension, BP >160/100 mmHg), but the objective in these acute situations is to maintain BP below these levels and not aim for optimal BP control.

Acute pulmonary embolism—prevention and diagnosis

Key points

- Prescribe anticoagulation at standard prophylactic doses in all patients admitted with COVID-19.
- Consider the presence of acute pulmonary embolism (PE) in patients with COVID-19 in the setting of unexpected respiratory worsening, new/unexplained tachycardia, a fall in BP not attributable to tachyarrhythmia, hypovolaemia or sepsis, (new-onset) ECG changes suggestive of PE, and signs of deep vein thrombosis of the extremities.
- When acute PE is confirmed, treatment should be guided by risk stratification in accordance with the current ESC guidelines.

Observational studies in China, Europe, and the USA have reported a high incidence of thrombotic and thromboembolic complications in patients with COVID-19 pneumonia.[137–143] The wide range of described incidence rates is mostly caused by detection bias with variable thresholds for diagnostic testing and, occasionally, limited availability of radiological tests. Most of the studies have demonstrated that acute PE is the most frequent thrombotic complication.[137–143] It is debateable whether the contrast-filling defects seen on computed tomography pulmonary angiography represent 'conventional' venous thromboembolism (VTE), or if they are induced by in situ immunothrombosis involving, among others, neutrophil extracellular traps.[144–146] Likely, VTE and immunothrombosis both contribute to the high incidence of PE in severe COVID-19 pneumonia. Therefore, in view of COVID-19-associated local and systemic inflammation, coagulation activation, hypoxaemia, and immobilization, anticoagulation at standard prophylactic doses should be considered for all patients admitted to the hospital with COVID-19. It has been argued that more intensive anticoagulation [such as low molecular weight heparin (LMWH) at intermediate dose or even full therapeutic-dose anticoagulation] may be indicated in critically ill patients with COVID-19 pneumonia, but such a practice is not supported by current evidence. In fact, it remains unknown whether bleeding rates on more intensive anticoagulation can be acceptably low, or if they outweigh the potential prevention of more thrombotic complications. Of note, patients with COVID-19 pneumonia have been shown to develop acute PE even when they were on full-dose anticoagulation.[137–143]

Patients with COVID-19 often present with respiratory symptoms and may also report chest pain and haemoptysis.[104] These symptoms largely overlap with the presentation of acute PE, and this fact may result in underdiagnosis of this relevant complication.[147] Unexpected respiratory worsening, new/unexplained tachycardia, a fall in BP not attributable to tachyarrhythmia, hypovolaemia, or sepsis (new-onset), ECG changes suggestive of PE, and signs of deep vein thrombosis of the extremities should trigger a suspicion of PE. It is recommended to order diagnostic tests for PE only when it is clinically suspected, although the threshold of suspicion should be kept low. The specificity of D-dimer tests may be lower in patients with COVID-19 compared to other clinical settings. Even so, it is still advised to follow diagnostic algorithms starting with pre-test probability and D-dimer testing, especially when pre-test probability-dependent D-dimer thresholds are being used.[148–150] This may help to rationalize the deployment of resources and personnel for transporting a patient to the radiology department with all the associated isolation precautions. In the clinical scenario of a patient with COVID who has just undergone computed tomography (CT) of the lungs but the findings cannot explain the severity of respiratory failure, CT pulmonary angiography should be considered before leaving the radiology department.

When acute PE is confirmed, treatment should be guided by risk stratification in accordance with the current ESC guidelines.[151] Patients in shock should receive immediate reperfusion therapy. Haemodynamically stable patients should be treated with unfractionated heparin (UFH), LMWH, or a non-vitamin K antagonist oral anticoagulant (NOAC), depending on the feasibility of oral treatment, renal function, and other circumstances. When choosing the appropriate drug and regimen (parenteral vs. oral) for initial, in-hospital anticoagulation, the possibility of rapid cardiorespiratory or renal deterioration due to COVID-19 should be taken into account. Acute renal deterioration or failure precludes continuation of (the same dose of) NOACs and should therefore be closely monitored. Because of the need for anticoagulation monitoring, which may contribute to spreading of the infection, vitamin K antagonists should only be considered in special clinical settings, such as the presence of mechanical prosthetic valves or the antiphospholipid syndrome.[151] Of note, several studies have described a high prevalence of antiphospholipid antibodies in patients with COVID-19.[152–154] The clinical relevance and implications of this finding are, at present, unknown. Antiphospholipid antibodies are common during infections. Whether the type and titre of the antiphospholipid antibodies described in COVID-19 patients, i.e. IgA isotype alone and low titres, may provoke thrombotic complications remains controversial. Based on current evidence, routine screening for antiphospholipid antibodies in

patients with COVID-19 cannot be recommended. However, if triple positivity for antiphospholipid antibodies is demonstrated, i.e. lupus anticoagulant, positive anti-beta-2-glycoprotein antibodies, and positive anti-cardiolipin antibodies, in patients with proven venous or arterial thrombosis, NOACs should be avoided.

Arrhythmias

Key points

- For monitoring and follow-up of patients with cardiac implantable devices, remote monitoring should be utilized as much as possible.
- When healthcare resources are scarce, elective ablation and cardiac device implantation procedures should be postponed and urgent procedures should only be performed after careful consideration of all pharmacological treatment options.
- In hospitalized patients with COVID-19, arrhythmias, especially new-onset or recurrent atrial fibrillation (AF) and atrial flutter (AFL), occur frequently. Occurrence of significant arrhythmias is a marker of COVID-19 severity and is associated with higher mortality.
- When treating arrhythmias, drug–drug interactions, including antiviral, antiarrhythmic, and anticoagulation therapies, should be considered before co-administration.
- In critically ill patients with hemodynamic instability due to recurrent ventricular tachycardia (VT)/ventricular fibrillation (VF) or AF/AFL, intravenous (i.v.) amiodarone is the choice for antiarrhythmic medication.
- Therapy of TdP VT consists of withdrawal of all QT prolonging drugs, targeting $K+ \geq 4.5$ mEq/L, i.v. magnesium supplementation and increasing heart rate (by withdrawing bradycardic agents and if needed by i.v. isoproterenol or temporary pacing); i.v. lidocaine or oral mexiletine may be considered for the treatment of refractory cases based on limited clinical data.
- New-onset primary malignant ventricular arrhythmia and sudden arrhythmic death seem to be relatively rare in COVID-19. In critically ill patients, malignant ventricular arrhythmias are a marker of disease severity and occur more frequently, especially in the terminal phase of the disease.
- New-onset malignant ventricular tachyarrhythmia or severe bradyarrhythmia not explained by end-stage respiratory failure may be a marker of acute myocardial injury and should trigger diagnostic cardiac evaluation. Ischaemia and hypoxaemia should be excluded, and inflammation and cardiac biomarkers should be followed. Echocardiography should be considered to assess ventricular function and myocardial involvement. In case myocarditis is suspected, magnetic resonance imaging (MRI) may be considered (see Guidance Part 1), as the diagnosis may warrant more aggressive immunosuppressive and antiviral treatment.
- After recovery from the COVID-19, in AF/AFL the therapeutic choices of rate and rhythm control should be re-assessed, and long-term anticoagulation should be continued based on the CHA_2DS_2-VASc score. The need for permanent pacing in bradycardia and for catheter ablation, secondary prophylactic implantable cardiac defibrillator (ICD) or wearable defibrillator in ventricular tachyarrhythmia needs to be re-evaluated.

The general principles of management of patients with cardiac arrhythmias and cardiac implantable devices during the COVID-19 pandemic are based on:

- Continuing to provide emergency high-quality care safely to all patients with life-threatening cardiac arrhythmias and implantable devices.
- Preserving healthcare resources to allow the appropriate treatment of all patients with COVID-19.
- Minimizing the risk of nosocomial infection of non-infected patients and healthcare workers.

Several national and international societies and health services including the Heart Rhythm Society, National Health Service (UK) and the Cardiac Society of Australia and New Zealand have issued similar local recommendations to achieve these goals and guide the management of patients with cardiac arrhythmias and cardiac implantable devices during the COVID-19 pandemic.[155–158]

Monitoring and follow-up of patients with cardiac implantable devices

Transition to remote interrogation (patient-initiated or automatic prescheduled transmissions) or remote monitoring (i.e. automatic daily or alert-triggered transmissions) of cardiac implantable electronic devices (CIEDs) during the COVID-19 pandemic was proven feasible in a small single-centre Italian study[159] and has been reviewed in detail in a recent worldwide document.[158]

- Remote interrogation and monitoring should be utilized as much as possible to replace routine device interrogation visits to hospitals, clinics and practices. In-person office visits should be replaced by remote contact by telephone or internet by the treating physician, using the device information obtained through remote interrogation or monitoring.
- For patients who are followed already through remote interrogation/monitoring, deferring in-office evaluation is usually possible. This may have psychological implications, as patients may feel that a delay of their regular check-up may prejudice the integrity of their device. Reassurance on these issues therefore is important when patients are called to postpone their visit.
- For patients not already followed via remote interrogation/monitoring, activation requires registering the transmitter, obtaining consent from the patient, and activating the feature in some cases. Initiating remote interrogation/monitoring without the patient coming to the office or hospital may be an option for Boston Scientific and Abbott devices [pacemaker (PM) and ICD] and for newer Medtronic devices using BlueSync, since remote monitoring is programmed ON as default on these CIEDs. Legacy Medtronic devices can be initiated at home by the patient for remote interrogation, but alert-based monitoring of non-BlueSync Medtronic ICDs requires an in-office programming ON. Also, for Biotronik CIEDs, remote monitoring needs an in-office programming ON of the CIED, unless that has been done at the time of implant, as is customary in some countries and centres. When the CIED is ready, for all manufacturers the patient only needs to plug in the transmitter device at home, which then activates automatically (Biotronik; Abbott) after a single push of a button (Boston Scientific or BlueSync Medtronic), or after a series of actions with a removable wand (legacy Medtronic) that can be guided over the phone. Manufacturers point to the restrictions by privacy

regulation (like General Data Protection Regulation) to directly send transmitters to the patient's home and should provide devices to the hospital from where they may be shipped to the patient.
- Remote interrogation/monitoring may require hospital re-organization, which can preclude large-scale transitioning from an outpatient setting to a telemetry-based model during hectic COVID-19 times when hospital operations are already stretched.
- Device patients for whom a scheduled in-office visit needs to be postponed can also be reassured that major alterations of device integrity will be signalled by an auditory alarm. Patients should be instructed to contact their centre if they notice such an alarm.
- Patients without new symptoms or alarms should be rescheduled for device follow-up after the pandemic.
- Urgent in-hospital or ambulatory device interrogations may be needed for patients with suspected new and severe lead dysfunction; battery depletion, especially in PM-dependent patients; malignant arrhythmia detection; appropriate or inappropriate ICD therapy delivery if this cannot be sufficiently managed by remote interrogation/monitoring.
- All patients should be screened for symptoms or exposure to confirmed COVID-19 prior to admission:
  - In patients without suspected or confirmed COVID-19
    - Preferably, interrogation should use wireless communication to minimize direct contact while maintaining a safe distance and using appropriate personal protective equipment (PPE).
    - Interrogation should be performed in separate designated non-infected areas (see Supplementary material online, *Section 1*).
  - In patients with suspected or confirmed COVID-19: Local hospital protocols for the use of a dedicated single set of programmers with appropriate storage in designated areas, cleaning before and after use, single use wand protection and the use of appropriate PPE (see Supplementary material online, *Section 1*) are recommended. Preferably, interrogation should use wireless communication, obviating direct contact.

Considerations for electrophysiological and implantable device procedures

The categorization of electrophysiology procedures in the context of COVID-19 is depicted in *Table 3*.

Management of cardiac arrhythmias in patients with COVID-19

The incidence and type of cardiac arrhythmias in patients with COVID-19 depends on the patient population studied, the intensity of monitoring, the definition of arrhythmias, and the length of follow-up. In an initial single-centre retrospective study including 138 hospitalized patients in Wuhan, China, cardiac arrhythmias occurred in 16.7% of patients. Arrhythmias occurred more frequently in patients who were transferred to the ICU (44% vs. 6.9%, $P < 0.001$, respectively).[41] However, the type and duration of arrhythmias were not specified in this report. In a more recent large study of 1053 hospitalized patients followed for a median of 7 days on telemetry, arrhythmia was reported in 25.6% of patients.[160] AF was the most frequent arrhythmia occurring in 15.8% of patients, with 9.6% being newly diagnosed, followed by frequent premature ventricular contractions in 13%, VT or VF in 2.6% (1.9% sustained VT or VF), and atrioventricular (AV) block in 0.4% of the patients. Age, male sex, and hypoxia on presentation were independently associated with occurrence of arrhythmias. The presence of arrhythmias correlated with disease severity, elevated markers of myocardial injury, inflammation, and fibrinolysis and was independently associated with 30-day mortality. Very similar results were recently reported in a large multicentre Italian study with 21.7% incidence of sustained tachyarrhythmias in 414 hospitalized patients.[161] Based on these studies, it seems that tachyarrhythmias are a marker of COVID-19 severity occurring more frequently in patients with more severe disease and are associated with higher mortality.

In general, the acute treatment of arrhythmias should not be significantly different from their management in non-COVID-19 patients and should be in line with the current ESC, European Heart Rhythm Association and related guidelines.[162–168]

Tachyarrhythmias

Supraventricular tachycardia. In an Italian multicentre study of 414 hospitalized patients, the incidence of non-AF/AFL type of supraventricular tachycardia (SVT) was 1.2%.[161] In theory, exacerbation of known SVT or new-onset SVT may occur in patients with COVID-19. Special considerations during the COVID-19 pandemic are necessary in a resource-constrained environment considering the transient unavailability of catheter ablation procedures for definitive treatment, the risk of nosocomial infection during repeated ED visits, and the possibility of therapy interactions with antiarrhythmic drugs (AADs) (see Section Treatment of severe acute respiratory syndrome coronavirus 2 infection).

- Intravenous adenosine can probably be used safely for acute termination, but confirmatory data are lacking
- Maintenance therapy with beta-blockers (or CCBs if beta-blockers are contraindicated) should be initiated with a low threshold. Drug interaction with antiviral drugs should be evaluated, including the avoidance of bradycardia to avoid excessive QT prolongation (see the Treatment of severe acute respiratory syndrome coronavirus 2 infection)
- After the COVID-19 pandemic, the indication for catheter ablation should be reassessed.

Atrial fibrillation and flutter. AF/AFL occur in ~15–20% of patients hospitalized with COVID-19.[160,161,169–173] New-onset AF occurs in around 10% of the patients, accounting for up to 60% of COVID-19 patients with AF.[169,171,172] The incidence of AF is higher, reaching up to 40% in critically ill COVID-19 patients.[169,171–173] Specific precipitating factors in this setting are hypokalaemia and hypomagnesemia (induced by nausea, anorexia, diarrhoea, and medications), metabolic acidosis, the use of inotropic agents (especially dobutamine and dopamine), ventilator dyssynchrony, volume overload, increased sympathetic tone, inflammation, hypoxia, ischaemia, bacterial superinfection, and acute myocardial injury.[162] Age, male sex, prior AF, renal disease, and hypoxia on presentation have been independently associated with the occurrence of AF.[172] The incidence of AF in COVID-19 is similar to other aetiologies of severe pneumonia, ARDS, and sepsis. Reportedly, 23–33% of critically ill patients with sepsis or ARDS have AF recurrence and 10% develop new-onset

Table 3 Categorization of electrophysiological procedures in the context of COVID-19

	Urgent (perform within days)	Lower priority (perform within <3 months)	Elective (may be postponed ≥3 months)	Personal protection level
Catheter ablation	• VT/VF ablation for electrical storm • AF or A flutter ablation for AF/A flutter causing tachycardiomyopathy or syncope • WPW syndrome with fast preexcited AF and or syncope and/or cardiac arrest	• VT ablation for medically refractory recurrent VT • AF/A flutter ablation for medically refractory AF/A flutter with repeated ER visits • Medically refractory SVT with repeated ER visits	• PVC ablation • PSVT ablation • AF/A flutter ablation • EP testing	II/III
Cardiac implantable electronic device	• Urgent PM implantation for symptomatic high-degree AV block or sinus node dysfunction with long asystolic pauses • Urgent secondary prevention ICD implantation for cardiac arrest or VT • ICD/PM battery replacement for imminent or actual EOL in PM-dependent patients • Lead revision for symptomatic malfunction • Lead extraction for infection	• ICD/PM battery replacement for ERI • Primary prevention ICD in very high-risk or life-threatening ventricular arrhythmias	• Primary prevention ICD • CRT implantation • CIED upgrade • Lead extraction in patient without infection • Lead revision for asymptomatic malfunction	II/III
Cardioversion/other EP procedures	• Highly symptomatic medically refractory new onset of AF/A flutter	• Symptomatic medically refractory AF/A flutter	• LAA closure • ILR implantation • Tilt table testing • Ambulatory rhythm monitoring	II/III

A, atrial; AF, atrial fibrillation; AV, atrioventricular; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; EOL, end of life; EP, electrophysiology; ER, emergency room; ERI, elective replacement indicator; ICD, implantable cardioverter–defibrillator; ILR, implantable loop recorder; LAA, left atrial appendage; PM, pacemaker; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff–Parkinson–White syndrome.

AF.[162,174–176] New-onset AF in sepsis and ARDS has been associated with higher short- and long-term mortality, very high long-term recurrence rate, and increased risk of HF and stroke.[162,174–176] Similarly, in COVID-19, AF has been independently associated in one large US study with significantly higher 30-day mortality (39.2% compared to 13.4% of patients without AF, $P < 0.001$).[172] In this study, 6% of patients with AF/AFL experienced stroke or TIA during their hospitalization, 20% of them while under therapeutic anticoagulation.[172] Long-term AF recurrence rate, HF, and mortality risks following recovery from COVID-19 and AF are unknown but are expected to be significant.

As in all patients with AF, treatment goals have to consider ventricular rate control, rhythm control, and thromboembolic prophylaxis. Specifically, in the context of COVID-19, the following considerations should be made (*Figure 5*):

- In patients with haemodynamic instability due to new-onset AF and AFL, electrical cardioversion should be considered. This, however, needs to be balanced vs. the need for more equipment and personnel at the side of the patient, and the possible need for intubation (with the risk of increased viral aerosol creation).
- In critically ill patients with haemodynamic instability due to new-onset AF/AFL, IV amiodarone is the choice for antiarrhythmic medication for rate and rhythm control. Its combination with hydroxychloroquine and/or azithromycin should be avoided, preferably (see Section Treatment of SARS-CoV-2 infection). Amiodarone may also interfere with cellular SARS-CoV-2 entry and amplification and is being investigated in a study as a candidate antiviral drug in the early stage of the disease.[177]
- In patients with severe acute respiratory insufficiency, cardioversion is unlikely to provide sustained benefit without concomitant intensified treatment of the underlying hypoxaemia, inflammation, and other reversible triggers, such as hypokalaemia and hypomagnesaemia, metabolic acidosis, catecholamine infusion, volume overload, increased sympathetic tone, and bacterial superinfection. In these patients, calcium antagonists may be preferred to beta-

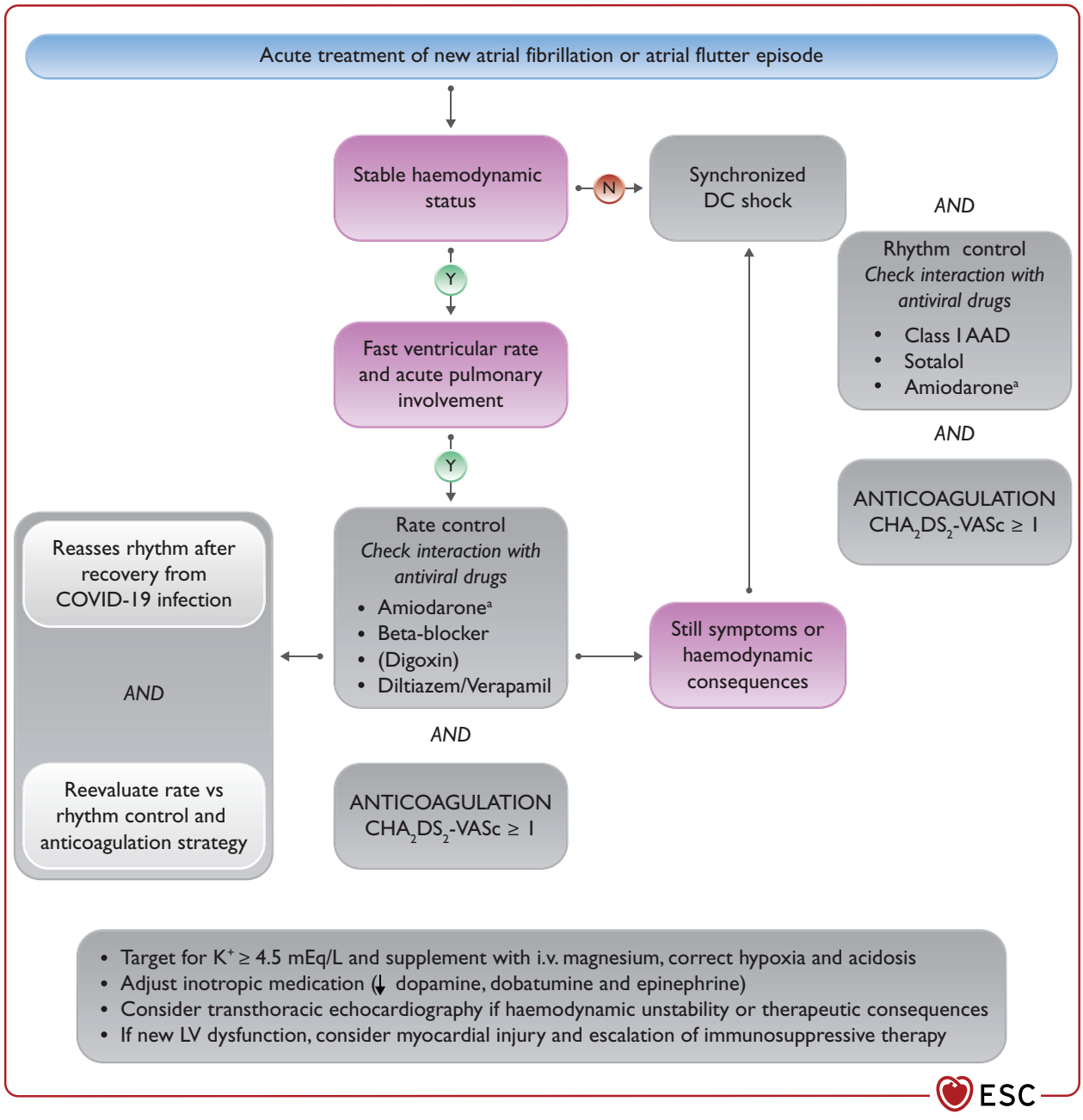


Figure 5 Atrial tachyarrhythmias. CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category (female); COVID-19, coronavirus disease 2019; DC, direct current. [a]The benefit of intravenous amiodarone treatment should be balanced against the proarrhythmic risk in patients taking QT-prolonging antiviral therapy.

blockers for rate control to avoid further worsening of the pulmonary status.

- In hospitalized patients with new-onset AFL, rate control may be more challenging than AF. If the patient remains symptomatic or there are haemodynamic consequences, electrical cardioversion may be considered.
- Anticoagulation for the prevention of AF-related stroke or systemic embolism should be guided by the CHA_2DS_2-VASc score. In spite of the thrombophilic environment in COVID-19, there is currently insufficient evidence to recommend a different anticoagulation scheme for patients with or without AF. Therapeutic anticoagulation should be considered in male and female patients with CHA_2DS_2-VASc score ≥1 and ≥2, respectively, and is indicated in male and female patients with CHA_2DS_2-VASc score ≥2 and ≥3, respectively.
- The need for an echocardiogram should be balanced against the need for close contact between HCP and patient, and contamination of equipment. Only when considered mandatory for

immediate therapeutic management, it can be used to assess LV function and pericardial and myocardial involvement. Transthoracic echocardiogram/echocardiography (TTE) is in general preferred to transoesophageal echocardiography (TOE) to avoid aerosol generation. If possible, TTE should be deferred until after convalescence.
- Similarly, TOE should be obviated by early start of anticoagulation in new-onset AF and in patients with a low CHA_2DS_2-VASc score to allow safe electrical cardioversion, also ≥48 h.
- Drug–drug interactions including antiviral, antiarrhythmic, and anticoagulation drugs should be considered before administration (see Section Treatment of SARS-CoV-2 infection).
- After recovery from the COVID-19, the therapeutic choices of rate and rhythm control should be re-assessed, and long-term anticoagulation should be continued based on the CHA_2DS_2-VASc score.

Ventricular arrhythmias. An initial single-centre retrospective study from Wuhan analysed the occurrence and significance of malignant ventricular arrythmias in 187 hospitalized patients with COVID-19. Among the 187 patients, 28% of patients had elevated troponin T levels and 23% died. During hospitalization, malignant ventricular arrhythmias (defined as sustained VT or VF) occurred in 5.9% of patients. VT/VF occurred more frequently in patients with elevated troponin levels (17.3% vs. 1.5%, $P < 0.001$).[178] In two more recent larger studies, the reported incidence of sustained ventricular arrhythmias in hospitalized patients was lower at 1.9% and 3.4%, respectively.[160,161] An anecdotal case series described critically ill patients with ARDS in the setting of severe COVID-19 dying of refractory ventricular arrhythmias despite normal baseline cardiac function.[179] In a recent study of 140 hospitalized patients reaching final disposition of discharge or death in New York, acute malignant cardiac arrhythmia defined as VT/VF or AV block with hemodynamic instability or cardiac arrest occurred in 9% of the study population; 5% had malignant VT/VF; and 3.5% AV block. Patients who died had higher troponin levels and, more frequently, acute malignant arrhythmia with a difference driven by ventricular tachyarrhythmias (17% as compared to 4% of patients who were discharged, $P = 0.01$). Fatal ventricular tachyarrhythmias invariably occurred in the presence of severe metabolic imbalance and hypoxia. Only 12% of all deaths were classified as CV death, and most (67%) of these deaths occurred in the setting of ST-elevation myocardial infarction.[180] In a similar study, also from New York, the last documented rhythm and circumstances of death were analysed in 133 patients who died during the index hospitalizations with COVID-19. Suspected or confirmed arrhythmic death occurred in only 8.3% of the study population and was associated with younger age, ventricular ectopy, mechanical ventilation, vasopressor use, longer QTc and LBBB on admission.[181] It should be noted that in all the above-mentioned studies, between 11% and 100% of the patients received hydroxychloroquine and in up to 100% of the patients in combination with azithromycin.[160,179–181]

In summary, recent studies suggest that sudden cardiac death (SCD) due to primary ventricular arrhythmia is infrequent in hospitalized patients with COVID-19. The incidence of primary malignant ventricular arrhythmias in asymptomatic or mildly symptomatic non-hospitalized patients with COVID-19 is currently unknown but is likely low. In these rare cases, malignant ventricular arrhythmia may occur in the setting of underlying myocardial infarction, pulmonary embolism, stress cardiomyopathy, or acute myocarditis. In contrast, in critically ill patients, malignant ventricular arrhythmias are a marker of disease severity and occur more frequently in the terminal phase of the disease, similar to the high incidence of ventricular arrhythmias in other aetiology ARDS and critical illnesses.[182] In patients with a history of CVD and ventricular arrhythmias, exacerbation of the known VT/VF may occur due to COVID-19 as the trigger. Although reports are not yet available for COVID-19, a correlation between influenza epidemic and increased appropriate ICD therapies has been shown.[183]

Special considerations for the treatment of ventricular arrhythmias during the COVID-19 pandemic are depicted in *Figure 6* and summarized below:

- In unresponsive, unbreathing patients, the local Basic and Advanced Life Support protocol should be followed. During basic life support, ventilation is not performed, only cardiac compressions, to avoid the risk of ingestion of aerosols. For Advanced Life Support, only HCP with full PPE are eligible to perform intubation
- In patients with VF, asynchronous defibrillation, and in patients with haemodynamically unstable VT, synchronized electrical cardioversion should be performed;
- In patients with sustained monomorphic VT:
  - Electrical cardioversion should be considered, especially if the patient is already ventilated.
  - Intravenous procainamide (if available and with follow-up of QT interval changes) or lidocaine could be considered in patients taking QT prolonging combination antiviral drugs and if the haemodynamic status permits.
  - Intravenous amiodarone should be considered in patients with known structural heart disease and impaired LV function. Its action is slow for conversion of VT. Its combination with antiviral drugs should be checked (see Section Treatment of severe acute respiratory syndrome coronavirus 2 infection).
  - In critically ill patients with COVID-19 and recurrent sustained VT and recurrent VF ('VT storm'), i.v. amiodarone is the antiarrhythmic medication of choice, though, its combination with antiviral drugs should be checked (see Section Treatment of SARS-CoV-2 infection).
- Intravenous lidocaine may be considered as a safer but less effective alternative to amiodarone, especially if underlying myocardial ischaemia is suspected:
  - Addition of sympathetic blockade (e.g. esmolol) should be considered.
  - Intubation, sedation and ventilation may be considered to abort VT storm.
  - Temporary PM implantation for overdrive termination may be considered, balancing the possible therapeutic benefit against the invasiveness of the lead placement with risk for personnel. In the absence of a functional cardiac catheterization laboratory, floatation-guided temporary wire insertion may be considered in case of emergency.
- In patients with severe acute respiratory insufficiency, correction of underlying reversible triggers should be considered, such as hypoxia, hypovolaemia, electrolyte abnormalities as hypokalaemia and hypomagnesaemia, metabolic acidosis, catecholamine infusions, volume overload, increased sympathetic tone, tamponade,

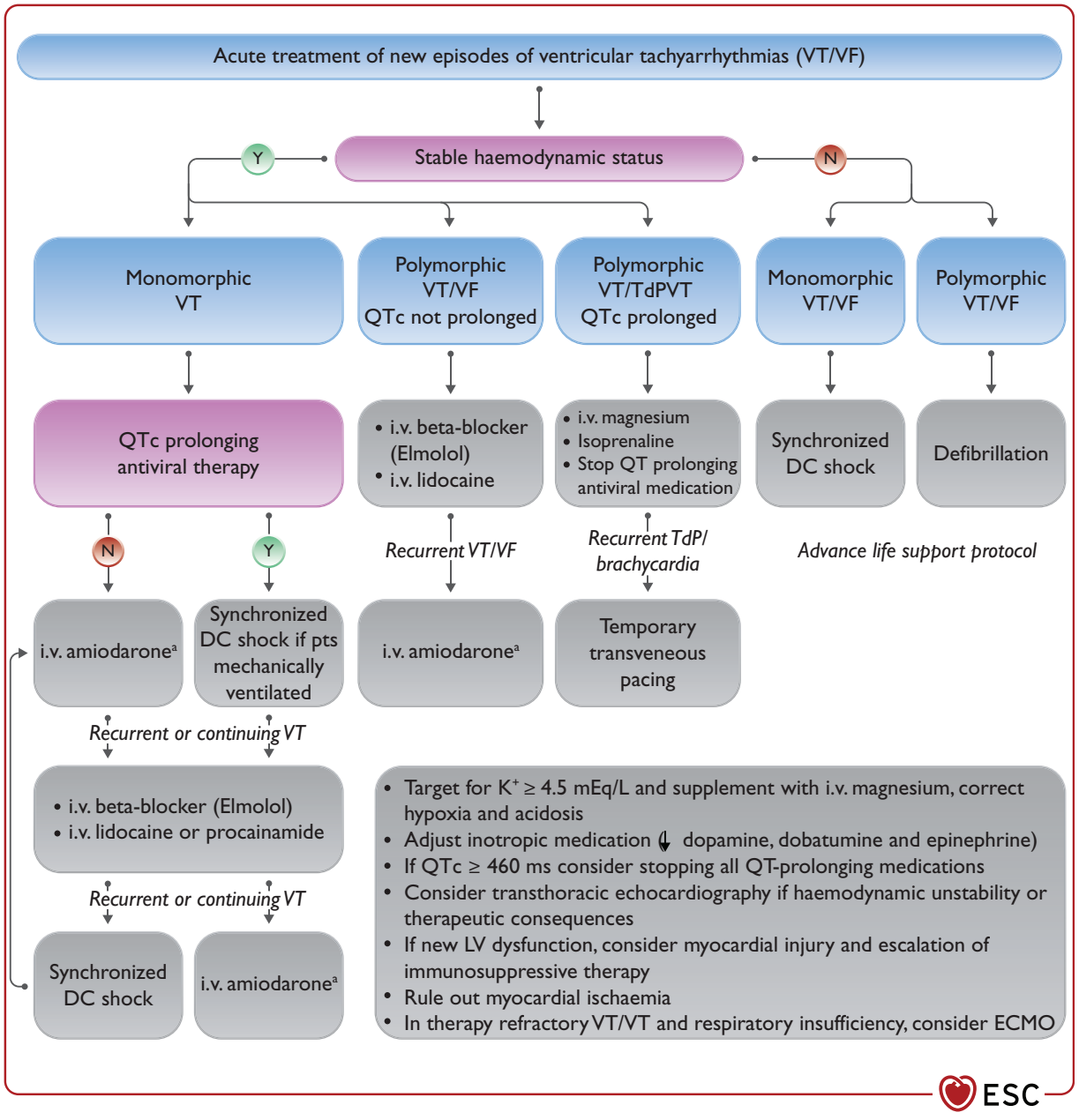


Figure 6 Ventricular tachyarrhythmias. DC, direct current; i.v., intravenous; QT, QT interval; QTc, corrected QT interval; TdP, torsade de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia. [a]The benefit of i.v. amiodarone treatment should be balanced against the proarrhythmic risk in patients taking QT-prolonging antiviral therapy.

pneumothorax, ischaemia, bacterial superinfection, and proarrhythmic drugs.

- Special attention should be paid to the prevention of TdP VT in the setting of COVID-19.
- TdP is a polymorphic VT associated with QT prolongation and may be triggered by QT prolonging antiviral drugs, especially in combination with AADs (mainly sotalol), electrolyte disturbances (in particular K^+ and Mg^{2+}), renal dysfunction, and/or bradycardia, especially in females and in patients with LV hypertrophy or diminished LV function.
- Therapy of TdP VT consists of:
  - TdP withdrawal of all QT prolonging drugs;
  - Normalizing potassium level (target ≥4.5 mEq/L);
  - Intravenous magnesium supplementation;
  - Increasing heart rate by withdrawing bradycardic agents and, if needed, by i.v. isoproterenol or temporary pacing (balancing benefit against the invasiveness of the lead placement with risk for personnel). Isoproterenol is contraindicated in the setting of congenital long QT syndrome (LQTS); and
  - In therapy refractory cases, i.v. lidocaine[184] or oral mexiletine[185] may be considered, based on limited clinical data.
- New-onset malignant ventricular arrhythmias may be a marker of acute myocardial injury and should trigger diagnostic cardiac evaluation. Polymorphic VT without QT prolongation is not TdP but

usually signals ischaemia or acute myocardial injury. Inflammation and cardiac biomarkers should be followed. Echocardiography should be considered in all patients with new malignant ventricular arrhythmia, to assess ventricular function and myocardial involvement. In case myocarditis is suspected, MRI could be considered (see Guidance Part 1), as the diagnosis may warrant more aggressive immunosuppressive and antiviral treatment.
- After recovery from COVID-19, the need for secondary prophylactic ICD, catheter ablation, or wearable defibrillator (in case of suspected transient cardiomyopathy due to myocarditis) needs to be evaluated.

Channelopathies. COVID-19 may occur in patients with known congenital LQTS, Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and short QT syndrome, with a risk of pro-arrhythmia. The specific interactions of these channelopathies and COVID-19 has recently been reviewed.[186]

In the initial phase of the pandemic, a combination of antiviral drugs including (hydroxy-) chloroquine and azithromycin was used extensively, with documented prolongation of the QTc and occurrence of related TdP.[187,188] Recent randomized drug trials have demonstrated that (hydroxy-)chloroquine is not beneficial, so its use is largely abandoned.[189] Similarly, azithromycin has been shown not to confer benefit as compared to usual care.[190] However, when used in isolation as an antimicrobial among patients with COVID-19 azithromycin may present a risk of QT prolongation.[191] Azithromycin in isolation may still be used and is under ongoing evaluation, though it may still present a risk of further QT prolongation.[191]

A special consideration in congenital LQTS with COVID-19 is the observation that in COVID-19 patients the QTc is consistently prolonged.[192] A combination of factors, including hypoxia, electrolyte disorders, high interleukin (IL)-1, and IL-6 levels, is probably responsible.[192] LQTS patients may, therefore, be at increased risk for ventricular arrhythmias. The QTc should be monitored as closely as is safe and practicable. All unnecessary QT prolonging drugs should be stopped, and if QTc is >500 ms or if QTc increases by ≥60 ms from baseline, then the safety of QT prolonging antiviral drugs, if still used, should be reviewed and serum potassium levels should be kept at >4.5 mEq/L (Section Treatment of SARS-CoV-2 infection).

In BrS with COVID-19, the main concern is fever-triggered malignant ventricular arrhythmia. As shown in recently published case reports, COVID-19-induced fever may uncover the type 1 Brugada pattern[193] and lead to symptomatic BrS in previously unsuspected cases.[194,195] It has also been reported to cause electrical storm in a known BrS patient with an ICD implant.[196] Therefore, in all COVID-19 patients with BrS, fever should be aggressively treated with paracetamol. ECG monitoring should be considered if antipyretic therapy is ineffective, and the temperature remains >38.5°C in higher-risk BrS patients (*Figure 7*).

In patients with CPVT and COVID-19, beta-blockers and flecainide should be continued with monitoring of drug interactions with antiviral drugs (see Section Treatment of SARS-CoV-2 infection) and in critically ill patients, catecholamine infusions should be administered with great caution, as they require continuous monitoring.

Bradyarrhythmias

In a recent US study of 107 hospitalized patients, first degree AV block was reported in 18.7% of the patients and 0.9% developed transient Mobitz II AV block. PR interval (regardless of medication use or troponin elevation), QRS duration, and QTc interval significantly prolonged in all patients during admission.[197] In a study of 135 hospitalized patients in Wuhan, 8.1% were reported to have sinus bradycardia on the ECG, 3.7% first-degree AV block, 0.7% type I second-degree AV block, and 1.5% third-degree AV bock.[198] In another study from Wuhan of 319 hospitalized patients, 6% were reported to have sinus bradycardia on the ECG, 3.4% first-degree AV block, and 0.6% second-degree AV block.[199] In a large US study of 1053 hospitalized patients followed on telemetry, second-degree or higher AV block was reported in 0.4% of the patients.[160] In another recent study of 140 hospitalized patients reaching final disposition of discharge or death in New York, acute malignant AV block defined as AV block with hemodynamic instability or cardiac arrest occurred in 3.5% (five patients) of the study population.[180] In two of the five patients, the AV block was associated with AMI, two other patients were critically ill and one patient had non-ST-segment elevation MI and newly depressed LV systolic function.[180] Anecdotal reports have described additional cases of in the majority transient type II second degree or third-degree AV block in most cases associated with troponin rise and myocarditis.[200–203] In one of these cases, MRI was performed and revealed oedema of the interventricular septum indicative of myocarditis.[204] Interestingly, this patient was asymptomatic with COVID-19, had no troponin rise and, as the AV block did not resolve, he underwent permanent PM implantation. Another anecdotal report described two patients with severe COVID-19 and moderate new-onset sinus node dysfunction not resolving during 2 weeks of follow-up but not requiring PM implantation at last follow-up.[205]

In summary, exacerbation of known conduction system or sinus node disease or severe new-onset AV conduction or sinus node dysfunction may occur in approximately up to 3% of patients with COVID-19. Mild-to-moderate AV conduction or sinus node dysfunction may occur in up to 10–20% of patients with COVID-19 and may be transient. In critically ill patients in the ICU, transient bradycardia and asystole may occur due to patient turning for prone respiration, intubation, or trachea suction and is probably due to transient increase in vagal tone.[162] Severe new-onset bradyarrhythmia may be a marker of acute myocardial injury due to ischaemia, hypoxia or myocarditis and, if unexplained by the respiratory status, it should trigger diagnostic cardiac evaluation. Long-term outcomes of new-onset bradyarrhythmia are unknown.

Special considerations for permanent PM implantation in patients with COVID-19 include the poor prognosis of patients requiring mechanical ventilation, increased risk of bacterial superinfection and device infection in the critically ill patients, risk of nosocomial infection during device implantation in COVID-19 negative patients, the possibly transient character of the bradyarrhythmia in myocarditis, and transient bradyarrhythmic side effects of antiviral therapy.

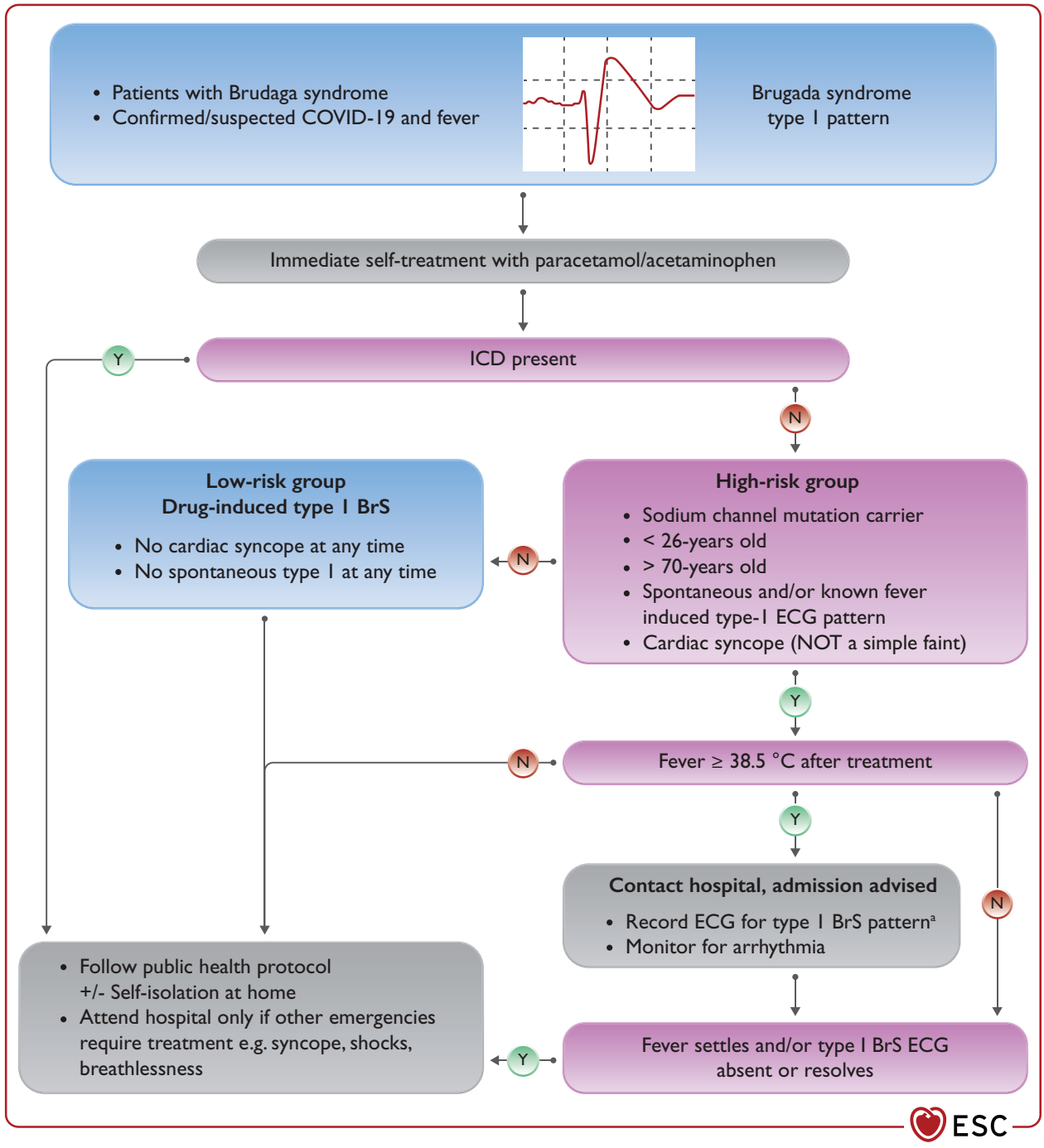


Figure 7 Channelopathies. BrS, Brugada syndrome; COVID-19, coronavirus disease 2019; CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiogram; ICD, implantable cardiac defibrillator. [a]Ideally ECG recordings with V1 and V2 in the fourth, third, and second intercostal spaces.

- Some treatments used for COVID-19 might increase the likelihood for conduction disturbances (see Section Treatment of SARS-CoV-2 infection). Some of these effects might become apparent only after several weeks.
- Recovered COVID-19 patients with mild-to-moderate conduction disturbances or bradyarrhythmic side effects from antiviral medications should be alerted to symptoms of dizziness, presyncope or syncope, and be instructed to contact medical care if these occur.
- To avoid bradycardia as the result of drug–drug interactions, monitoring drug levels and dose adjustment may be required (see Section Treatment of SARS-CoV-2 infection).

- In case of persistent severe symptomatic bradycardia due to AV block or recurrent sinus node dysfunction with pauses:
  - All medication causing bradycardia should be stopped.
  - Isoprenaline and atropine should be administered.
  - Temporary PM implantation should be considered.
  - New-onset severe symptomatic AV conduction or sinus node dysfunction not explained by respiratory status should trigger diagnostic cardiac evaluation. Ischaemia and hypoxaemia should be excluded. Echocardiography should be considered to assess ventricular function and myocardial involvement. In case myocarditis is suspected, MRI could be considered (see Guidance Part 1) as the diagnosis may warrant more aggressive immunosuppressive and antiviral treatment.
  - After recovery from the COVID-19, the need for permanent PM implantation should be reassessed.

Treatment of SARS-CoV-2 infection

Key points

- The evidence regarding the efficacy and risk of different treatment strategies in patients with COVID-19 is extensive and continuously evolving; the current and regularly updated version of the World Health Organization (WHO) 'living guidelines' is online available.[206]
- Recent randomized clinical trials suggest that, with the exception of glucocorticoids (especially dexamethasone) in hospitalized patients with severe and critical COVID-19, the majority of the initially used antiviral, anti-inflammatory, or immunomodulatory experimental drugs have no or limited effect on the natural history of COVID-19.
- In all patients undergoing antiviral treatment, it is of major importance to correct modifiable predisposing factors to QTc prolongation: electrolyte imbalances, concomitant drugs, and bradycardia.
- Baseline ECG may not be needed in all before starting treatment, especially if recent prior ECGs are available and there are no clinical signs suggesting CVD (e.g. unexplained syncope).
- Resource allocation will need to be adjusted locally depending on availability and demand. According to the context, it is worth exploring alternative ECG monitoring methods (e.g. single lead and telemonitoring, smartphone-enabled mobile ECG, handheld devices).
- In COVID-19 patients with an indication for oral anticoagulant therapy, renal and liver function and drug–drug interactions between oral anticoagulant and COVID-19 therapies should be considered to minimize the risk of bleeding or thromboembolic complications.
- In NOAC-eligible patients (i.e. those without mechanical prosthetic heart valves, moderate to severe mitral stenosis or antiphospholipid syndrome), NOACs are preferred over vitamin K antagonists (VKAs), owing to their better safety and fixed dosing without the need for laboratory monitoring of anticoagulant effect, notwithstanding the importance of proper NOAC dosing and adherence to treatment.
- Whereas apixaban, rivaroxaban, or edoxaban can be given as oral solutions or crushed tablets (via enteral tubes), severely ill COVID-19 patients may be switched to parenteral anticoagulation, which has no clinically relevant drug–drug interactions with COVID-19 therapies (with the exception of azithromycin, which should not be co-administered with UFH).
- Acute renal deterioriation or failure precludes continuation of (the same dose of) NOACs and should therefore be closely surveilled.

Medical treatment of COVID-19

Despite the lack of definitive evidence on their efficacy, several drugs with antiviral, anti-inflammatory or immunomodulatory properties have been used 'off-label' to treat SARS-CoV-2 infection. Large randomized trials have now identified several therapies, which in combination can approximately halve mortality for patients hospitalized with COVID-19.

Anti-viral therapies

Several agents have been tested as repurposed antiviral agents.

Chloroquine, and its analogue hydroxychloroquine, has been widely used as an antimalarial drug and in the treatment of rheumatological diseases like systemic lupus erythematosus and rheumatoid arthritis. Following the observations of *in vitro* suppression of SARS-CoV-2 growth,[207–209] and in preliminary studies with reduced SARS-CoV-2 positivity in nasopharyngeal secretions,[207] these drugs were initially used to treat COVID-19. However, randomized trials have not confirmed that hydroxycholoroquine is beneficial for the treatment of patients hospitalized with COVID-19.[189,210–214] Hence, chloroquine and hydroxychloroquine have no indication anymore in the treatment of COVID-19, although trials are ongoing of their role in prophylaxis.[215]

The protease inhibitor lopinavir–ritonavir was shown to be effective against SARS coronavirus and MERS coronavirus *in vitro* and in animal models,[216–218] but these findings have not been confirmed in randomized controlled trials of hospitalized patients with severe COVID-19.[214,219,220]

In vitro and animal studies suggest that remdesivir (GS-5734) is effective against zoonotic and epidemic SARS coronavirus and MERS coronavirus.[221–224] *In vitro* studies suggest that remdesivir compared to lopinavir–ritonavir.[224] Preliminary studies suggested that remdesivir shortened the recovery time in hospitalized patients with COVID-19.[225] However, larger randomized trials have reported little or no effect on key outcomes such as or mortality, initiation of ventilation, and duration of hospital stay among hospitalized patients.[214]

Antibody-based therapies

Convalescent plasma obtained from people who have recovered from COVID-19 is also being used. Preliminary results from a large expanded-access program in the USA suggested that higher titres of antibody had a larger impact on mortality as well as better outcomes when administered within the first 3 days after diagnosis.[226] Importantly, this study did not have an untreated control group, so findings should be considered with caution. The RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial assessed high-titre convalescent plasma among 11 558 patients hospitalized with

COVID-19 and found no benefit on major clinical outcomes.[227] It remains possible that convalescent plasma may have a role in earlier disease, but this hypothesis needs to be tested.

More recently, synthetic monoclonal antibodies directed against the SARS-CoV-2 spike protein have been assessed in randomized trials. In the USA, Emergency Use Authorization has been given for the use of bamlanivimab with etesevimab, REGEN-COV, and sotrovimab in non-hospitalized patients with mild-to-moderate COVID-19, based on their ability to reduce viral load more quickly and prevent need for hospitalization.[228–230] Although small studies of these agents among hospitalized patients were terminated early for futility,[231,232] REGEN-COV was assessed among 9785 participants hospitalized with COVID-19 in the RECOVERY trial.[233] Among seronegative participants (i.e. those without a detectable humoral response to SARS-CoV-2), allocation to REGEN-COV reduced mortality at 28 days by 20% (24% vs. 30%: rate ratio 0.80, 95% CI 0.70–0.91).

Immunomodulatory therapies

In the RECOVERY trial, dexamethasone reduced mortality in hospitalized COVID-19 patients receiving oxygen, with the largest effect among patients receiving mechanical ventilation.[54] This benefit was confirmed in a meta-analysis by the WHO REACT working group of seven randomized clinical trials of critically ill patients with COVID-19. The administration of systemic corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone), compared with usual care or placebo, was associated with lower 28-day all-cause mortality.[56] Benefits were also observed on progression to invasive mechanical ventilation and need for renal replacement therapy.

In vitro, azithromycin has shown to be active against the SARS-CoV-2 virus.[234] However, the COALITION I and II and RECOVERY randomized trials did not show any benefit of adding azithromycin therapy in either mild-to-moderate or severe COVID-19.[211,235]

In COVID-19 patients, IL-6 level is associated with viral load, disease severity, and prognosis.[236] Tocilizumab, an IL-6 receptor monoclonal antibody, has been proposed to treat severe COVID-19. The largest trial to date is RECOVERY, which demonstrated that among patients with hypoxia and inflammation (CRP ≥75 mg/L), tocilizumab reduced the risk of death by 15% (rate ratio 0.85, 95% CI 0.76–0.94).[237] A WHO-led meta-analysis of all trials of IL-6 antagonists confirms this benefit.[238]

Colchicine has been proposed as an oral anti-inflammatory medication for the treatment of COVID-19 and several small studies, including the GRECCO-19 trial in 105 hospitalized patients,[239] yielded promising findings. In the COLCORONA randomized placebo-controlled trial in community-treated patients including those with suspected but with diagnostic test not confirmed COVID-19, the effect of colchicine on COVID-19-related clinical events was not statistically significant, although an analysis just among patients with PCR-confirmed COVID-19 did suggest that there may be a reduction in the composite of death or hospital admission in such patients.[240] However, a much larger randomized trial among patients with more severe illness who had been hospitalized with COVID-19 found no benefit of colchicine.[241]

Antithrombotic therapies

Antiplatelet agents had been proposed as a potential therapy, in part because of the high rate of venous and arterial thrombosis observed in severe COVID-19. Among 14 892 patients in the RECOVERY trial, aspirin did not improve clinical outcomes.

Trials of heparin-based anticoagulation have shown different results by severity of disease. Among critically ill patients, no benefit of therapeutic anticoagulation compared to usual care was seen in three trials. By contrast, these trials have separately reported that among non-critically ill hospitalized patients therapeutic anticoagulation increased organ support-free days.

In summary, the current version (as of 31 March 2021) of the WHO living guidelines recommends not to use ivermectin in patients with COVID-19 except in the context of a clinical trial; strongly recommends against the use of hydroxychloroquine and lopinavir/ritonavir in patients with COVID-19 of any severity; conditionally recommends against the use of remdesivir in hospitalized patients and systemic corticosteroids in patients with non-severe COVID-19; and strongly recommends for systemic corticosteroids use in patients with severe and critical COVID-19.[206]

Arrhythmologic consideration of COVID-19 therapies

One major concern with drugs used in COVID-19 is the very rare risk of QTc prolongation and TdP/sudden death or the potential occurrence of conduction disturbances. A recent meta-analysis on arrhythmogenic cardiotoxicity of the quinolines and structurally related antimalarial drugs suggested that this risk is minimal (no events of SCD or documented VF of TdP in 35 448 individuals, 1207 of whom were taking chloroquine).[222] During COVID-19, the QT-related risk may be amplified by concomitant use of other QTc-prolonging drugs and/or electrolyte imbalances (hypokalaemia, hypomagnesaemia, and/or hypocalcaemia). Furthermore, important drug–drug interactions have been described [mainly because these potent CYP3A4 inhibitors interfere with (hydroxy)chloroquine metabolism] that should be taken into consideration. In some combinations, dose adjustments or changes may be needed (*Table 4*).

For a detailed overview of all known direct or indirect (through drug–drug interactions) pro-arrhythmic effects of experimental pharmacological therapies in COVID-19 patients, see *Table 4*.

Corrected QT interval evaluation to prevent drug-induced arrhythmia

QTc prolongation by some drugs can theoretically lead to polymorphic VT (TdP). This is, however, a very rare complication, and its risk has to be balanced against the anticipated benefit of therapy for the COVID-19 patient. *Figure 8* provides a practical flow chart for the management of patients to prevent TdP, guidance on the timing and repetition of ECG recordings, and QTc measurements that would alter therapy. Other guidance flowcharts have been published.[186,291] Briefly, the following steps are required to reduce the risk of drug-induced TdP:

(1) Identify risk factors associated with QTc prolongation:
   - Non-modifiable risk factors: congenital LQTS, QT prolongation on known QT prolonging drugs, female sex, age >65 years, structural heart disease (ACS, uncompensated HF,

Table 4 Pro-arrhythmic considerations of novel experimental pharmacological therapies in COVID-19

	Heart rate	AV conduction	QRS interval	QTc interval	TdP risk	AAD drugs interactions[242]	Comments
Chloroquine	Mild ↓	Mild ↑ ΔPR = 14.8 ms[243]	Mild ↑ ΔQRS = 9.9 ms[243]	Moderate–severe ↑ ΔQTc = 33–35 ms[243–249] QTc > 500 ms or ΔQTc > 60 ms in 15–23% of patients[244,246–248]	Very low risk of TdP (2 VT cases with high dosage and 1 case report of TdP in COVID patients)[188,250,251]	**Severe**[a] Amiodarone, flecainide, mexiletine **Moderate**[b] Disopyramide, digoxin, dofetilide, propafenone, quinidine **Mild**[c] Metoprolol, nebivolol, propranolol, timolol, verapamil	• Very low risk of cardiotoxicity during chronic therapy is reported[252,253] • In a study in SLE, it was negatively associated with AVB ($P = 0.01$) as was its longer use (6.1 ± 6.9 vs. 1.0 ± 2.5 years, $P = 0.018$)[247] • Proarrhythmia occurs mostly with overdosage or in chronic therapy (> years)[254] • Proemetic effect is common • Risk of retinopathy, myo/neuropathy during chronic therapy is reported
Hydroxychloroquine	Mild ↓ ΔHR = -5 ms[254–258]	No changes in COVID patients[256]	Mild ↑ ΔQRS = 0–3.7 ms[251,259]	Moderate ↑ ΔQTc= 5.5–16 ms QTc > 500 ms or ΔQTc > 60 ms in 1–19% of patients[187,244,251,256,259–264] **When associated with azithromycine** Moderate–severe ↑ ΔQTc = 11–35 ms QTc > 500 ms or ΔQTc > 60 ms in 1–36% of patients[187,244,251,256,259–264]	Very low risk of TdP (3 cases of TdP in COVID patients)[187,189,210,211,261,265]	*See chloroquine*	• Very low risk of cardiotoxicity during chronic therapy is reported[250,253] • Proarrhythmia occurs mostly with overdosage or in chronic therapy (> years)[250] • Less cardiotoxicity reported than with chloroquine[250] • In a study of pregnant women with Ro/La antibodies, AVB was more frequent in those

Continued

Table 4 *Continued*

	Heart rate	AV conduction	QRS interval	QTc interval	TdP risk	AAD drugs interactions[242]	Comments
							not using hydroxychloroquine[211] • Risk factors for severe QTC prolonging in COVID patients are the use of loop diuretics, history of myocardial infarction, CKD, and heart failure, prolonged QTc at baseline[187,189,210,211,251,254,256,259–265]
Azithromycin	Mild ↓[266]	Mild ↑[266]	Mild ↑[266]	Moderate–severe ↑ ΔQTc = 0.5–25 ms QTc >500 ms or ΔQTc >60 ms in 19% of patients[187,189,210,211,235,244,251,256,259–266]	Low risk of TdP Cumulative incidence SCD = 64.6/1 million[267] ROR for TdP = 4.76 compared to other medication (2.81–7.98)[268] RR for SCD or VT = 3.40 compared to no macrolide use[267,269,270]	**Severe**[a] Amiodarone, dofetilide, dysopiramide, flecainide, propafenone, sotalol **Moderate**[b] Beta-blockers, digoxin	In a study during treatment days 1–5, patients receiving azithromycin had significantly increased risk of serious arrhythmia (hazard ratio = 1.77; 95% CI, 1.20–2.62) compared with patients receiving amoxicillin[271,272]
Lopinavir/ritonavir	Moderate ↓[273]	Moderate ↑ ΔPR = 33.5 ms[243]	Mild ↑ ΔQRS = 7 ms[274] (1 case of bundle branch block reported in COVID patients)[273]	Moderate–severe ↑ ΔQTc = 14–20 ms QTc >500 ms in 21% of patients[273,275]	Low risk of TdP (1 case of TdP reported in COVID patients)[219,273,275]	**Severe**[a] Amiodarone, disopyramide, dofetilide, dronedarone, flecainide **Moderate**[b] All beta-blockers, Ca^{2+} blockers, digoxin, lidocaine mexiletine, propafenone, quinidine	5 cases of bradycardia and one bundle branch block regressed upon drug discontinuation[273]

Continued

Table 4 *Continued*

	Heart rate	AV conduction	QRS interval	QTc interval	TdP risk	AAD drugs interactions[242]	Comments
Tocilizumab	No ECG changes described[276]	No ECG changes described[276]	No ECG changes described[276]	No ECG changes described[276]	Clinical data showed safety[277–279]	**Mild**[c] Amiodarone, quinidine	
Fingolimod	Moderate–severe ↓ ΔHR = -23 bpm[280]	Mild–moderate ↑	Unknown	Mild ↑	Unknown	**Moderate**[b] Amiodarone, beta-blockers, Ca^{2+} blockers, flecainide, ivabradine, propafenone	Reported risk of rare, transient and benign bradycardia and AV conduction abnormalities:[281] • In a study of 3591 patients, 31 patients (0.8%) developed bradycardia (<45 b.p.m.), 62 patients (1.6%) had second-degree Mobitz Type I, and/or 2:1 AV blocks[282] • In a study of 5573 patients, new-onset first-degree AVB was experienced by 132 (2.4%) in-home and 74 (0.5%) in-clinic patients, and Wenckebach (Mobitz Type I) second-degree AVB by four (0.07%) and nine (0.1%) patients, with no cases of third-degree AVB.[283] • In a study of 66 patients with MS, fingolimod lead to an increase of vagal activation, which persisted even after

Continued

Table 4 *Continued*

	Heart rate	AV conduction	QRS interval	QTc interval	TdP risk	AAD drugs interactions[242]	Comments
							14 months of treatment.[280]
Remdesivir	No ECG changes described[284]				Clinical data showed safety[285,286]	Unknown	
Corticosteroids	No ECG changes described[287,288]				Clinical data showed safety[286,287]	NR	• May cause electrolyte disturbance • High-dose intravenous prednisolone might cause acute sinus bradycardia[289,290] or, in MS patients, sinus tachycardia, bradycardia, and rarely AF and VT[289]
Interferon alfacon-1	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Limited data: cases of hypotension, arrhythmia, and cardiomyopathy reported
Ribavirin	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	No cardiac side effect

AF, atrial fibrillation; AV, atrio-ventricular; AVB, AV block; AAD, antiarrhythmic drugs; CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; HR, heart rate; LAFB, left-anterior fascicle block; LQTS, long QT syndrome; MS, multiple sclerosis; NR, not reported; OR, odd Ratio; QTc, corrected QC interval; RBBB, right-bundle branch block; ROR, reporting odd ratio; RR, risk rate; SCD, sudden cardiac death; SLE, systemic lupus erythematosus; TdP, torsade de pointes; VT, ventricular tachycardia.

[a]These drugs should not be co-administered.

[b]Potential interaction (need dose adjustments/close monitoring).

[c]Weak intensity interaction (need dose adjustments/close monitoring unlikely to be required).

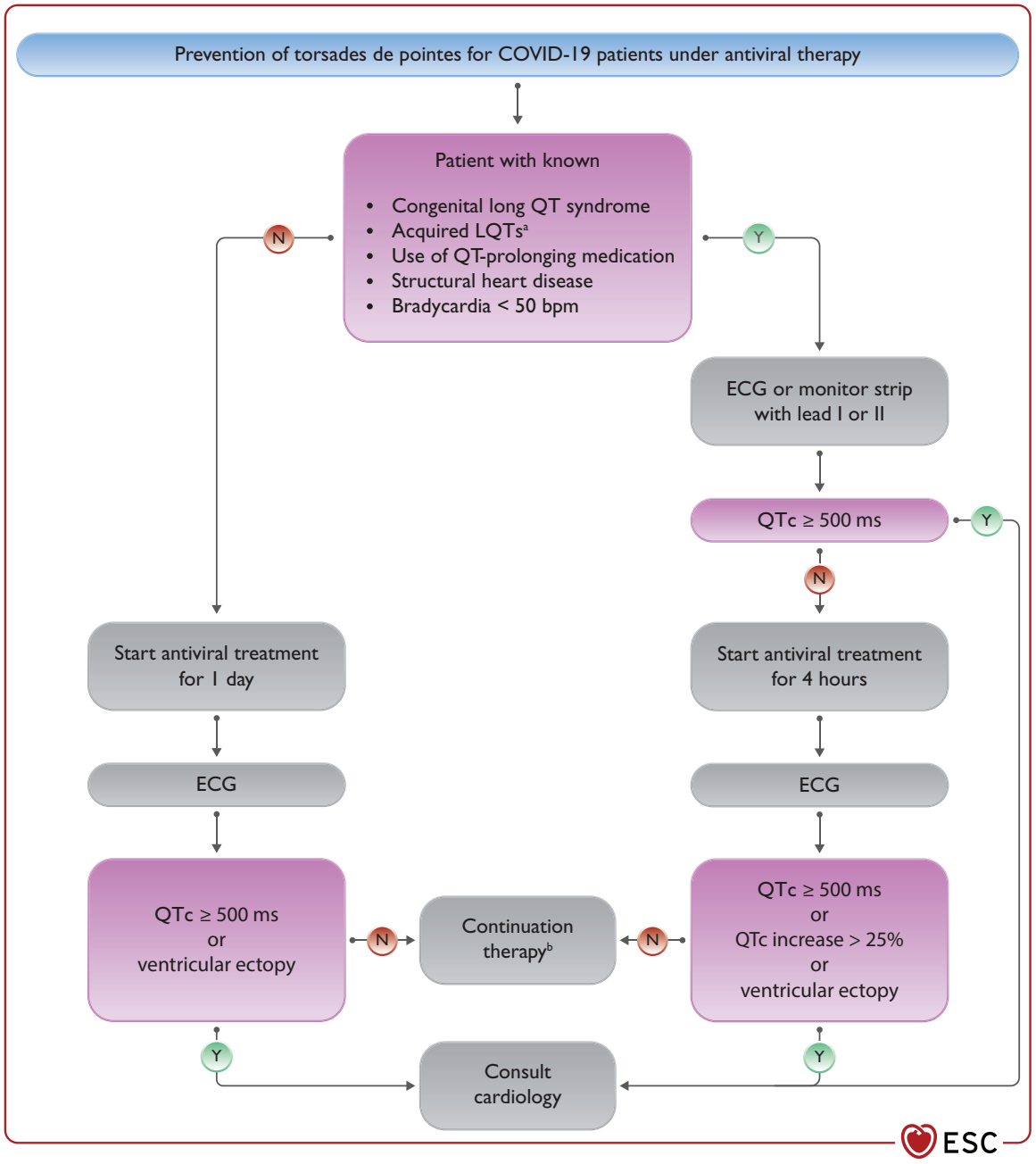


Figure 8 QTc management. COVID-19, coronavirus disease 2019; ECG, electrocardiogram; LQTS, long QT syndrome; QTc, corrected QC interval. [a]As long as the patient is clinically stable (e.g. no pronounced vomiting, diarrhoea, signs/symptoms of heart failure or deterioration of respiratory, or other organ function).

hypertrophic cardiomyopathy), renal impairment, and liver impairment.

- Modifiable risk factors: hypocalcaemia, hypokalaemia, hypomagnesaemia, concomitant use of QTc-prolonging medications, and bradycardia.

(2) Identify and correct modifiable risk factors in all patients. Serum potassium should be kept in the higher range (≥ 4.5 mEq/L).[292]

(3) Perform a baseline ECG (12-lead or single strip, depending on resource availability). Patients with a baseline QTc ≥500 ms are at risk of developing TdP or sudden death. The risk-benefit ratio of treatment in this group should be carefully assessed. In some patients with a recent ECG showing normal QTc and no evidence of major CV alterations due to COVID-19, one may consider not taking a baseline ECG to avoid exposure to HCP and contamination of equipment.

(4) Perform ECG once on treatment. If the patient has a QTc ≥500 ms or shows a ΔQTc ≥60 ms, switching to a drug with lower risk of QTc prolongation, reduction of the administered dose, or continuing treatment plan are the options to consider. Close surveillance of

QTc interval (preferably including telemetry for arrhythmia monitoring) and electrolyte balance are mandatory.

Bradycardia prolongs QT and facilitates TdP. While some COVID-19 drugs have a weak bradycardic effect, the concomitant use of beta-blockers, CCBs, ivabradine and digoxin should also be evaluated. If digoxin is considered mandatory for the patient, plasma level monitoring should be considered (with ensuing dose reduction if needed).

Technical aspects of QT measurements

For patients with wide QRS complex (≥120 ms) due to bundle branch block or ventricular pacing, QTc adjustment is needed. Formulae are available, but a simpler approach may be to use a QTc cut-off of 550 ms instead of 500 ms. Others propose to calculate adjusted QT interval by subtracting QRS width and adding 100 ms.

A standard 12-lead ECG may not always be feasible to obtain, especially in times of sudden outbreak and scarce healthcare resources. As an alternative, enhanced use of handheld ECG devices should be encouraged to reduce traditional ECG recording to preserve resources and limit virus spread. In a recent study, the QTc in lead-I and lead-II derived from a standard 12-lead ECG was compared with the QTc measured from a rhythm strip from a handheld ECG device in 99 healthy volunteers and 20 hospitalized patients in sinus rhythm treated with dofetilide or sotalol.[293] QT on the handheld device had an excellent agreement with standard 12-lead ECG both in the normal range and in patients with QT prolongation.[293] This handheld ECG device (KardiaMobile 6L Alivecor) had a high specificity for detecting a QTc >450 ms and should thus be considered as an effective outpatient tool for monitoring patients with prolonged QTc. Recently, KardiaMobile 6L received expedited approval from the FDA for QT monitoring and can thus be used in COVID-19 patients treated with QT prolonging drugs.

Considerations on the use of anticoagulants in COVID-19 patients

Recent studies confirm that COVID-19 is associated with increased risk of venous, arterial, and microvascular thrombotic and thromboembolic disease, including disseminated intravascular coagulation (see Guidance Part 1 and Section Acute pulmonary embolism—prevention and diagnosis).[294–297] In general, the risk of thrombotic complications and bleeding should be assessed in all patients with COVID-19, and current guidelines for the prevention and treatment of thrombotic and thromboembolic diseases should be followed.[151,298] Specific in COVID-19, in two recent studies, the use of reduced and therapeutic-dose anticoagulation has been associated with improved outcomes and mortality in hospitalized patients.[295,296] The indications and details of venous and pulmonary embolism prophylaxis and treatment of thrombotic complications of COVID-19 are discussed in Section Acute pulmonary embolism—prevention and diagnosis and have been reviewed in several recent consensus documents.[294,297]

Many patients with CV history have an indication for anticoagulation and are already under anticoagulation therapy when affected by COVID-19. *Table 5* lists the possible interactions of COVID-19 therapies with VKAs, NOACs, LMWHs, and UFH. The table includes information that was derived from several drug interaction sites, which have been referenced. Drug summary of product characteristics often do not contain information for older drugs and/or drugs with a narrow spectrum of indications (like chloroquine). Antimalarial drugs have a P-glycoprotein inhibiting effect, which may affect NOAC plasma levels. COVID-19 patients on oral anticoagulation may be switched over to parenteral anticoagulation with LMWH and UFH when admitted to an ICU with a severe clinical presentation.

We would like to reiterate here also that the conventional dose reduction criteria for NOACs for AF patients on oral treatment for stroke prevention can be continued. For more details, including the assessment of renal and liver function and other considerations in patients taking an NOAC, please see the 2021 EHRA Practical Guide on the use of NOACs in patients with AF.[302] Of note, none of the NOACs is recommended in patients with a creatinine clearance (CrCl) <15 mL/min according to the EU label.

- Apixaban: the standard dose (2 x 5 mg) should be reduced to 2 x 2.5 mg if two out of three criteria are met [body weight ≤60 kg, age ≥80 years, serum creatinine ≥133 μmol/L (1.5 mg/dL)], or if the CrCl is 15–29 mL/min.
- Dabigatran: the standard doses 2 x 150 and 2 x 110 mg. No prespecified dose reduction criteria but, per the drug label, 2 x 110 mg should be used if age >80 years, concomitant verapamil, increased risk of gastrointestinal bleeding.
- Edoxaban: the standard dose (1 x 60 mg) should be reduced to 1 x 30 mg if weight <60 kg, CrCl <50 mL/min, concomitant therapy with a strong P-gp inhibitor.
- Rivaroxaban: the standard dose (1 x 20 mg) should be reduced to 1 x 15 mg if CrCl <50 mL/min.

For patients with impaired swallowing, NOACs can be administered in the following ways:

- Administration in a crushed form (e.g. via a nasogastric tube) does not alter the bioavailability of apixaban, edoxaban and rivaroxaban.[303–305]
- Apixaban can be given as oral solution or via nasogastric or gastric tube on an empty stomach (food impairs bioavailability of the crushed tablets).[306]
- Rivaroxaban tablet can either be crushed and mixed in water or apple puree and taken orally, or suspended in water and given via nasogastric tube (enteral tubes must not be distal to the stomach) followed by food.[304]
- Dabigatran capsules must not be opened, as it would result in a 75% increase in the drug bioavailability.[306]

Patient information

While there remain unknown features of COVID-19,[307] it is clear that transparent patient-centred information is an essential component to support patients to reduce risk of transmission, maintain a healthy lifestyle and manage their CVD (*Figure 9*). What is the full spectrum of disease severity? What is the transmissibility? What is the role of asymptomatic/pre-symptomatic infected persons? How long is the virus present? What are the risk factors for severe illness?

Table 5 **Interactions of anticoagulant drugs with experimental COVID-19 therapies**

COVID-19 therapies anticoagulants	NOACs				Comments	VKAs			LMWH, UFH			
	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban		Warfarin	Aceno-coumarol	Phenpro-coumon	Enoxaparn	Fonda-parinux	Dalteparin	Heparin
Chloroquine[242,299,300]	↑	↑	↑	↑	Any NOAC may be used (with caution)							
Hydroxychloroquine[242,299,300]	↑	↑	↑	↑								
Azithromycine[20,70,272]	↑		↑		If CrCl <30 mL/min dabigatran should be avoided. If renal function is impaired (CrCl <50 mL/min), rivaroxaban should be used with caution.	↑						↑[a]
Atazanavir[242,300,301]	↑[b]	↑[b]	↑[c]	↑[b]	Reduced-dose edoxaban (30 mg o.d.) may be used with caution	↑		↑				
	↑[d]	↑[d]		↑[d]								
Lopinavir/ritonavir[242,299–301]	↔or↓	↑[e]	↑[b]	↑	Dabigatran may be used with caution (should be avoided if CrCl <30 mL/min)	↓	↓	↓↑				
Darunavir/cobicistat												
Ribavirin[242,299–301]					Any NOAC may be used (with caution)	↓						
Remdesivir[242,299,300]												
Favipiravir[300]												
Bevacizumab[300]												
Eculizumab[300]												
Tocilizumab[242,299,300]		↓		↓		↓	↓	↓				
Fingolimod[299,300]												
Interferon[299,300]												
Pirfenidone[299,300]												
Methylprednisolone[299,300]						↓						↓
Nitazoxanide[242,300]						↑	↑	↑				

Light grey colour: no information found. Green colour: no clinically significant interaction is expected, or potential interaction is likely to be of weak intensity, not requiring additional action/monitoring or dose adjustment. Yellow colour: potential interaction which may require additional monitoring (e.g. more frequent INR monitoring if on VKAs). Orange colour: potential interaction which may require a dose adjustment. Red colour: the drugs should not be co-administered. ↑, potential increased exposure to the anticoagulant drug; ↓, potential decreased exposure to the anticoagulant drug; ↔, no significant effect on the exposure to the drug.

COVID-19, coronavirus disease 2019; CrCl, creatinine clearance; LMWH, low molecular weight heparin; NOACs, non-vitamin K antagonist oral anticoagulants; o.d., once daily; UFH, unfractionated heparin; VKAs, vitamin K antagonists.

[a]Azithromycin increases the effect of heparin by decreasing its metabolism.[300]

[b]There is an overall agreement that the use of NOACs is not recommended when atazanavir is given in combination with its enhancers, ritonavir or cobicistat.

[c]The EMA product label for edoxaban advises the consideration of dose reduction from 60 mg once daily to 30 mg once daily with concomitant use of strong P-glycoprotein inhibitors.

[d]No data on the safety/efficacy of use of NOACs when co-administered with atazanavir are known; if their use is deemed indicated, one should consider monitoring plasma level of the NOACs in this unknown condition, in line with the recommendation that was made in the last EHRA Practical Guide.[298]

[e]The US product label for apixaban proposes the use of apixaban at reduced dose (2.5 mg twice daily) if needed.

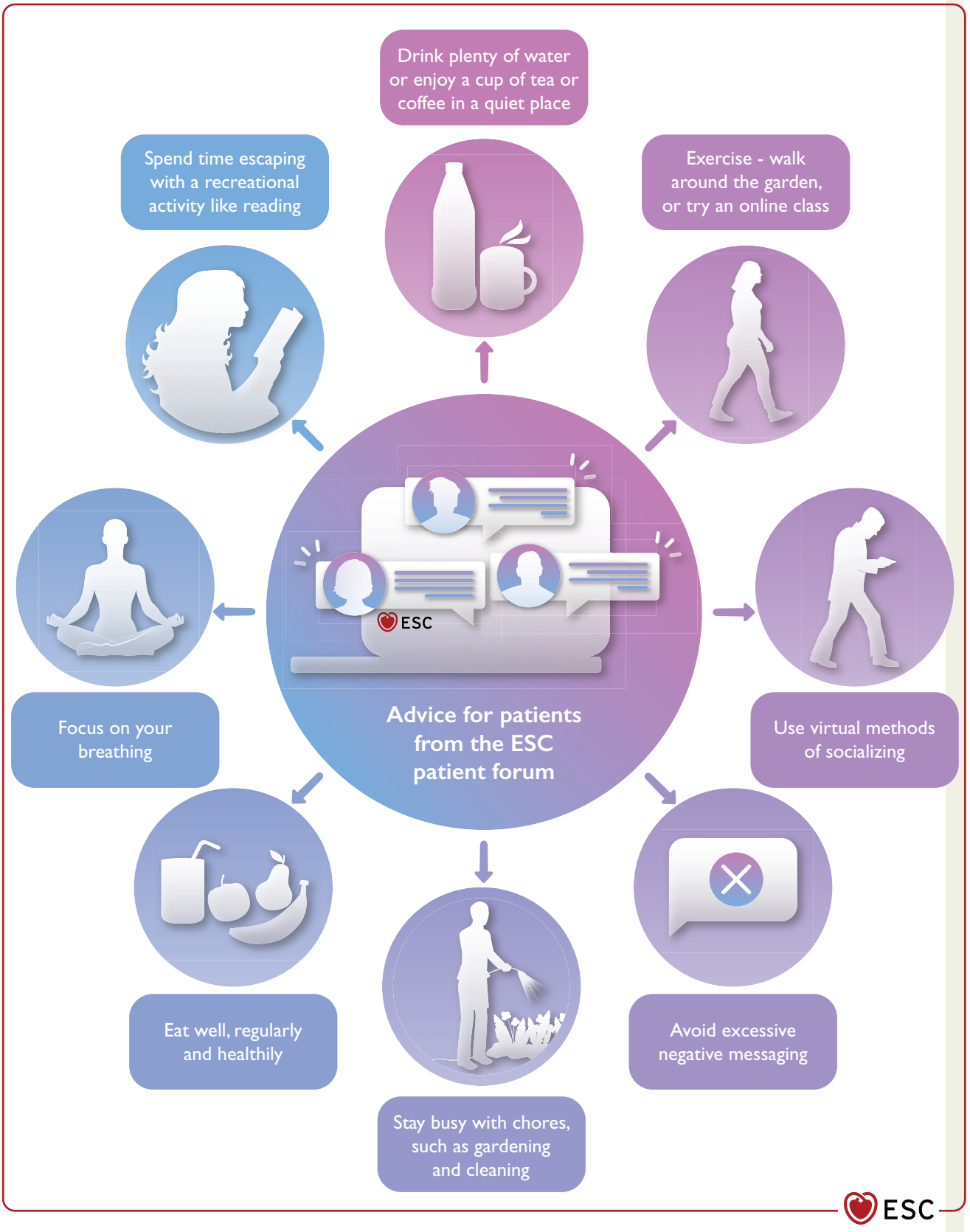


Figure 9 Advice for patients from the European Society of Cardiology patient forum.

Knowledge is being accumulated very fast and our task is to deliver key information for patients with CVD.

Key points

- Patient-centred information is of paramount importance during the COVID-19 pandemic when the allocation of medical resources is a matter of debate.[308]
- Pre-existing CVD has a direct impact on the risk of SARS-CoV-2, severity of COVID-19 disease, and survival.[112]
- The occurrence of SARS-CoV-2 may lead to CV complications as well as treatments used to cure the COVID-19 disease.
- Unambiguous information to the population and patients is key for better control of the disease and the rapid development of specific treatment strategies, including vaccines.

Who is at risk for severe SARS-CoV-2?

There are several clinical features associated with a worse short-term outcome of SARS-CoV-2 manifestations (see Guidance Part 1). These include: age >65-year old with a least one comorbidity, or age >70-year old, with the risk being highest in age >80-year old; COPD, asthma, chronic HF, certain cardiac arrythmias, recent unstable coronary artery disease or coronary revascularization (<3 months), BMI >35 kg/m^2 or BMI >30 kg/m^2 plus one or more comorbidities, sickle cell anaemia, transplant <6 months, hypertrophic cardiomyopathy with obstruction, chronic kidney disease (eGFR <15 mL/min), and dysregulated diabetes.[309] The effect of social background and ethnicity on survival remains controversial, but it appears that long-standing disparities in nutrition and obesity play a crucial role in the health inequities unfolding during the pandemic (see Guidance Part 1).[310–313] A cause-and-effect relationship between drug therapy and survival should not be inferred given the lack of ongoing randomized trials. Patients should be informed and take appropriate precautions with emphasis on measures for social distancing when the potential risk is high and medical resources are scarce.

My treatment during the COVID-19 pandemic

- COVID-19 disease may trigger destabilization of chronic CVD. This may also be favoured by chronic oral treatment interruption, and patients should be informed to seek medical guidance prior to any treatment modifications.
- Aspirin dosage given for the secondary prevention of atherothrombosis has no anti-inflammatory potential and should not be interrupted in COVID-19 patients without any other relevant reasons, such as ongoing bleeding complication or the need for an unplanned invasive procedure.
- Many patients at potential risk for SARS-CoV-2 are treated with inhibitors of the RAS, including ACEIs. ACE2 facilitates coronavirus entry into cells, but it is not inhibited by ACEIs or Ang II type 1 receptor blockers or upregulated by these treatments. For these reasons, patients should not discontinue their treatments without medical guidance.[134,314] Two randomized controlled trials have shown that there was no difference in major outcomes from COVID-19 whether or not the patients were randomized to continue or discontinue their treatment with ACEIs or ARBs (see Section Hypertension).[126,127]
- There are some treatments that may need to be adjusted when concomitant specific therapy for the COVID-19 disease is initiated. These treatments are initiated during hospital admission and potential drug–drug interactions are summarized in *Tables 6 and 7*.

Table 6 Concomitant conditions that may be associated with a more severe course of SARS-CoV-2 infection[a]

Chronic pulmonary disease
History of heart failure
Waiting list for cardiac surgery
Immunodeficiency or prior organ transplantation
Hypertension
Coronary artery disease
Cerebrovascular disease
Diabetes
Severe overweight (BMI >40 kg/m^2)
Arrhythmias

BMI, body mass index.
[a]Many of these features are confounded by age.

Interactions with others, healthy lifestyle, and medical advice during COVID-19 pandemic

The following information is important for individuals with CVD (*Figures 9 and 10*):

- Interaction with others:
  - Avoid people who are sick.
  - Keep a two-metre distance from other individuals whenever possible.
  - Wash hands thoroughly with soap and warm water for at least 20 s.
  - Cover the mouth or nose with a tissue or use the inside of the elbow when you cough or sneeze.
  - Avoid touching the eyes, nose and mouth when you are with other people.
  - To remove the virus, clean surfaces like doorknobs or handles often with a disinfectant.
  - Self-isolate in case of symptoms of fever, cough or a chest infection and look for medical assistance.
  - Limit/avoid situations with high risk of becoming infected.
  - Stay at home as much as possible.
  - Maintain physical activity to avoid VTE and maintain well-being.

In addition, individuals should be encouraged to follow the instruction of the Department of Health and local authorities in the resident countries, as these may differ.

- Healthy lifestyle:
  - Maintain a healthy lifestyle (e.g. eat healthy, quit smoking, restrict alcohol intake, get adequate sleep and keep physically active).[315]

Table 7 Potential interactions of drugs to treat COVID-19[a]

Drugs used to treat COVID-19	Interactions	Action
Dexamethasone	Warfarin	Monitor INR
Methylprednisolone	Warfarin	Monitor INR
Antiretroviral drugs	Antiarrhythmics	Use QT prolonging or low-dose digoxin with caution
	NOACs	Avoid apixaban and rivaroxaban
	Statins	Start with low-dose rosuvastatin or atorvastatin
	Warfarin	Monitor INR
Colchicine	Statins	Consider reducing dose of statin therapy
	CYP3A4 inhibitor	Consider reducing dose of colchicine
Chloroquine or hydroxychloroquine	Beta-blockers and QT prolonging drugs	Monitor ECG

COVID-19, coronavirus disease 2019; ECG, electrocardiogram; INR, international normalized ratio; NOACs, non-vitamin K antagonist oral anticoagulants.
[a]These medications will be administered during hospital admission.

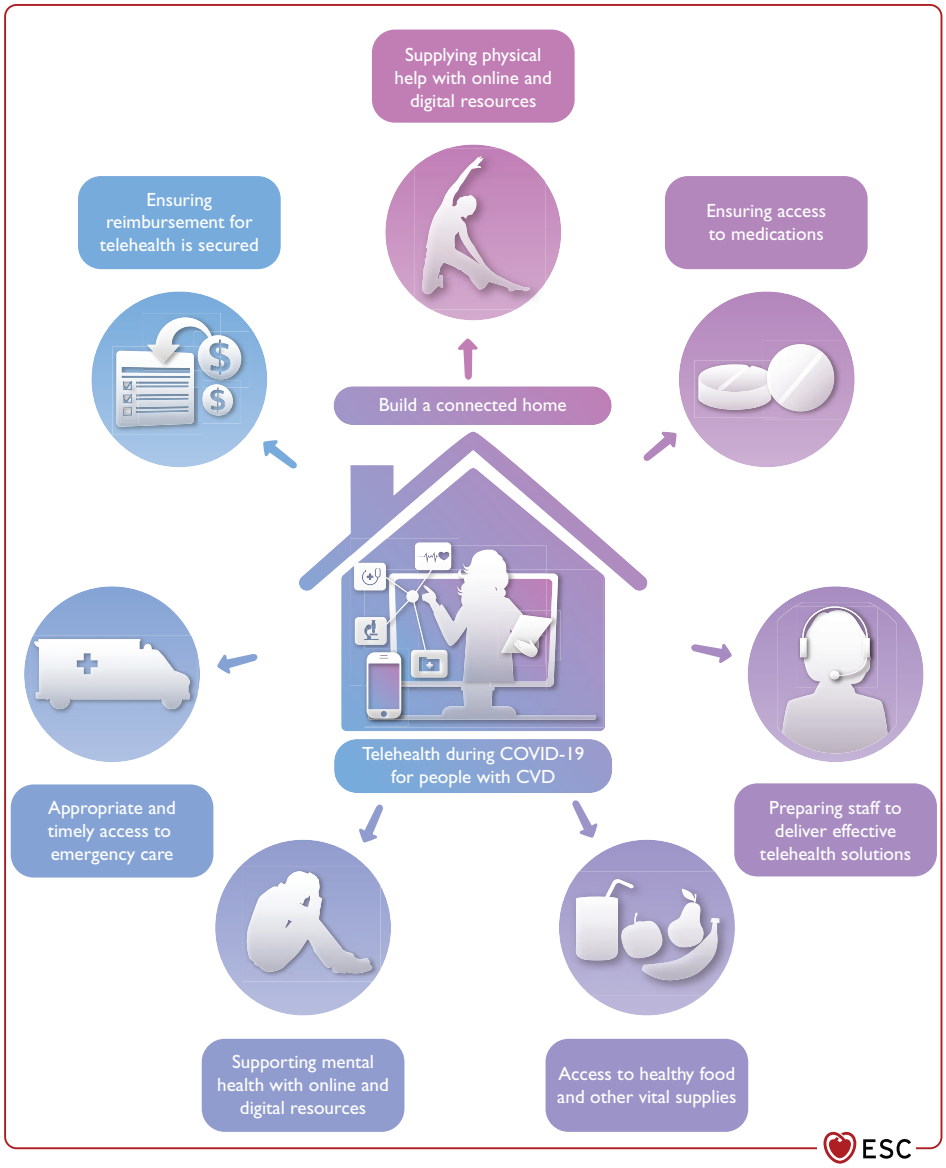


Figure 10 Telehealth during COVID-19 for people with cardiovascular disease.

- Isolation and physical restrictions may lead to inactivity, increased risk of VTE, and loss of functional autonomy, especially among elderly with co-morbidities.
- Physical activity should be strongly encouraged, either in a home setting or outdoor areas with social space, and will also improve well-being.
- Attending cardiac rehabilitation (in person or virtual) should be encouraged for those with an indication.
- Maintaining a social network (virtually if required) should be encouraged.
- Stay mentally active. Undertake enjoyable activities, which require concentration (e.g. read books, listen to music, paint) and take breaks from watching news on COVID-19.
- Physical activity trackers significantly increase physical activity and may be a useful adjunct to promote a healthy lifestyle remotely.[316]

- Medical advice:
  - Continue with prescribed medications for CVD.
  - Seek medical help immediately if experiencing symptoms such as chest pain. Do not neglect symptoms.
  - Do not interrupt cardiac follow-up. Seek advice of a cardiologist promptly in case of deterioration of the CV condition.

SARS-CoV-2 vaccines

Patients with prior CVD should be informed that:

- Vaccines are very effective therapies to prevent severe SARS-CoV-2 infection and have been tested in large-scale randomized trials.
- There are very few contraindications to vaccines and CVD are not a contraindication per se.
- A time delay is needed prior to vaccine therapy after a recent SARS-CoV-2 infection.
- The ones deemed at the highest risk should be treated first, according to local policies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

No new data were generated or analysed in support of this research.

Appendix

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