Diagnosis and Management of CV Disease

During the COVID-19 Pandemic

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1. Introduction

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has reached pandemic levels;
- Patients with cardiovascular (CV) risk factors and established cardiovascular disease (CVD) represent a vulnerable population when suffering from COVID-19;
- Patients with cardiac injury in the context of COVID-19 have an increased risk of morbidity and mortality.

The SARS-CoV-2 causing COVID-19 has reached pandemic levels since March 2020. In the absence of vaccines or curative medical treatment, COVID-19 exerts an unprecedented global impact on public health and health care delivery. Owing to the unexpected need for large capacities of intensive care unit (ICU) beds with the ability to provide respiratory support and mechanical ventilation, temporary redistribution and reorganization of resources within hospitals have become necessary with relevant consequences for all medical specialties. In addition, protective measures against SARS-CoV-2 gain particular significance for health care personnel (HCP) in direct contact with patients suffering from COVID-19 as well as for ambulatory and hospitalized patients without infection. In view of finite health care resources, health care providers are confronted with ethical considerations on how to prioritize access to care for individual patients as well as providing care for COVID-19 while not neglecting other life-threatening emergencies. Of note, assays to detect the virus in asymptomatic and symptomatic patients have important limitations in terms of sensitivity and specificity and will be complemented by tests for antibodies to identify those that already have been infected previously.

SARS-CoV-2 not only causes viral pneumonia but has major implications for the CV system. Patients with CV risk factors including male sex, advanced age, diabetes, hypertension and obesity as well as patients with established CV and cerebrovascular disease have been identified as particularly vulnerable populations with increased morbidity and mortality when suffering from COVID-19. Moreover, a considerable proportion of patients may develop cardiac injury in the context of COVID-19 which portends an increased risk of in-hospital mortality. Aside from arterial and venous thrombotic complications presenting as acute coronary syndromes (ACS) and venous thromboembolism (VTE), myocarditis plays an important role in patients with acute heart failure (HF). Moreover, a wide range of arrhythmias has been reported to complicate the course of COVID-19 including potential pro-arrhythmic effects of medical treatment targeted at COVID-19 and associated diseases.

For all these reasons, the European Society of Cardiology (ESC) has assembled a group of experts and practitioners with experience in the care of COVID-19 patients to provide a guidance document relevant for all aspects of CV care during the COVID-19 pandemic. While the document

is comprehensive, it is important to point the reader to what the document is unable to do and what the limitations are:

- The document is **not a guideline** but rather a **guidance** document. The recommendations are the result of observations and personal experience from health care providers at the forefront of the COVID-19 pandemic. Current evidence related to SARS-CoV-2 and its disease manifestations is observational and prospectively designed interventions are missing to form the basis for evidence-based recommendations;
- This guidance document does not replace any of the official ESC guidelines and is valid only as long as the pandemic status is maintained by the World Health Organization (WHO),
- This guidance document does not override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, and the final decisions concerning an individual patient must be made by the physician(s) responsible;
- The guidance provided in the document should in no way interfere with recommendations provided by local and national health care authorities;
- The pandemic represents a moving target with peak and plateau reached at various timepoints in different regions worldwide. Accordingly, some aspects discussed in this document may only apply to regions most heavily affected by the COVID-19 pandemic, whereas other criteria may apply to less affected geographies;
- The document provides only a snapshot with preliminary information that may change and mature over time with increasing knowledge, evidence from prospective studies and changes in the pandemic. Therefore, comments may be placed on the website that may be considered by the authors for future updates;
- Currently there is no evidence-based treatment of COVID-19 infections and experimental treatment may have cardiac side-effects. We encourage experimental treatments to be part of controlled trials whenever possible.

2. Epidemiology

1. Impact of Cardiovascular Comorbidities on COVID-19 Infection Outcomes

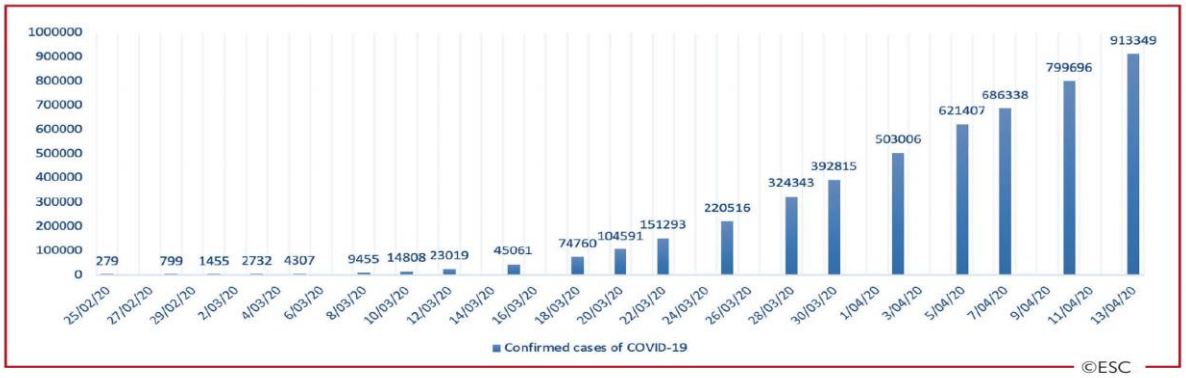
- CV comorbidities are common in patients with COVID-19 infection;
- Presence of CVD is associated with increased mortality in COVID-19 infections;
- CVD risk factors and disease correlate with increasing age

For most countries, it is uncertain how the registration is organized which makes the comparison of case-fatality rates between countries difficult. The excess death rate is a more reliable approach to compare the impact of the COVID-19 pandemic in different countries. An article in the New York Times demonstrated that there are large differences in the excess date rates. Germany has only an excess death rate of 4% which is surprisingly low in comparison with other countries or cities such as Italy (49%), the United Kingdom (65%) (UK), Spain (67%) or New York City (297%).[3]

Furthermore, COVID-19 infection has similar infection rates in both sexes; however, mortality rates are higher in men.[4] Daily situation reports of the COVID-19 pandemic are disseminated by the WHO on their website.

After the start of the COVID-19 pandemic in Wuhan, China, the epicenter of the epidemic is now in Europe. Figure 1 gives an overview of the evolution of laboratory-confirmed cases of COVID-19 in Europe.

Figure 1 Cumulative laboratory-confirmed cases of COVID-19 in Europe (World Health Organization)



2. Cardiovascular Manifestations and Clinical Course of COVID-19 Infection

- Severe COVID-19 infection is associated with myocardial damage and cardiac arrhythmia;
- Monitoring of cardiac toxicity of antiviral drugs is recommended.

Preceding Coronaviruses outbreaks such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) were associated with a significant burden of CV comorbidities and complications.[20,21] Common cardiac complications in SARS were hypotension, myocarditis, arrhythmias, and sudden cardiac death (SCD).[22,23] Diagnostic workup during SARS infection revealed electrocardiographic changes, sub-clinical left ventricular (LV) diastolic impairment and troponin elevation. MERS was associated with myocarditis and HF.[22]

COVID-19 infection seems to have comparable cardiac manifestations. Autopsies of patients with COVID-19 infection revealed infiltration of the myocardium by interstitial mononuclear inflammatory cells.[24] COVID-19 infections are associated with increased cardiac biomarkers levels due to myocardial injury.[24-26] The myocardial injury and the increased levels of biomarkers are likely associated with infection-induced myocarditis and ischaemia.[27] In a study by Shi et al.[26] in 416 patients of whom 57 died, cardiac injury was a common finding (19.7%). In the patients who died, 10.6% had coronary artery disease (CAD), 4.1% had HF, and 5.3% had cerebrovascular disease.[26] Moreover, in multivariable adjusted models, cardiac injury was significantly and independently associated with mortality (hazard ratio [HR]: 4.26).[26] Similarly, in a study by Guo et al.[25], elevated troponin T levels due to cardiac injury was associated with significantly higher mortality. These patients were more likely to be men, to be older and to have more comorbidities such as hypertension, coronary heart disease.[25] Severe COVID-19 infections are also potentially associated with cardiac arrhythmias at least in part due to infection-related myocarditis.[90]

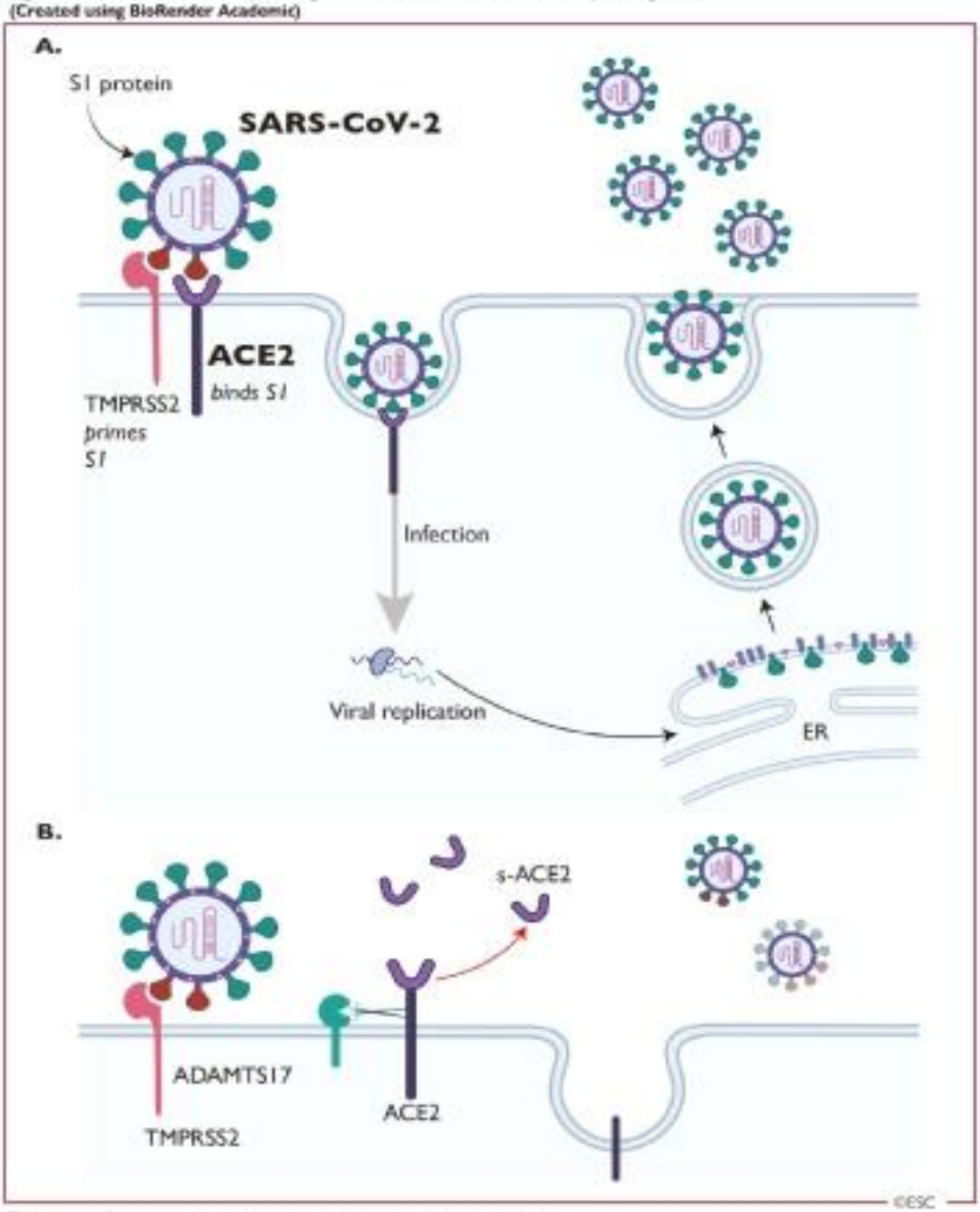
3. Pathophysiology - Mechanism of Disease in Relation with the Cardiovascular System

- The pathobiology of coronavirus infection involves SARS-CoV-2 binding to the host receptor angiotensin-converting enzyme 2 (ACE2) to mediate entry into cells;
- ACE2, which is expressed in the lungs, heart and vessels, is a key member of the renin angiotensin system (RAS) important in the pathophysiology of CVD;
- CVD associated with COVID-19, likely involves dysregulation of the RAS/ACE2 system due to SARS-CoV-2 infection and due to comorbidities, such as hypertension;
- CVD may be a primary phenomenon in COVID-19, but may be secondary to acute lung injury, which leads to increased cardiac workload, potentially problematic in patients with pre existing HF;
- Cytokine release storm, originating from imbalance of T cell activation with dysregulated release of interleukin (IL)-6, IL-17 and other cytokines, may contribute to CVD in COVID-19. IL-6 targeting is being tested therapeutically;
- Immune system activation along with immunometabolism alterations may result in plaque instability, contributing to development of acute coronary events.

COVID-19 is caused by a novel betacoronavirus officially named by the WHO as SARS-CoV-2. Coronaviruses are enveloped, single-stranded ribonucleic acid (RNA) viruses with surface projections that correspond to surface spike proteins.[28] The natural reservoir of SARS-CoV-2 seems to be the chrysanthemum bat,[29] but the intermediate host remains unclear. SARS-CoV-2 is highly virulent and the transmission capacity is greater than the previous SARS virus (outbreak in 2003), with high abundance in infected people (up to a billion RNA copies/mL of sputum) and long-term stability on contaminated surfaces.[30] SARS-CoV-2 is more stable on plastic and stainless steel than on copper and cardboard, and viable virus has been detected for up to 72 hours after application to these surfaces.[30] While the infectivity of SARS-CoV-2 is greater than that of influenza or SARS-coronavirus, more data are needed for accurate assessment.[31] Transmission occurs primarily by a combination of spread by droplet, and direct and indirect contact, and may possibly be airborne as well. The viral incubation period is 2–14 days, (mostly 3–7 days).[32] It is contagious during the latency period. SARS-CoV-2 can initially be detected 1–2 days prior to onset of upper respiratory tract symptoms. Mild cases were found to have an early viral clearance, with 90% of these patients repeatedly testing negative on reverse transcriptase polymerase chain reaction (RT-PCR) by day 10 post-onset. By contrast, all severe cases still tested positive at or beyond day 10 post-onset.[33] Median duration of viral shedding was 20 days (interquartile range: 17–24) in survivors.[34] The longest observed duration of viral shedding in survivors was 37 days.[96]

The host receptor through which SARS-CoV-2 enters cells to trigger infection is ACE2 (Figure 2).[35,36] ACE2 is a multifunctional protein. Its primary physiological role is the enzymatic conversion of angiotensin (Ang) II to Ang-(1–7), and Ang I to Ang-(1–9), which are CV protective peptides.[37] .

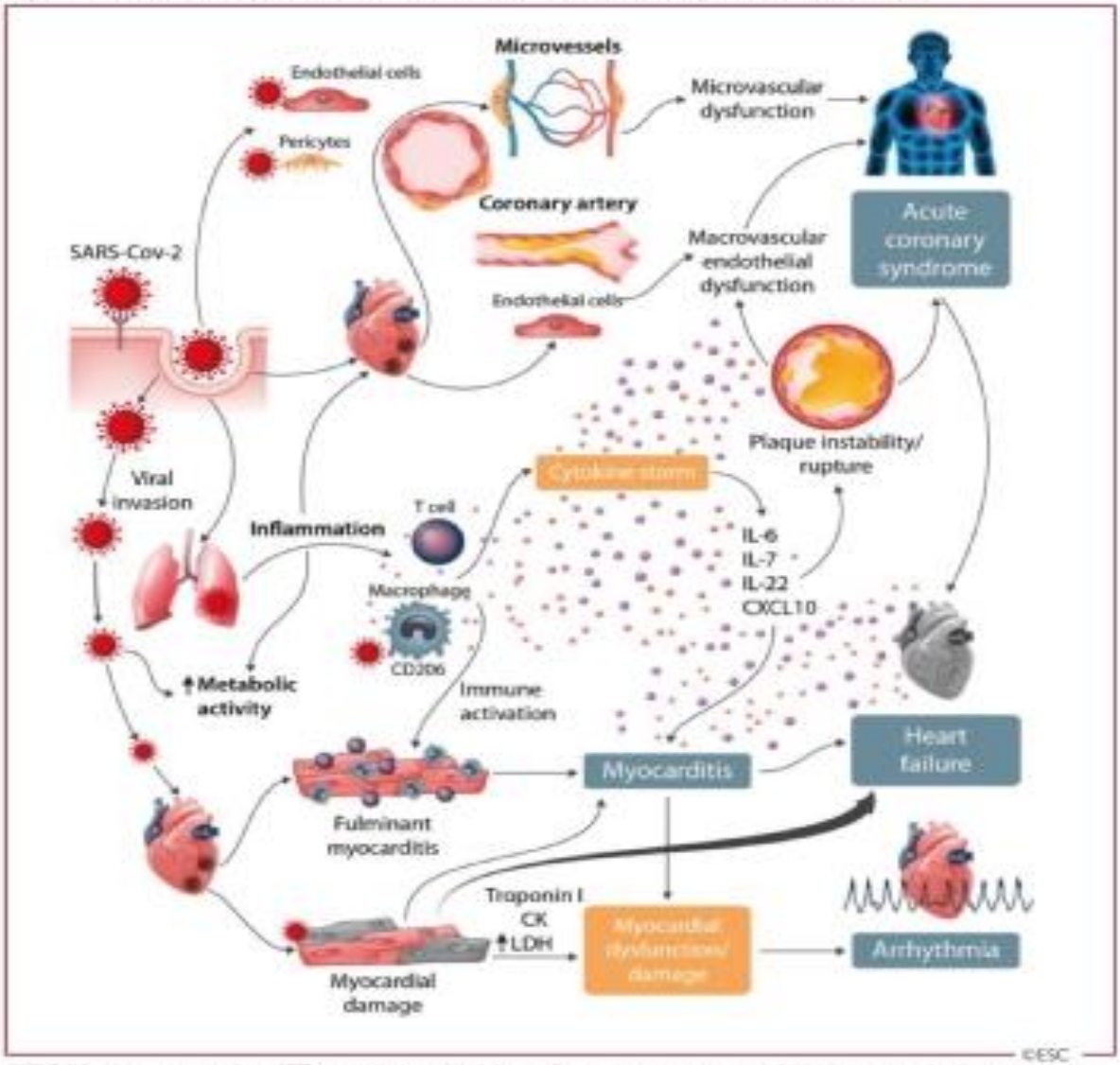
Figure 2 Critical role of ACE2 in the regulation of viral invasion in ACE2 expressing cells (Created using BioRender Academic)



This includes type 2 pneumocytes, cardiomyocytes, pericytes, endothelium and possibly other cell types.
Panel A. SARS-CoV-2 spike protein (S1) is primed by the serine protease TMPRSS2 (transmembrane protease serine 1) which enables its interaction with the membrane bound form of ACE2. This is required for virus internalization and subsequent replication.
Panel B. Membrane bound ACE2 may be shed from the cell membrane by ADAMTS17 disintegrin and metalloproteinase 17) producing soluble ACE2. This mechanism may limit viral invasion.

COVID-19 is primarily a respiratory disease, but many patients also have CVD, including hypertension, acute cardiac injury and myocarditis (Figure 3 from Guzik et al.[43]).[21,44] This may be secondary to the lung disease, since acute lung injury itself leads to increased cardiac workload and can be problematic especially in patients with pre-existing HF. CVD may also be a primary phenomenon considering the important (patho)physiological role of the RAS/ACE2 in the CV system and the fact that ACE2 is expressed in human heart, vascular cells and pericytes.[45]

Figure 3 Cardiovascular involvement in COVID-19 – key manifestations and hypothetical mechanisms



SARS-CoV-2 enters via transmembrane ACE2 to enter the host cells including type-2 pneumocytes, macrophages, endothelial cells, pericytes and cardiac myocytes leading to inflammation and multi-organ failure. Infection of endothelial cells or pericytes of particular importance because the could lead to severe microvascular and macrovascular dysfunction. In addition, immune over-reactivity can potentially destabilize atherosclerotic plaques and explain the development of acute coronary syndromes. Infection of the respiratory tract, particularly type-2 pneumocytes, by SARS-CoV-2 is manifested by the progression of systemic inflammation and immune cell over-activation leading to 'cytokine storm', resulting in increased levels of cytokines such as IL-6, IL-7, IL-22 and CXCL10. Subsequently, it is possible that activated T cell and macrophages may infiltrate infected myocardium resulting in the development of fulminant myocarditis and severe cardiac damage. This process may be further intensified by a cytokine storm. Similarly, the viral invasion may cause cardiac myocyte damage directly leading to myocardial dysfunction and contribute to the development of arrhythmias. From Guzik et al. COVID-19 and the cardiovascular system – implications for risk assessment, diagnosis and treatment options. Cardiovasc Res. 2020; doi: 10.1093/cvr/cvaa106.[43]

Relationships Between Hypertension, Angiotensin-Converting Enzyme 2 and COVID-19

The prevalence of pre-existing hypertension seems to be higher in COVID-19 patients who develop severe disease versus those who do not.[34,46] This seems to also be true for acute respiratory distress syndrome (ARDS) or death. These earlier studies were not age-adjusted and the impact of age still needs to be addressed. The mechanisms underlying potential relationships between hypertension and COVID-19 are thought most likely to relate confounding due to age and associated comorbidities.[47] Previous speculation proposed that treatment of hypertension with RAS inhibitors may influence SARS-CoV-2 binding to ACE2, promoting disease.[48] This is based on some experimental findings that RAS inhibitors cause a compensatory increase in tissue levels of ACE2,[49] and that ACE-inhibitors or ARBs may be detrimental in patients exposed to SARS-CoV-2.[50] It is however important to emphasize that there is no clear evidence that using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) lead to up-regulation of ACE2 in human tissues. The available data from blood samples suggest that there is no association between circulating levels of ACE2 and use of RAAS antagonists.[51] It also appears that in experimental models ARBs may have a potentially protective influence.[52,]

Acute Cardiac Injury and Myocarditis in COVID-19

Myocarditis appears in COVID-19 patients several days after initiation of fever. This indicates myocardial damage caused by viral infection. Mechanisms of SARS-CoV-2-induced myocardial injury may be related to upregulation of ACE2 in the heart and coronary vessels.[44,61] Respiratory failure and hypoxia in COVID-19 may also cause damage to the myocardium and immune mechanisms of myocardial inflammation may be especially important.[27,44,61] For example, cardiac injury leads to activation of the innate immune response with release of proinflammatory cytokines, as well as to the activation of adaptive auto-immune type mechanisms through molecular mimicry.

Immune System Dysregulation and Cardiovascular Disease in COVID-19

Inflammatory mechanisms and activation of immune responses underlie a large range of CVDs including atherosclerosis, HF and hypertension.[62,63] This dysregulation may have different degrees in COVID-19. Firstly another receptor through which SARS-CoV-2 may enter cells is cluster of differentiation 209 (CD209).[101] CD209 is expressed in macrophages promoting virus invasion into immune cells in cardiac and vascular tissues. More importantly, in severe cases of COVID-19, systemic increases of numerous cytokines including IL-6 IL-2, IL-7, granulocyte colony-stimulating factor, C-X-C motif chemokine 10 (CXCL10), chemokine (C-C motif) ligand 2, and tumour necrosis factor-α have all been observed in subjects with COVID-19,[65] which corresponds to the characteristics of a cytokine release syndrome (CRS).

4. Strategies for Diagnosing SARS-CoV-2

- Diagnosis of COVID-19 relies on a combination of epidemiological criteria (contact within incubation period), presence of clinical symptoms as well as laboratory testing (nucleic acid amplification tests) and clinical imaging based tests;
- Antibody and SARS-CoV-2 antigen based enzyme-linked immunosorbent assay (ELISA) tests are under development and are not yet fully validated;
- Widespread testing proves efficient in the containment phase of the epidemic;
- Quality of sample collection (deep nasal swab) and transport (time) to laboratories are essential to avoid false negative outcomes;
- Lung computed tomography (CT) imaging may be used as a diagnostic test in COVID-19.

Table 1 Types of diagnostic approaches in COVID-19[54,65]; *- still in experimental phase, now available for research; POC – point of care

Test	Mechanism of detection	Testing material	Availability for POC	Positive Test indicates	Use of tests
Nucleic acid amplification tests (NAAT)	RT-PCR and NGS detection of genetic sequences of conserved regions for regions of the virus e.g. N, E, S and RdRP genes. Two independent sequences need to be detected	Ambulatory: nasopharyngeal swabs, sputum In hospital: sputum, endotracheal aspirate, BAL blood, feces	No; Needs to be performed in the lab	Confirms current SARS-CoV2 infection	Individual testing
Antibody based immunoassay*	ELISA detecting IgM or IgG anti- SARS-CoV-2 antibodies	Serum	Yes (depending on test design)	IgM+: 3-5 days post onset IgG: past infection	Overall infection/ immunity rates in a community
Antigen based immunoassay*	ELISA detecting viral proteins e.g. S (spike protein) or N protein (nucleocapsid)	nasopharyngeal swabs, sputum and other lower respiratory tract secretions, BAL blood, feces.	Yes (depending on test design)	Confirms current SARS-CoV2 infection	Individual testing
Clinical tests	Clinical symptoms (fever/ cough) Epidemiologial history Imaging (CT)	CT – detection of radiological features	Yes	Infection possible	Triage to identify candidates for further testing

5. Protective Measures for Health Care Personnel and Patients in Cardiology

1. General Risk Assessment and Protective Measures

Taking into account that there are only a few documents regarding type and level of protection of HCP, the ESC Guidance Document considered the WHO document,[73] the American Center for Disease Control and Prevention guidelines on COVID-19,[74] the European Centre for Disease Control guidelines on COVID-19;[75.103] but also Chinese data[76,77] and experiences from European countries with the largest outbreaks of COVID-19. Importantly, the ESC Guidance

document aims to suggest a high level of protection for HCP in the worst transmission scenario of SARS-CoV-2 infection. Different settings, such as countries with no cases, countries with sporadic cases, countries experiencing case clusters in time, geographic location and/or common exposure should prepare to respond to different public health scenarios, recognizing that there is no one size fits all approach to managing cases and outbreaks of COVID-19. Each country should dynamically assess its risk and rapidly change the definitions according to their local situation, depending on the phase of the epidemic, demography, healthcare capacity, and governmental/local health authorities' decisions.

Risk of SARS-CoV-2 Infection in Health Care Providers

Generally, protection against COVID-19 needs to be differentiated according to the level of risk based on patient presentation, type of procedures and interaction and HCP risk status. provides general recommendations.

Table 3 General recommendations for Health Care Personnel, with adaption differentiated according to local community level of risk and containment strategies

• Monitor and record the health status, including body temperature and respiratory symptoms, of all Health Care Personnel.
• In case of any relevant symptom, Health Care Personnel should be isolated immediately, cease patient care activities and perform nasopharyngeal swab or a nucleic acid testing (NAT), if available.
• Symptoms compatible with SARS-CoV-2 infection include:[79, 80] ◆ fever (>37.2°C, may be intermittent or may not be present in some patients) ◆ cough ◆ shortness of breath ◆ sore throat ◆ anosmia and/or ageusia (loss of smell and/or taste) ◆ muscle aches ◆ nausea and/or vomiting ◆ diarrhoea ◆ abdominal pain ◆ headache ◆ runny nose ◆ fatigue
• It is advisable that Health Care Personnel wear medical surgical masks in hospital facilities (at least in the worst transmission scenario for SARS-CoV-2 infection, such as countries experiencing community transmission).
• Use Level II or III protective masks (FFP2, FFP3 or N95) when assessing a probable/suspected case or managing a confirmed case.
• Emphasize hand hygiene; limit the numbers of staff providing their care, implement personal protective equipment (PPE) optimization strategies.
• Health Care Personnel should try to avoid transmission to family members (hygiene measures: e.g. physical distancing, hand washing) particularly if they live with persons at risk (e.g. elderly, patients with multiple morbidities). In case of shortage of medical-grademasks, they could use home-made mask at home and public settings.
• Limit how virus can enter the hospital to reduce the infection risk for both Health Care Personnel and patients: cancel elective outpatient visit, use telemedicine when possible, limit hospital entrance points and number of caregivers. Well separated in-hospital pathways should be organized even when the risk is reduced for separating SARS-CoV-2-positive patients from negative patients.
• Observe social distancing rules inside the hospital.
• Relevant precautions should be taken locally to limit COVID-19 exposure for Health Care Personnel with co-morbidities and/or pregnancy.

The precautions taken depend on COVID-19 case definition as defined in Table 4

Table 4 Patient risk status[73]

Confirmed case	A person with laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical signs and symptoms.
Probable case	A) A suspected case for whom testing for the SARS-CoV-2 virus is inconclusive, OR B) A suspected case for whom testing could not be performed for any reason.
Suspected case	A) A patient with fever or at least one sign/symptom compatible with SARS-CoV-2 infection AND a history of travel to or residence in a location reporting community transmission of COVID-19 during the 14 days prior to symptom onset, OR B) A patient with fever or at least one sign/symptom compatible with SARS-CoV-2 infection AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset, OR C) A patient with severe acute respiratory disease AND requiring hospitalization AND in the absence of an alternative diagnosis that fully explains the clinical presentation.
Negative case	A) A person without COVID-19 symptoms who had contacts with a confirmed or probable COVID-19 case[a] who has a negative SARS-CoV-2 test, OR B) A suspected case with two negative SARS-CoV-2 tests, OR C) COVID-19 patient who recovered from COVID-19 infection who has two negative tests with an interval between the two tests of at least 48 h.

[a]**Definition of a contact[73]**

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

- Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
- Direct physical contact with a probable or confirmed case;
- Direct care of a patient with probable or confirmed SARS-CoV-2 infection without using proper personal protective equipment;
  OR
- Other situations as indicated by local risk assessments.

The level of protection of HCP depends on patient risk status, setting and procedure performed (Table 5). In addition to personal protective equipment (PPE) for HCP, all suspected/probable or confirmed SARS-CoV-2 patients should wear a disposable surgical mask when in room with HCP or other persons.

Figure 4 Different types of masks to be used according to type of procedures and level of risk.
FFP3, FFP2 and N95 are designed to achieve a very close facial fit and very efficient filtration of airborne particles. Powered air-purifying respirator (PAPR) is a type of PPE consisting of a respirator in the form of a hood, which takes ambient air contaminated with pathogens, actively filters these hazards, and delivers the clean air to the user's face and mouth.

Table 5 SARS-CoV-2 related personal protection management[73, 81]

Protection level	Personal Protective Equipment (PPE)	Application Setting/procedures
Level I protection	• Disposable surgical cap • Disposable surgical mask • Work uniform • Latex gloves	• Pre-examination triage, outpatient department (not suspected/not probable SARS-CoV-2 patients)[a] • SARS-CoV-2 negative in-patient
Level II protection	• Disposable surgical cap • Medical protection mask (N95/FFP2) • Work uniform • Gown • Disposable surgical gloves • Goggles	• All suspected/probable or confirmed SARS-CoV-2 patients should wear a disposable surgical mask[b] • Outpatient department (suspected/probable or confirmed SARS-CoV-2 patients) • Isolation ward and ICU areas • Nasopharyngeal swab • Non-respiratory specimen examination of suspected/probable or confirmed SARS-CoV-2 patients • Percutaneous invasive procedures (coronary angiography, PCI, EP procedures) in suspected/probable or confirmed SARS-CoV-2 patients. • Cleaning of surgical or diagnostic instruments (TTE/TEE transducers, stethoscope) used in suspected/probable or confirmed SARS-CoV-2 patients
Level III protection	• Disposable surgical cap • Medical protection mask (FFP3) • Work uniform • Gown • Disposable surgical gloves • Full-face respiratory protective devices or powered air-purifying respirator, if available	• TEE in suspected/probable or confirmed SARS-CoV-2 patients • Areosol generation procedures (AGP): nasopharyengeal swab, endotracheal intubation or other procedures during which the suspected/probable or confirmed SARS-CoV-2 patient may spray or splash respiratory secretions, body fluids or blood

[a]In some countries masks are worn extensively in accordance with local customs or with advice by national authorities in the context of COVID-19. In areas with high community prevalence surgical masks may be worn in all HCP-patient interaction whereas this may not be necessary in low community prevalence areas.

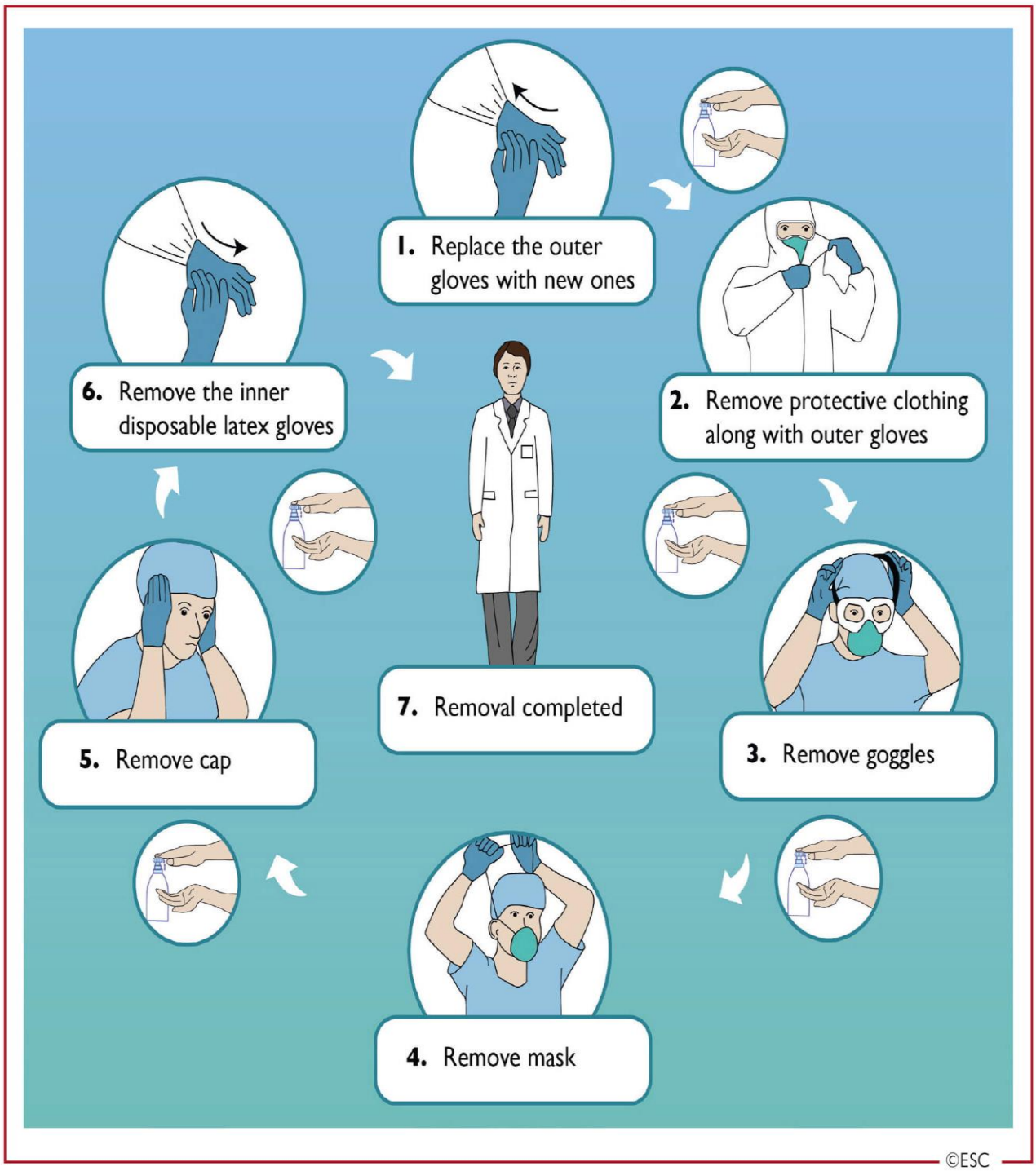
[b]Suspected/probable or confirmed SARS-CoV-2 patients should wear a surgical mask:

- FFP2 and FFP3: Class 2 and 3 filtering face-piece (FFP) respirator masks
- In case of shortage of masks, FFP2 and FFP3 masks can be worn up to 6 hours
- For TEE, a FFP3 mask, if available, may be used for increased safety
- Gloves should be changed for any patient visit
- Personal eyeglasses and contact lenses are NOT considered adequate eye protections
- All Health Care Personnel should avoid touching their face while working

All HCP should be well-versed in proper techniques for donning and removing PPE including eye protection (Figure 5 and Figure 6).[77](TMPRSS2)[39] (Figure 2). Within the host cell cytoplasm, the viral genome RNA is released and replicates leading to newly formed genomic RNA, which is processed into virion-containing vesicles that fuse with the cell membrane to release the virus. SARS-CoV-2 is spread mainly through the respiratory tract by droplets, respiratory secretions and direct contact. The RAS/ACE2 seems to be disrupted by SARS-CoV-2 infection, which likely plays a pathogenic role in severe lung injury and respiratory failure in COVID-19.[40] In addition to the lungs, ACE2 is highly expressed in human heart, vessels and gastrointestinal tract.[41,]

Figure 5 Guidance on donning personal protective equipment (PPE) to manage COVID-19 patients (modified from the "Handbook of COVID-19 Prevention and Treatment")[77]

Figure 6 Guidance on removing personal protective equipment (PPE) to manage COVID-19 patients (modified from the "Handbook of COVID-19 Prevention and Treatment")[77]



2. Settings

Ambulatory Setting

- If possible, it is advisable to provide a surgical mask to every outpatient and health care giver especially in countries experiencing community transmission;
- The facility should perform a triage to assess patient risk status (Table 4);[74]
- This will allow distinguishing of two types of patients, the probable/suspected case or the not probable/suspected or negative case. The first one should be managed in a dedicated ambulatory setting with HCP protection Level II, while the second one should be managed in another ambulatory with HCP protection Level I (Table 5).

Ward Setting

- If possible, it is advisable to provide a surgical mask to every inpatient and care giver, especially in countries experiencing community transmission;[74,76,77]
- Newly admitted patients in a cardiology ward should be regarded as possibly infected by SARS-CoV-2 according to Table 4.[82] In these cases, the patient should undergo a swab test and should be managed in the meantime with level II or III protections (Table 5). These patients need to be managed in a dedicated area of the ward;
- Confirmed cases should be managed with level II or III protection if possible, in airborne precaution single rooms with a dedicated bathroom. Most hospitals will however be cohorting confirmed COVID-19 patients, since there may not be enough individual isolation capacity;
- The use of dedicated medical equipment (e.g. blood pressure [BP] cuffs, stethoscopes and thermometers) for confirmed/probable/suspected COVID-19 cases is strongly recommended.[75] If not possible, equipment must undergo disinfection according to local instructions;
- If the swab test is negative, but suspicion of SARS-CoV-2 infection is maintained, it is advisable to perform either a second swab test, endotracheal aspirate and/or a lung CT scan, depending on local capabilities and symptoms, bearing in mind the limited sensitivity of swab tests. These patients should be maintained in a dedicated area of the ward, with private room and bathroom, and isolated until the result of the new test is available;[65]
- Other cases should be managed with level I protection (Table 5), in a "clean" area of the ward;[74]
- If there are sufficient resources, there is a benefit in testing patients without COVID-19 symptoms, in particular in high-prevalence areas.

Emergency Department

- It is advisable to provide a surgical mask to every emergency department (ED) patient, especially in countries experiencing community transmission;

- The safety of HCP in the setting of ED and ICU is a major challenge and requires detailed and dedicated training on the appropriate use of PPE;
- COVID-19 triage should be performed and dedicated areas should be identified to manage not suspected from suspected/probable cases;[74]
- Before performing cardiology consultations in the ED, it is advisable to carry out a quick telephone interview to assess if the patient has suspected COVID-19 symptoms or risk factors for COVID-19 (see Table 3) or suspicious chest X ray/CT scan;[74]
- If any suspicion is present and cardiology advice is urgent, without having the chance to postpone it until the result of the swab test, the patient should be deemed positive for SARS-CoV-2 infection and maximum protection measures must be taken (Level II protection, Level III protection in case of aerosol generation procedure [AGP]) (Table 5);
- Other ED cases should be managed with level I protection (Table 5).

Intensive Care Unit

- Since patients admitted to ICU are critical and may be supported by ventilation (i.e. continuous positive airway pressure [CPAP], orotracheal intubation), a high threshold of protection should be applied to patients with confirmed/suspected/possible COVID-19, with Level II protection or Level III protection in case of AGP (Table 5);
- It is advisable that every patient has his own room and non-COVID-19 patients should be managed with Level I protection (Table 5) by dedicated HCP different from the ones who care for COVID-19 patients.[89]**.Catheterization Laboratory**

- HCP should be well-versed in proper techniques for donning and removing PPE including eye protection (Figure 5 and Figure 6). [90] Catheterization laboratory directors should ensure adequate availability, replacement and training in the use of this equipment;
- All patients entering the catheterization laboratory should wear a surgical mask..

ST-Segment Elevation Myocardial Infarction

Because there is no time to wait for nasopharyngeal swab result, the procedure should be performed in a dedicated COVID-19 catheterization laboratory if available and patients should be triaged according to Table 4. In regions with high rates of community transmission, it is reasonable to regard all patients as possible SARS-CoV-2 positive and HCP protected accordingly (Table 5)

Non-ST-Segment Elevation Myocardial Infarction – Acute Coronary Syndrome

- Very high-risk non-ST-segment elevation (NSTE)-ACS should follow the ST-segment elevation myocardial infarction (STEMI) pathway and HCP protected accordingly;
- Others should undergo a nasopharyngeal swab immediately after admission (Figure 12). Waiting for swab result, patients must be isolated in a dedicated and monitored ED area because of the prevalence of asymptomatic patients with SARS-CoV-2 infection, with the aim to reduce the risk of infection spreading within the hospital. When there are two negative results within 48 hours and absence of suspicious symptoms of virus infection, coronary angiography and eventual percutaneous coronary intervention (PCI) may be performed in a catheterization laboratory reserved for SARS-CoV-2-negative patients.

- **Patients with SARS-CoV-2 positive test**
  - If an invasive approach is clinically indicated, the procedure should be performed in a dedicated COVID-19 catheterization laboratory if available;
  - Intubation threshold should be lowered in patients with borderline respiratory status to avoid emergent intubation and aerosol generation in the catheterization laboratory;
  - Because patient transportation from the ward to the catheterization laboratory may carry the risk of in-hospital infection transmission, some procedures routinely performed in the catheterization laboratory (e.g. Swan-Ganz catheter placement, pericardiocentesis, and intra-aortic balloon pump insertion) should be considered for bedside performance;
  - The catheterization laboratory staff should be minimized and, in case of haemodynamic instability of the patient, should wear Level II or Level III PPE (Table 5), including gown, gloves, goggles (or shields), and a FFP2/FFP3 mask (Figure 4);
  - Any intubation, suction, or cardiopulmonary resuscitation (CPR) may cause aerosol dispersion of respiratory secretions with increased likelihood of exposure to the staff. For this reason, use of powered air-purifying respirator (PAPR) systems, if available, may be reasonable (Figure 4);
  - In case of manual ventilation during CPR, a high-efficiency particulate air filter may be placed between the tube and the bag valve mask to reduce the risk of aerosol dispersion;
  - Because most catheterization laboratories are not designed for infection isolation with negative pressure, a terminal cleaning and sanitization should be performed after each procedure. Of note, air exchange times of the catheterization laboratory should be checked (minimum 15 exchanges per hour, ideally 30 exchanges per hour).

Patients

- CV patients should be always protected from the exposition to SARS-CoV-2 infection, in particular because of the worse outcome for this patient group;
- Patients should be educated on how to protect themselves from virus contact and the information should be preferably provided in illustrative format (e.g. below Figure 7).
- Patients admitted to the ward services should stay in the hospital for the shortest time possible, minimizing both professionals and patient's exposure to the virus;
- Enough resources should be kept active to cope with all the CV emergencies both for COVID-19-free and for infected patients;
- Any elective admittance for diagnostic or therapeutic purposes that may be postponed should not take place during the virus outbreak (complying with the purpose of not overwhelming institutions with non-urgent hospitalizations and at the same time with the obligation of not making stable CV patients unnecessarily exposed to virus infection);
- Staff members should be educated to respect barrier measures and dedicated lounge where social distancing is possible should be provided.

It is now well known that CV patients who develop a COVID-19 infection have a higher risk of poor in-hospital outcome.[103] This is why it is mandatory to effectively protect them from being in contact with infected subjects whose COVID-19-related symptoms are still not evident or not specific. Wang et al reported a significant percentage of hospital-associated transmission of the virus (12.3% of all patients) in a cohort of hospitalized patients with novel coronavirus-infected pneumonia in Wuhan, China at the start of the pandemic.[10] Based on this data, patients accessing the hospital for an acute cardiac disease with no signs or symptoms of viral infection should complete their diagnostic workflow in a clean area and finally access a COVID-19-free ward. All the measures to keep chronic cardiac outpatients at home as much as possible as well as to limit in-hospital stay of cardiac patients to the shortest acceptable time should be implemented. The adoption of a restrictive visitor policy is also strongly recommended.[85]

Elective procedures should be avoided during the current COVID-19 pandemic so as not to overload the health system or increase the risk of disease propagation. In this context, in order to minimize risk for COVID-19 transmission, the use of telemedicine is highly desirable especially for vulnerable groups, such as older patients. Additionally, telemedicine provides an opportunity for tele-consultations with different specialists and professionals, thus allowing patients to receive a comprehensive therapeutic approach without moving from home to the outpatient clinic or to the hospital. Also telerehabilitation (or home based rehabilitation with telephone contact with the rehab team) is an option for patients discharged from the hospital after an acute event. Finally telemedical follow up of HF and device patients is becoming more and more standard and may be considered. Telemedicine has been considered relevant in contributing to viral outbreak containment while preventing patient health from deteriorating because of misdiagnosed or mistreated CVDs .97

Triage Systems (Reorganization and Redistribution)

Overriding Principles of Triage

- The high priority given to patients with COVID-19 infection may compromise the rapid triage of non-COVID-19 patients with CVD;
- A proper patient triage favours the right in-hospital allocation based on the infective status and allows the prompt adoption of protective measures both by HCP and by patients;
- Acute cardiac patients accessing the intensive cardiac care unit (ICCU) or the catheterization laboratory in a fast track fashion should be considered as likely SARS-CoV-2 positive, until they are proved not infected.

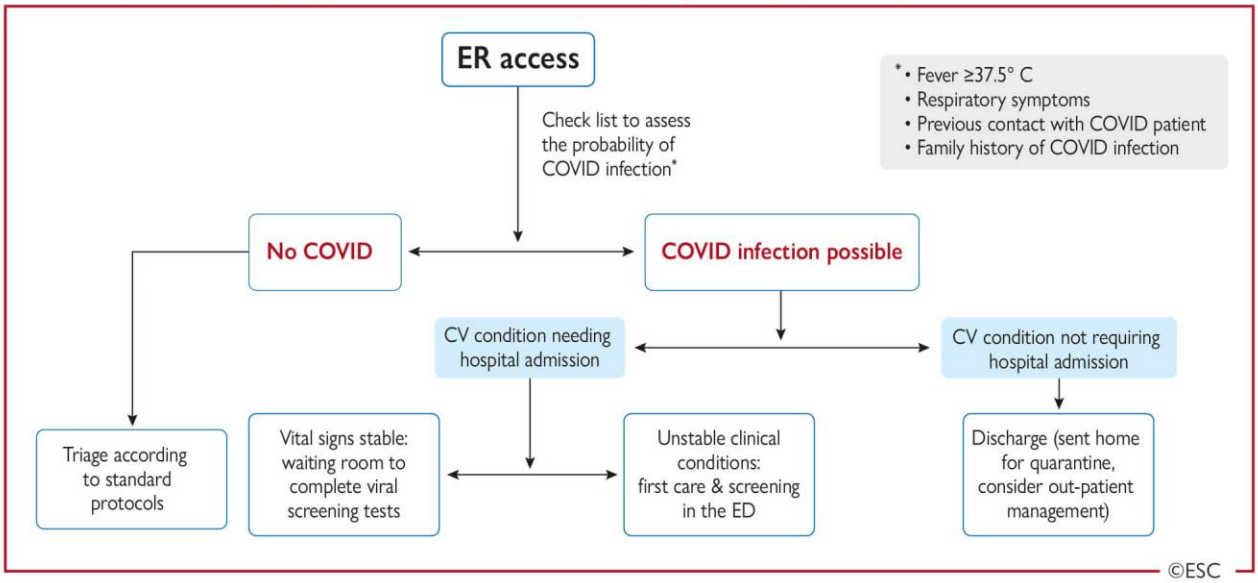
Hospital and Ambulance Networks

- A contained number of hospitals equipped with a catheterization laboratory operating 24 hours/7 days should still maintain their hub role for the management of time-dependent acute CVD;
- Resources and cardiac specialists should be concentrated in the hub centres to guarantee the appropriate acute treatment to all the cardiac patients in need of it;
- The ambulance networks should be rearranged according to the new hub and spoke organization.

Emergency Department

- A rearrangement of the ED is mandatory to separate suspected COVID-19 patients from patients without SARS-CoV-2 infection;
- Local protocols to rapidly triage patients with respiratory symptoms should be available as well as facilities where patients wait for the results of COVID-19 screening tests. Patients with mild, stable diseases should be promptly discharged.

Figure 8 Algorithm for triaging patients admitted to the Emergency Room (ER) for a suspect acute CV disease



Intensive Care Unit and Intermediate Care Unit

- Non-COVID-19 patients with acute CVDs should be preferably admitted to COVID-19 free ICUs/ICCUs, mostly available in the COVID-19 referral centres;
- Care of COVID-19 patients with severe CVDs might be downgraded to lower intensity levels, if the patient prognosis is poor and ICU/ICCU beds are in short supply.

Diagnosis of Cardiovascular Conditions in COVID-19 Patients

Clinical Presentation

1. Chest Pain

- Chest pain and breathlessness is a frequent symptom in COVID-19 infection;
- Chronic and acute coronary syndrome presentations can be associated with respiratory symptoms.

The symptom of chest pain or tightness is common in patients with active COVID-19 infection. It is usually poorly localized and may be associated with breathlessness due to the underlying pneumonia. Associated profound hypoxaemia together with tachycardia may result in chest pain and electrocardiographic changes suggestive of myocardial ischaemia. Where biomarkers are altered, Type 2 myocardial infarction (MI) may be suggested. Patients with ACS do, however, experience the more typical symptoms related to ischaemia. The presence of a COVID-19 infection can make the differential diagnosis more difficult, as shortness of breath and respiratory symptoms may be present and may precede or precipitate cardiac signs and symptoms.

2. Dyspnoea, Cough, Respiratory distress

- COVID-19 patients may present with cough, dyspnoea, and ARDS

1. Dyspnoea

Dyspnoea (shortness of breath) is one of the typical symptoms in COVID-19. Of 1099 adult inpatients and outpatients in China, 18.7% presented with dyspnoea.[80] With increasing disease severity, the proportion of dyspnoea significantly increases (31–55% in hospitalized patients and up to 92% of patients admitted to ICUs).[10,33]

2. Cough

Cough is present in 59.4–81.1% of patients with COVID-19, irrespective of disease severity.[34,60] Unproductive (dry) cough is more frequent, whereas sputum production is present in 23.0–33.7%.[10,34,65,80]

3. Acute Respiratory Distress Syndrome

ARDS is characterized by bilateral opacifications on chest imaging (e.g. bilateral ground glass opacifications on CT) and hypoxaemia that cannot be explained by other causes.[45] Among 1099 adult inpatients and outpatients in China, ARDS occurred in 3.4%,[30] but in hospitalized patients, the rates are significantly higher (19.6–41.8%).[10,34,] The median time from disease onset to ARDS is 8–12.5 days.[65] The risk of ARDS increases with older age (≥ 65 years old), presence of comorbidities (hypertension, diabetes), neutrophilia, lymphocytopenia, elevated laboratory markers of organ dysfunction (e.g. lactate dehydrogenase [LDH]), inflammation (C reactive protein) and D-dimer.[99] Mortality of patients treated for ARDS in COVID-19 is high (e.g. 52–53%).[10,34,65,]

Cardiogenic Shock

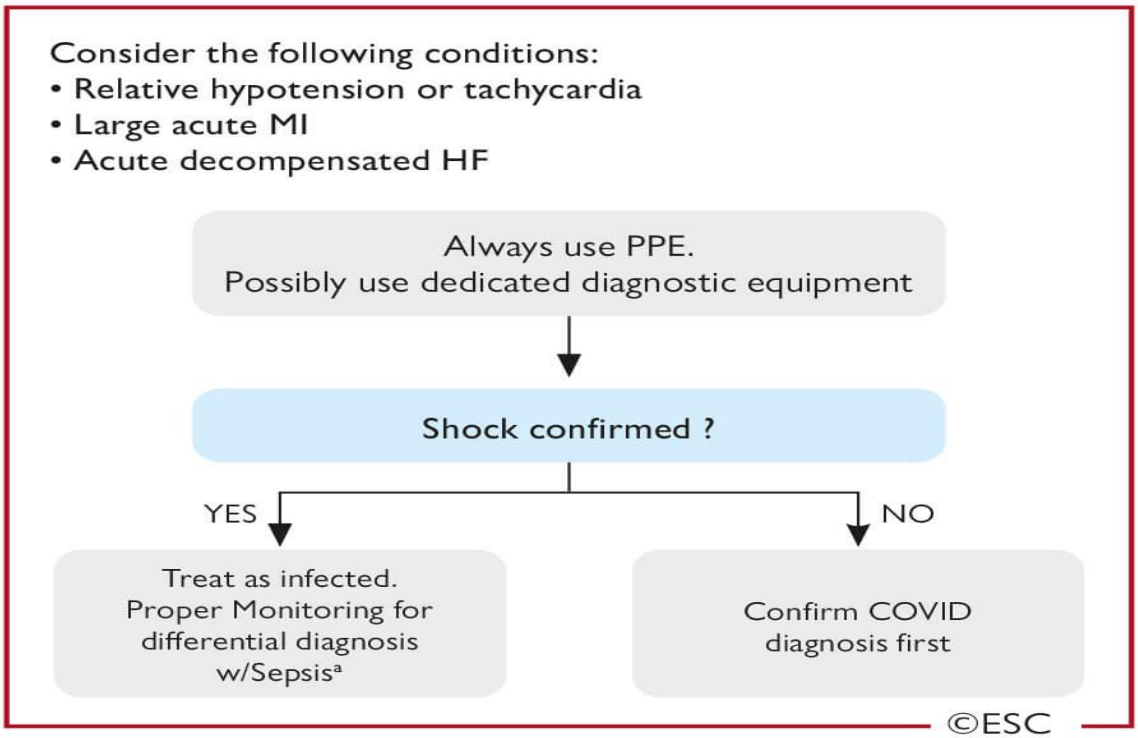
- In COVID-19 patients with impaired end-organ perfusion at risk of cardiogenic shock (CS) (e.g. large acute myocardial infarction [AMI]), consider also sepsis as possible or mixed aetiology;
- Myocarditis should be considered as precipitating cause of CS.

An early, accurate, and rapid diagnosis of CS in patients with confirmed or suspected COVID-19 is essential.[104] The exact incidence of CS in these patients is unknown. However, the median duration between onset of symptoms and admission to ICU in critically ill COVID-19 patients has been 9–10 days, suggesting a gradual respiratory deterioration in most patients.[65]A simple, actionable classification scheme for CS diagnosis has recently been proposed.[103]

In critically ill COVID-19 patients at risk for CS (such as those with large AMI, acute decompensated HF; Society for Cardiovascular Angiography and Interventions stage A)[103] and sepsis, a mixed aetiology of CS and septic shock should be considered in addition to the sole cardiogenic component. Parameters allowing for a differential diagnosis between CS and septic shock, such as the presence of vasodilatation and central venous oxygen saturation values may be assessed. In selected cases, such as in patients with unclear reasons for haemodynamic deterioration, invasive haemodynamic monitoring via a pulmonary artery catheter may provide useful information.

The diagnostic work-up of critically ill patients with confirmed or suspected COVID-19 infection requires specific considerations:

Figure 9 Considerations in patients with suspected (or at risk for) cardiogenic shock and possible COVID-19 infection



[a]consider also myocarditis as potential cause.

4. Out-of-Hospital Cardiac Arrest, Pulseless Electric Activity, Sudden Cardiac Death, Tachyarrhythmias, Bradyarrhythmias

- Symptoms of brady- and tachyarrhythmias do not differ from the usual clinical presentation;
- In the context of the SARS-CoV-2 pandemic, HCP remain alert for symptoms suggestive of brady- or tachyarrhythmias as patients are still at risk of conduction disturbances and supraventricular/ventricular arrhythmias;
- Healthcare authorities and hospital managers should ensure that there is a proper pathway for the early detection and management of rhythm disorders.

There is very limited literature available on the occurrence of arrhythmia in the context of an infection by the SARS-CoV-2 virus. The clinical presentation of brady- or tachyarrhythmias in the context of COVID-19 does not differ from those previously described (i.e. palpitations, dyspnoea, dizziness, chest pain, syncope, etc.). However, there are concerns that in areas where the epidemic is extended, hospitals have experienced a significant decrease in emergency consultations for cardiac. Whether the underlying reason is concern for in-hospital contagion, a result of self-isolation measures or a saturation of the EDs and ambulances needs to be explored.

5. Hospitalization for Pneumonia and Time Course of Increased Subsequent Risk of Cardiovascular Death

- Pneumonia, influenza and SARS are well known to be associated with a markedly increased short-term risk for subsequent CV events, such as ACS;
- There needs to be a high alertness for CV events, such as ACS and thromboembolic events, in the short-term after pneumonia and a careful risk management approach in individuals with pre-existing CVD

Pneumonia and severe influenza infections have been associated with a markedly increased short term risk of MI and subsequent mortality, that is more common among patients at older age, nursing home resident, and patients with history of HF, coronary disease or hypertension.[44-105] Moreover, for influenza epidemics it has been demonstrated that there is a consistent rise in autopsy-confirmed coronary deaths.[50] Fatal AMIs have also been observed in the short term after coronavirus associated SARS.[62]

Electrocardiogram

- The same ECG diagnostic criteria for cardiac conditions apply in patients affected by the SARS-CoV-2 infection and in the general population

Biomarkers

- Cardiomyocyte injury, as quantified by cardiac troponin T/I concentrations, and haemodynamic stress, as quantified by B-type natriuretic peptide (BNP) and N-terminal B type natriuretic peptide (NT-proBNP) concentrations, may occur in COVID-19 infections

as in other pneumonias. The level of those biomarkers correlate with disease severity and mortality;

- Cardiac troponin T/I and BNP/NT-proBNP concentrations should be interpreted as quantitative variables;
- In patients hospitalized with COVID-19, mild elevations in cardiac troponin T/I and/or BNP/NT-proBNP concentrations are in general the result of pre-existing cardiac disease and/or the acute injury/stress related to COVID-19;
- In the absence of typical angina chest pain and/or ischaemic ECG changes, patients with mild elevations (e.g. < 2–3 times the upper limit of normal [ULN] do NOT require work-up and/or treatment for Type 1 myocardial infarction [T1MI]);
- In patients with COVID-19, as in patients with other pneumonias, it is suggested to measure cardiac troponin T/I concentrations only if the diagnosis of T1MI is being considered on clinical grounds, or in new onset LV dysfunction. Independently from diagnosis, monitoring of cardiac troponin T/I may help for the purpose of prognostication;
- D-Dimers quantify activated coagulation, a prominent feature in COVID-19. Due to the central role of endotheliitis and VTE in COVID-19, serial measurements of D-dimers may help physicians in the selection of patients for VTE-imaging and/or the use of higher than prophylactic doses of anticoagulation.

Biomarker Elevation Suggesting Cardiovascular Conditions in Patients with COVID-19 Infection

Cardiac Troponin I/T

COVID-19 is a viral pneumonia that may result in severe systemic inflammation and ARDS, and both conditions have profound effects on the heart.[26,34,102] As a quantitative marker of cardiomyocyte injury, the concentrations of cardiac troponin I/T in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease AND the acute injury related to COVID-19.[34,,55] elevations in cardiac troponin T/I concentrations (e.g. > 5 times the ULN) may indicate the presence of shock as part of COVID-19, severe respiratory failure, tachycardia, systemic hypoxaemia, myocarditis, Takotsubo syndrome or T1MI triggered by COVID-19.[26,34,] In the absence of symptoms or ECG changes suggestive of T1MI, echocardiography should be considered in order to diagnose the underlying cause. Patients with symptoms and ECG changes suggestive of T1MI should be treated according to ESC-guidelines irrespective of COVID-19 status.[24,66,]

B-Type Natriuretic Peptide/N-Terminal B-Type Natriuretic Peptide

BNP/NT-proBNP as quantitative biomarkers of haemodynamic myocardial stress and HF are frequently elevated among patients with severe inflammatory and/or respiratory illnesses.[26,-]While experience in patients with COVID-19 is limited, very likely the experience from other pneumonias can be extrapolated to COVID-19.[26,]

D-Dimers

D-dimers are generated by cleavage of fibrin monomers by prothrombin and indicate the presence of thrombin formation or reflect an unspecific acute phase response from infection or

inflammation. D Dimers also may indicate the presence of disseminated intravascular coagulation associated with shock.[18] It is tempting to speculate that markers of activated coagulation or impaired fibrinolysis might contribute to acute myocardial injury, eventually also affecting coronary capillaries. Therefore, markers of haemostasis including activated partial thromboplastin time, prothrombin time, fibrin degradation products and D-Dimers should be monitored routinely. In particular, elevations of D-Dimers have been associated with poor outcome.[43]

Which Biomarkers Should be Measured and When?

As in patients without COVID-19, cardiac troponin T/I concentrations should be measured whenever on clinical grounds T1MI is suspected.[13] In patients with COVID-19, diagnostic algorithms for rapid rule out and/or rule-in of MI in patients with acute chest discomfort such as the ESC high-sensitivity cardiac troponin (hs-cTn) T/I 0/1-h algorithm can be expected to provide comparable performance characteristics as in other challenging subgroups with higher baseline concentrations such as the elderly and patients with renal dysfunction: very high safety for rule-out and high accuracy for rule-in, but reduced efficacy with a higher percentage of patients remaining in the observe zone.[53] Detailed clinical assessment including chest pain characteristics, assessment of COVID-19 severity, hs-cTn T/I measurement at 3 hours, and cardiac imaging including echocardiography are the key elements for the identification of MI in this heterogeneous subgroup.[55]

Similarly, BNP/NT-proBNP should be measured whenever on clinical grounds HF is suspected.[26,17] In patients who are not critically ill, rule-in cut-offs for HF maintain high positive predictive value even in patients with pneumonia.[26,]In contrast, currently recommended cut-offs should not be applied in critically-ill patients, as most critically-ill patients have substantial elevations in BNP/NT-proBNP, most likely due to the near-universal presence of haemodynamic stress and HF in these patients.[87,]

Therefore, routine measurements of cardiac troponin T/I and/or BNP/NT-proBNP in patients with COVID-19 given the current very limited evidence for incremental value for clinical decision-making is discouraged.

Non-Invasive Imaging

- Do not perform routine cardiac imaging in patients with suspected or confirmed COVID-19;
- Prevent contamination from patients to other patients, to imagers and imaging equipment;
- Perform imaging studies in patients with suspected or confirmed COVID-19 only if the management is likely to be impacted by imaging results;
- Re-evaluate which imaging technique is best for your patients both in terms of diagnostic yield and infectious risk for the environment;
- The imaging protocols should be kept as short as possible.

Table 6 Non-invasive cardiovascular stress testing and imaging tests with the potential for deferral in the light of the COVID pandemic (Reproduced from Gluckman et al.[127])

- Stress testing (ECG alone or with imaging [echocardiography, radionuclide, MRI]) for suspected stable ischaemic heart disease (outpatient and inpatient)
- Cardiopulmonary exercise testing for functional assessment (outpatient and inpatient)
- Transthoracic echocardiograms (outpatient)
- Transoesophageal echocardiograms in stable patients (outpatient and inpatient)
- Cardiovascular CT (outpatient)
- Cardiovascular magnetic resonance imaging (MRI) (outpatient)
- Nuclear cardiac imaging (SPECT and PET) (outpatient and inpatient)
- Vascular imaging for asymptomatic carotid artery disease (outpatient and inpatient)
- Vascular imaging for claudication (outpatient and inpatient)
- Imaging for screening purposes (e.g., coronary calcium score, screening ultrasound to assess for an AAA or carotid disease) (outpatient and inpatient)

AAA = abdominal aortic aneurism; CT = computed tomography; ECG = electrocardiogram, MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography.

Transthoracic and Transesophageal Echocardiography

- Avoid performing transthoracic, transesophageal and stress echocardiograms in patients in which test results are unlikely to change the management strategy;
- TEE carries increased risks of spread of COVID-19 due to exposure of HCP to aerosolization of large viral load and should not be performed if an alternative imaging modality is available;
- In COVID-19 infected patients, the echocardiogram should be performed focusing solely on the acquisition of images needed to answer the clinical question in order to reduce patient contact with the machine and the HCP performing the test;
- POCUS, focused cardiac ultrasound study (FoCUS) and critical care echocardiography performed at bedside are effective options to screen for CV complications of COVID-19 infection.

Computed Tomography

- CV CT should be performed in hospitalized patients only with indications in which imaging results will likely impact management;
- CCTA may be the preferred non-invasive imaging modality to diagnose CAD since it reduces the time of exposure of patients and personnel;
- Cardiac CT may be preferred to TEE in order to rule-out left atrial appendage (LAA) and intracardiac thrombus prior to cardioversion;
- In patients with respiratory distress, chest CT is recommended to evaluate imaging features typical of COVID-19;
- Check renal function when contrast is indicated.

Nuclear Cardiology

- Nuclear cardiology should be performed only in specific indications and when no other imaging modalities can be performed;
- The shortest duration of scan time and exposure should be used;
- Standard dose imaging with rapid protocols of data acquisition are recommended.;
- Attenuation corrected imaging should be considered;
- Positron emission tomography (PET) minimizes the acquisition times.

Many of the diagnoses can be evaluated with other imaging modalities that limit the risk of virus spread. Nuclear cardiology tests require long acquisition times and exposure of patients and personnel.[32]

Cardiac Magnetic Resonance

Use shortened cardiac magnetic resonance (CMR) protocols focused to address the clinical problem;

- Check renal function when contrast is indicated;
- CMR is preferred in acute myocarditis.

The risks of contamination during a CMR scan is probably similar to a CT scan, but lower than during an echocardiographic study. Only clinically urgent CMR scans should be accepted.[33]

Longer time exposure in the scanner will probably increase the chances of contamination of equipment and staff. In order to minimize the examination time, shortened CMR protocols focused to address the clinical problem should be used.[103] A dedicated MR scanner for patients with suspected or confirmed COVID-19 is a clear advantage. Allow time for a deep cleaning after each patient with suspected or confirmed COVID-19 infection.

Exercise Testing

Performance of exercise testing (either conventional, Echo or nuclear) has major limitations in the COVID-19 era. During exercise the patient increases breath rate and the amount of aerosol or droplets production, even if wearing a surgical maske[105]

Differential Diagnosis

- The presence of COVID-19 infection should not preclude a systematic search for CV events, including ACS;
- COVID-19 infection-related injury should be kept in mind as differential diagnosis;
- Other manifestations and complications of COVID-19 infection mimicking heart disease should also have been ruled out

In COVID-19-infected patients with clinical presentation compatible with CVD, three main entities should be considered:

- Patients with COVID-19 infection can present cardiac events, that can be favoured by the infection or unrelated. Those include ACS (STEMI and NSTEMI), acute HF, arrythmias, thoromboembolic events, CS, and cardiac arrests. Those syndroms require a quick diagnosis and management, and should not be overlooked due to the presence of COVID-19 infection;
- Infection-related cardiac injury can also lead to a clinical presentation suggestive of cardiac event, and should also be considered as a differential diagnosis.
- Patients with COVID-19 infection can present with symptoms mimicking CV events, including chest pain, dyspnoea, and shock, even in the absence of cardiac injury.

Categorization of Emergency/Urgency of Invasive Procedures

Table 7 Impact on the healthcare system and regional involvement in the epidemic

	Regional involvement in the epidemic		
	Marginal	Moderate	Heavy
Impact on the healthcare system and regular services	None or minor restrictions	Major restrictions	Inability to provide

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The indications provided in this document refer mainly to the scenario of heavy involvement and, in part, to the scenario of moderate involvement. Importantly, healthcare services should continue to be provided according to standard-of-care as described by current clinical practice guidelines, as long as the degree of regional involvement in the epidemic allows it. The rationale to importantly reduce the number of elective hospitalizations is three-fold:

1. To increase capacity for COVID-19 patients;
2. To reduce the unjustified exposure of individuals (i.e. patients in need of non-urgent procedures and their relatives) to the hospital and surrounding environment;
3. To reduce the exposure of health care providers to asymptomatic COVID-19 patients.

This strategy comes at the expense of time-to-treatment delays for urgent CV interventions and extension of waiting times for patients in need of elective coronary, heart valve or other CV interventions.

Table 8 Strategical categorization of invasive cardiac procedures during the COVID-19 pandemic

Clinical condition	EMERGENCY (do not postpone)	URGENT (perform within days)*	LOWER PRIORITY (perform within <3 months)*	ELECTIVE (may be postponed >3 months)
Ischaemic heart disease	• STEMI • NSTE-ACS in very high risk and high risk patients • Cardiogenic shock	• NSTE-ACS in intermediate risk patients • Unstable angina • Left main PCI • Last remaining vessel PCI • Decompensated ischaemic heart failure • Angina pectoris class IV • CABG in patients with NSTE-ACS unsuitable for PCI	• Advanced CAD with angina class III or NYHA III symptoms • Staged PCI of non-culprit lesions in STEMI • Proximal LAD PCI	• CTO interventions • CCS with angina class II or NYHA II symptoms
Valvular heart disease	• BAV as a bridge to TAVI/SAVR in highly selected decompensated patients • Surgery in aortic dissection or cardiovascular trauma • Valve repair/replacement for acute failing native or prosthetic valve causing shock	• TAVI in patients with decompensated aortic stenosis • Transcatheter mitral edge-to-edge repair in haemodynamically unstable patients with acute MR who are unsuitable for surgery • Mitral valve surgery in haemodynamically unstable patients with acute ischaemic MR • MR and aortic regurgitation in patients with endocarditis • High risk of embolism in acute infective endocarditis • Surgery for left atrial myxoma	• TAVI/SAVR in severe aortic stenosis (AVA <0,6 cm², mean transvalvular gradient >60 mmHg, symptoms with minimal exertion) • TAVI/SAVR in symptomatic patients with low-flow low-gradient AS (AVA <1.0 cm², mean transvalvular gradient <40 mmHg, LVEF <50%) • Mitral valve surgery or transcatheter mitral edge-to-edge repair in patients with MR and congestive HF who cannot be stabilized with medical therapy	• TAVI/SAVR for symptomatic severe aortic stenosis (AVA <1.0 cm², mean transvalvular gradient >40 mmHg) • TAVI/SAVR with symptomatic paradoxical low-flow low-gradient aortic stenosis (AVA <1.0 cm², mean transvalvular gradient <40 mmHg, LVEF> 50%) • Mitral valve surgery or transcatheter mitral edge-to-edge repair for secondary MR with stable HF
Acute / chronic heart failure	• Mechanical circulatory support for cardiogenic shock (<65 years)	• Urgent heart transplant	• LVAD	
Arrhythmic heart disease	• PM implantation in symptomatic AV block or symptomatic sinus node dysfunction with asystolic pauses	• ICD implantation in cardiac arrest or VT with syncope as secondary prophylactic indication • Catheter ablation in recurrent therapy-refractory VT/VF • Catheter ablation in AF with WPW syndrome and rapid preexcited ventricular rates; • Battery replacement in case of EOL in pacing dependency • Lead extraction in patients with infective endocarditis	• Catheter ablation in treatment-resistant AF with fast ventricular rate	• Elective ablation and cardiac device implantation procedures
Other interventions	• Pericardiocentesis in cardiac tamponade		• Biopsies	• LAA occlusion in stable patients • PFO closure • ASD closure • Right heart catheterization • Alcohol ablation in hypertrophic cardiomyopathy • Invasive evaluation of dilated cardiomyopathy

*Timing might be affected by overwhelming demand on the system in the setting of a COVID-19 outbreak.

ASD = atrial septal defects; AVA = aortic valve area; CCS = chronic coronary syndromes; CTO = chronic total occlusions; STEMI = ST-segment elevation myocardial infarction; LAA = left atrial appendage; LAD = left anterior descending coronary artery; LVAD = left ventricle assist device; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association; NSTE-ACS = non-ST-segment elevation acute coronary syndromes; PCI = percutaneous coronary interventions; PFO = patent foramen ovale; TAVI = transcatheter aortic valve interventions.

9. Management/Treatment Pathways

Non-ST-Segment Elevation Acute Coronary Syndromes

The management of patients with NSTE-ACS should be guided by risk stratification.[65] Testing for SARS-CoV-2 should be performed as soon as possible following first medical contact, irrespective of treatment strategy, in order to allow HCP to implement adequate protective measures and management pathways (section 5). Patients should be categorized into 4 risk groups (i.e. very high risk, high risk, intermediate risk, and low risk) and managed accordingly (Figure 12).

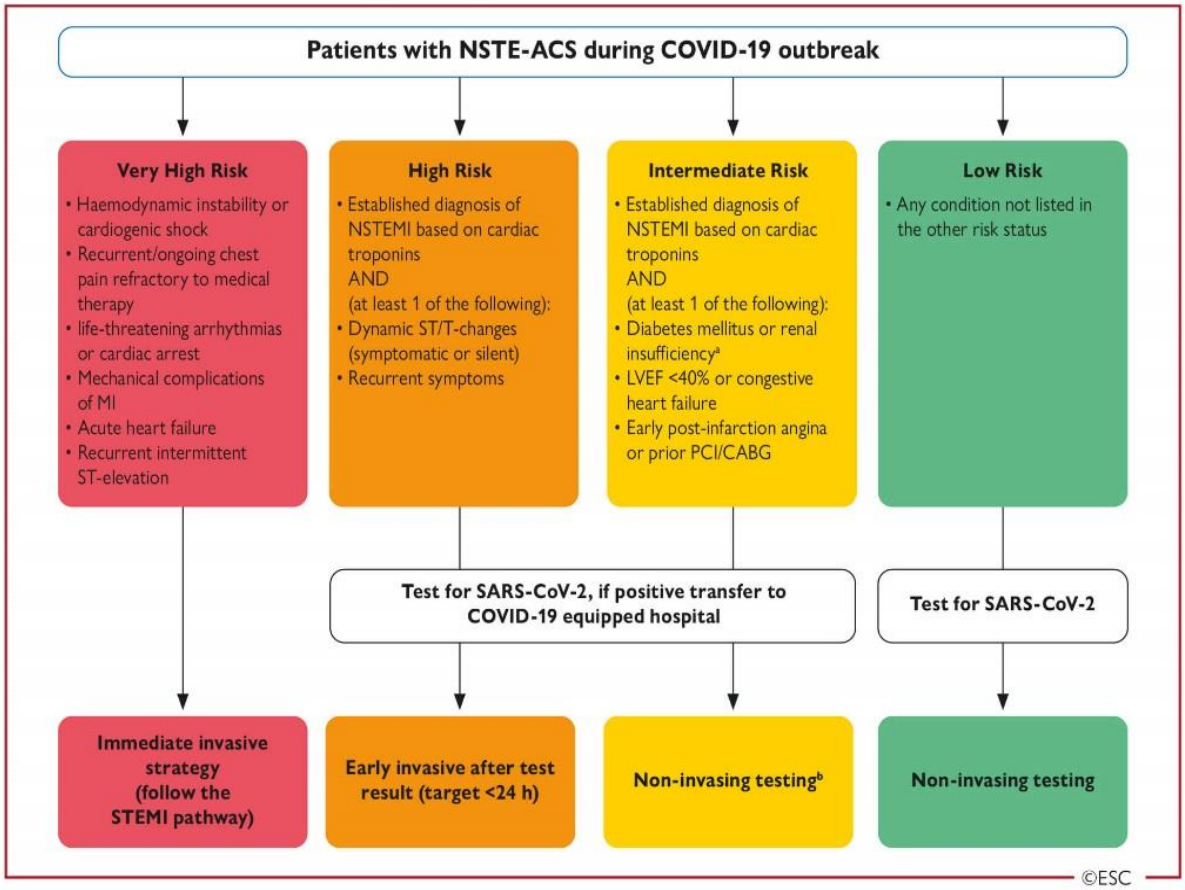
Patients with Troponin rise and no acute clinical signs of instability (ECG changes, recurrence of pain) might be managed with a primarily conservative approach. Non-invasive imaging using CCTA may speed-up risk stratification, avoid an invasive approach[39] allowing early discharge.

For patients at high risk, medical strategy aims at stabilization whilst planning an early (< 24 hours) invasive strategy. The time of the invasive strategy may however be longer than 24 hours according to the timing of testing results. If feasible, a dedicated area to manage these patients while waiting for the test result should be arranged in the emergency department. In the case of positive SARS-CoV-2 test, patients should be transferred for invasive management to a COVID-19 hospital equipped to manage COVID-19-positive patients.

Patients at intermediate risk should be carefully evaluated taking into consideration alternative diagnoses to T1MI, such as Type II MI, myocarditis, or myocardial injury due to respiratory distress or multiorgan failure or Takotsubo. In the event any of the differential diagnoses seem plausible, a non invasive strategy should be considered and CCTA should be favored, 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.

Figure 12 Recommendations for management of patients with NSTE-ACS in the context of COVID-19 outbreak



LVEF = left ventricular ejection fraction; MI =myocardial infarction; NSTEMI = non-ST-segment-elevation MI.
[a]estimated glomerular filtration rate <60mL/min/1.73m^2.
[b]Coronary computed tomography angiography (CCTA) should be favored, if equipment and expertise are available. In low risk patients other non-invasive testing might be favored in order to shorten hospital stay. It is suggested to perform left ventriculography during catheterization if echocardiography not performed before cathlab admission.

ST-Segment Elevation Myocardial Infarction

The COVID-19 pandemic should not compromise timely reperfusion of STEMI patients. In line with current guidelines, reperfusion therapy remains indicated in patients with symptoms of ischaemia of < 12 hours duration and persistent ST-segment elevation in at least two contiguous ECG leads.[104] Concurrently, the safety of HCP should be ensured.[96] To that purpose, and in the absence of previous SARS-Co-V2 testing, all STEMI patients should be managed as if they are COVID-19 positive. We provide general guidance to address the healthcare system organization and delineate possible pathways for specific STEMI settings. The proposed actions are not evidence-based, may need to be adapted to meet local hospital and health authority regulations and may be subject to change in view of the evolving COVID-19 pandemic. While general measures for healthcare systems on redistribution of hub and spoke hospital networks for CV emergency and reorganization of ED and hospital paths are described in sections 7 and 8, respectively, the main principles of STEMI management in the COVID-19 pandemic are the following:

Figure 13 Management of patients with STEMI during COVID-19 pandemic

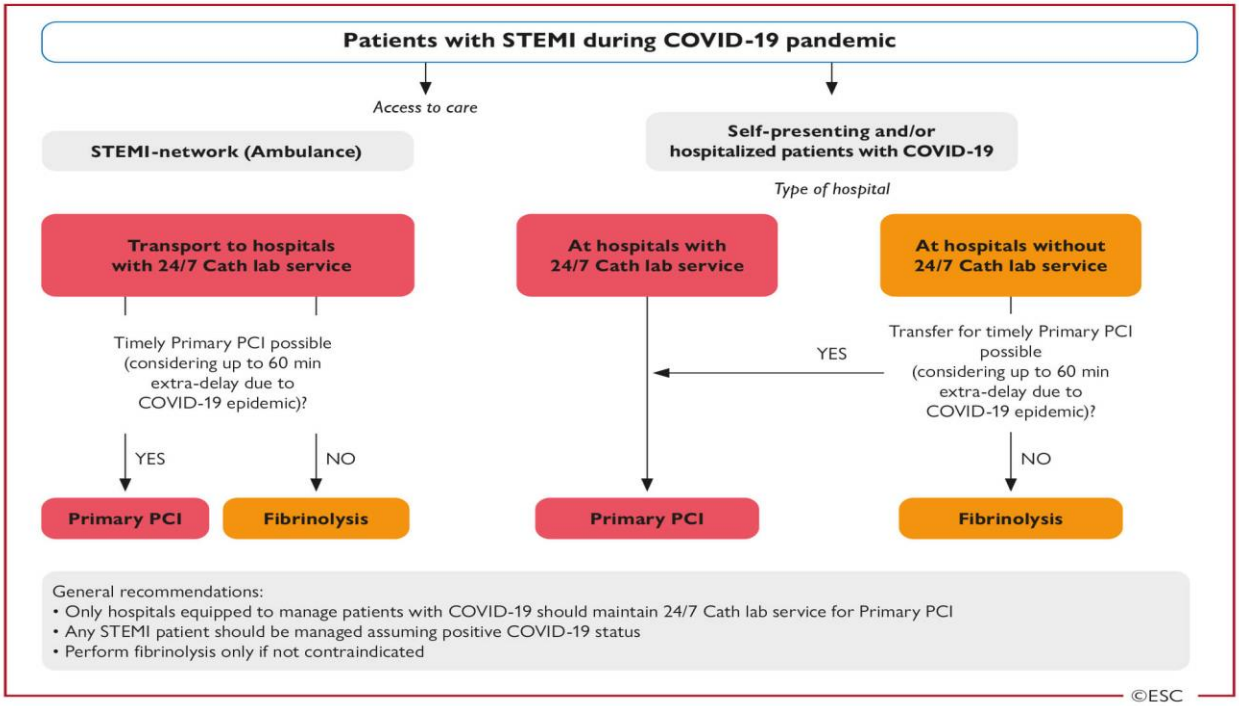


Table 9 Recommendations for fibrinolytic therapy (Extracted from[114])

Recommendations	Class[a]	Level[b]
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended	I	B
A half-dose of tenecteplase should be considered in patients ≥75 years of age	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Oral or i.v. aspirin is indicated	I	B
Clopidogrel is indicated in addition to aspirin	I	A
DAPT (in the form of aspirin plus a $P2Y_{12}$ inhibitor) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A
• Enoxaparin i.v. followed by s.c. (preferred over UFH)	I	A
• UFH given as a weight-adjusted i.v. bolus followed by infusion.	I	B
• In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 h later.	IIa	B
Interventions following fibrinolysis		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis	I	B

[a]Class of recommendation.
[b]Level of evidence.

Table 10 Doses of fibrinolytic agents and antithrombotic co-therapies (Extracted from[114])

Drug	Initial treatment	Specific contra-indications
Doses of fibrinolytic therapy		
Streptokinase	1.5 million units over 30–60 min i.v.	Previous treatment with streptokinase or anistreplase
Alteplase (tPA)	15 mg i.v. bolus 0.75 mg/kg i.v. over 30 min (up to 50 mg) then 0.5 mg/kg i.v. over 60 min (up to 35 mg)	
Reteplase (rPA)	10 units + 10 units i.v. bolus given 30 min apart	
Tenecteplase (TNK-tPA)	Single i.v. bolus: 30 mg (6000 IU) if <60 kg 35 mg (7000 IU) if 60 to <70 kg 40 mg (8000 IU) if 70 to <80 kg 45 mg (9000 IU) if 80 to <90 kg 50 mg (10000 IU) if ≥90 kg It is recommended to reduce to half-dose in patients ≥75 years of age.	
Doses of antiplatelet co-therapies		
Aspirin	Starting dose of 150–300 mg orally (or 75–250 mg intravenously if oral ingestion is not possible), followed by a maintenance dose of 75–100 mg/day.	
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients ≥75 years of age: loading dose of 75 mg, followed by a maintenance dose of 75 mg/day.	
Doses of anticoagulant co-therapies		
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 hours until revascularization or hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg per injection. In patients ≥75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg per injection for the first two s.c. doses. In patients with eGFR <30 mL/min/1.73 m^2, regardless of age, the s.c. doses are given once every 24 hours.	
UFH	60 IU/kg i.v. bolus with a maximum of 4000 IU followed by an i.v. infusion of 12 IU/kg with a maximum of 1000 IU/hour for 24–48 hours. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 hours.	
Fondaparinux (only with streptokinase)	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge.	

aPTT = activated partial thromboplastin time; eGFR = estimated glomerular filtration rate; i.v. = intravenous; IU = international units; rPA = recombinant plasminogen activator; s.c. = subcutaneous; tPA = tissue plasminogen activator; UFH = unfractionated heparin.

Cardiogenic Shock

- Management of CS and 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 infection, escalation to MCS should be carefully weighed against the development of coagulopathy associated with COVID-19 infection and the need for specific treatment (prone position) required for acute lung injury;
- In case of requirement for MCS, extracorporeal membrane oxygenation (ECMO) 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 SOFA and therapeutic intervention scoring system (TISS) scores should be assessed, for most critical patients, in order to improve decision making;
- The safety of HCP is of predominant importance to avoid any HCP infections.

CS and OHCA are time-dependent diseases needing relevant resources and optimal trained systems and dedicated networks for optimal outcome. In general, treatment of CS and OHCA should follow current guidelines and current evidence.[61,44]However, considering that in an overwhelmed critical care system stressed by the pandemic COVID-19 infection it will not be possible for all the patients to receive 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 multiple groups have considered and recommend fundamental principles to be applied in accordance with the following rules of precedence:

1. Equity: Available resources are to be allocated without discrimination (i.e. without unjustified 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 minimising 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 in order to maximize benefits and relieve HCP from improvising decisions about whom to treat or making them in isolation.

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 of CV events allowing to defer diagnostic and/or interventional procedures in most of the 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.

Table 13 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.

[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.

Heart Failure

Patients with CV comorbidities are at increased risk of the more severe presentation and complications of COVID-19. In a meta-analysis of 6 studies (n = 1527), hypertension and cardio/cerebrovascular diseases were present in 17.1%, and 16.4%, of hospitalized COVID-19 patients, respectively, and conferred ~2-fold and ~3-fold higher risk, respectively, for the more severe COVID-19.[50]

Acute Heart Failure

- Acute HF may complicate the clinical course of COVID-19, particularly in severe cases;
- Underlying mechanisms of acute HF in COVID-19 may include acute myocardial ischaemia, infarction or inflammation (myocarditis), ARDS, acute kidney injury and hypervolaemia, stress-induced cardiomyopathy, myocarditis and tachyarrhythmia;
- COVID-19 pneumonia may lead to the worsening haemodynamic status due to hypoxaemia, dehydration and hypoperfusion;
- Clinical presentation, pre-existing CV comorbidities, and chest imaging findings suggestive of HF (e.g. cardiomegaly and/or bilateral pleural effusion) are of an utmost importance;
- Significantly elevated BNP/NT-proBNP levels also suggest acute HF. Prudent use of bedside point of care (POC) transthoracic echocardiography (TTE) could be considered, with an attention to prevent contamination from the patient of the personnel and/or the equipment;
- The same treatment strategy for acute HF can be applied in patients with and without COVID-19. Data on acute HF in COVID-19 are scarce. In one report, 23% of all hospitalized patients developed HF, whilst HF prevalence was significantly higher in fatal cases compared with survivors (52% vs. 12%, $P < 0.0001$).[34]

Myocarditis

- Limited clinical experience indicates that SARS-CoV-2 may lead to fulminant myocarditis;
- Myocarditis should be suspected in patients with COVID-19 and acute-onset chest pain, ST segment changes, cardiac arrhythmia and haemodynamic instability. In addition, LV dilatation, global/multi-segmental LV hypocontractility (on POC echocardiography), and significant increase in cardiac troponin and BNP/NT-proBNP levels, without significant CAD could also be present;
- Suspicion of myocarditis should be raised in COVID-19 patients with acute HF/CS without pre existing CV disorder;
- CCTA should be the preferred approach to rule out concomitant CAD;
- CMR (if available) may be used for further diagnostic assessment;
- Endomyocardial biopsy is not recommended in COVID-19 patients with suspected myocarditis;
- No clear recommendation can be given for SARS-CoV-2-associated myocarditis treatment.

Incidence, underlying mechanisms and risk factors of SARS-CoV-2-associated myocarditis are currently unclear. Recently, a high viral load has been reported in 4 patients who subsequently developed fulminant myocarditis.[33] and a marked decrease in LV ejection fraction (LVEF), and a 2 mm thick pericardial effusion. Troponin I and BNP levels were notably high .

The patient Chronic Heart Failure;

- The risk of COVID-19 infection may be higher in chronic HF patients due to the advanced age and presence of several comorbidities;
- In HF patients suspected of COVID-19, routine clinical assessment, temperature measurement with noncontact devices, ECG (arrhythmias, myocardial ischaemia, myocarditis), 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;
- TTE and chest CT scan can be used for further assessment. 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 stable HF patients (with no cardiac emergencies) should refrain from hospital visits;
- Guideline-directed medical therapy (including beta-blocker, ACEI, ARB or sacubitril/valsartan and mineralocorticoid receptor antagonist), 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 stable HF patients.

Telemedicine and Home Drug Delivery

The more widespread use of telemedicine should be encouraged to minimize the risk of SARS-CoV-2 transmission, in both HF patients, and HCP. Whenever possible, this technology should be utilized to provide medical advice and follow-up of stable HF patients, and to reserve direct patient provider contact for the emergency situations. It is advisable that HCP make a telephone contact with the ambulatory chronic HF patient to verify the need for the hospital visit, but also to provide psychological support. If feasible (and necessary), home delivery and mailing of standard HF drugs to the patients is a viable option.

Valvular Heart Disease

- Patients with valvular heart disease (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

Management of Aortic Stenosis

- Priority should be given to patients with syncope and HF, and those with high (or very high) 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 aortic stenosis (AS) depends on several factors, including age, symptomatic status, peak aortic jet velocity/mean transvalvular gradient,[102,101] LVEF, pulmonary hypertension,[64] and elevated biomarkers (natriuretic peptides or troponin).[65-67] Mortality of patients with severe symptomatic AS who are treated conservatively is high, reaching 50% at 1 year and 70–80% at 2 years.[68] Deferring surgical aortic valve replacement (SAVR) or TAVI by several months may therefore affect prognosis.

Management of Mitral Regurgitation

- The majority of patients with mitral regurgitation (MR) are stable and surgical or transcatheter intervention can be deferred;
- Priority should be given to the treatment of patients with acute MR complicating 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 (flail leaflet and Barlow disease) is usually stable and well tolerated. In contrast, SMR is a more variable entity and whilst many patients remain stable under guideline directed medical and device treatment (including sacubitril/valsartan and cardiac resynchronization therapy when indicated),[43] others may develop unstable HF syndromes that are refractory to medical treatment, particularly in the context of acute infection.[55]

Hypertension

- It now seems likely that the reported association between hypertension and risk of severe complications or death from COVID-19 infection is confounded by the lack of adjustment for age and comorbidities associated with ageing and 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 infection;
- Despite much speculation, evidence from a recently published series of observational cohort studies suggests that prior or current treatment with ACEIs or ARBs does not increase the risk of COVID-19 infection when compared to the risk in patients taking other antihypertensive drugs;

- 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 BP monitoring, with videoconference or phone consultations only if needed;
- Hypertensive patients may be at increased risk of cardiac arrhythmias due to underlying cardiac disease, or the reported high frequency of hypokalaemia in patients with severe COVID-19 infection;
- 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 infection;
- 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 infection.[10,65] These analyses did not adjust for age, which is important because hypertension is very common in older people (~50% in people aged over 60 years are hypertensive) and hypertension prevalence increases sharply in the very old. Older age is also 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 because of their older age. Indeed, a higher frequency of hypertension would be expected in older COVID-19-infected patients, than has been reported.

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 infection and unable to attend for 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.[18]

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 Infection

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.[192] Plasma potassium levels should be monitored because arrhythmias may be exacerbated by the frequent occurrence of low plasma potassium levels or hypokalaemia that was first noted in SARS coronavirus infection[100] and early reports suggests is also prominent in hospitalized COVID-19-infected patients.[104] 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 but sometimes needed for hypertensive patients who are ventilated and have sustained and 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

- Consider anticoagulation at standard prophylactic doses in all patients admitted with COVID-19 infection;
- Consider the presence of acute PE in patients with COVID-19 infection 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;
- Non-vitamin K antagonist oral anticoagulants (NOACs) may have interactions with some of the investigational drugs for COVID-19, notably lopinavir/ritonavir. In such cases, NOACs should be avoided. No major interactions have been reported between investigational drugs for COVID-19 and heparin anticoagulation.

Arrhythmias

- For monitoring and follow up of patients with cardiac implantable devices, remote monitoring should be utilized as much as possible;
- Elective ablation and cardiac device implantation procedures should be postponed and urgent procedures should only be performed in exceptional cases after careful consideration of all pharmacological treatment options;
- In hospitalized patients with AF/atrial flutter without haemodynamic instability, discontinuation of AADs and initiation of rate control therapy to allow safe use of hydroxychloroquine and/or azithromycin as antiviral medication is a reasonable therapeutic option;
- Drug-drug interactions including antiviral, antiarrhythmic and anticoagulation drugs should be considered before administration;
- In critically ill patients with haemodynamic instability due to recurrent haemodynamically unstable VT/VF or AF/atrial flutter, i.v. amiodarone is the choice of antiarrhythmic medication. However, its combination with hydroxychloroquine and azithromycin should be preferably avoided;

- Special attention should be paid to the prevention of Torsades de Pointes (TdP) VT in the setting of COVID-19 and administration of QT interval (QT) prolonging antiviral drugs (hydroxychloroquine and azithromycin) in combination with AADs, electrolyte disturbances, kidney dysfunction, and/or bradycardia;
- Therapy of Torsades VT consists of withdrawal of all QT prolonging drugs, targeting K+ > 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);
- Echocardiography should be considered in patients with new malignant ventricular arrhythmias not related to QT prolongation, to asses ventricular function and myocardial involvement;
- After recovery from the COVID-19 infection, in AF/atrial flutter the therapeutic choices of rate and rhythm control should be re-assessed, and long-term anticoagulation should be continued based on the CHA2DS2-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.

Management of Cardiac Arrhythmias in Patients with COVID-19 Infections

Supraventricular Tachycardia

There are no specific reports on the incidence of non-AF/atrial flutter type of paroxysmal supraventricular tachycardia (PSVT) during COVID-19 infection. In theory, exacerbation of known PSVT or new-onset PSVT may occur in patients with COVID-19 infection. Special considerations during the COVID-19 pandemic are 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 AADs .

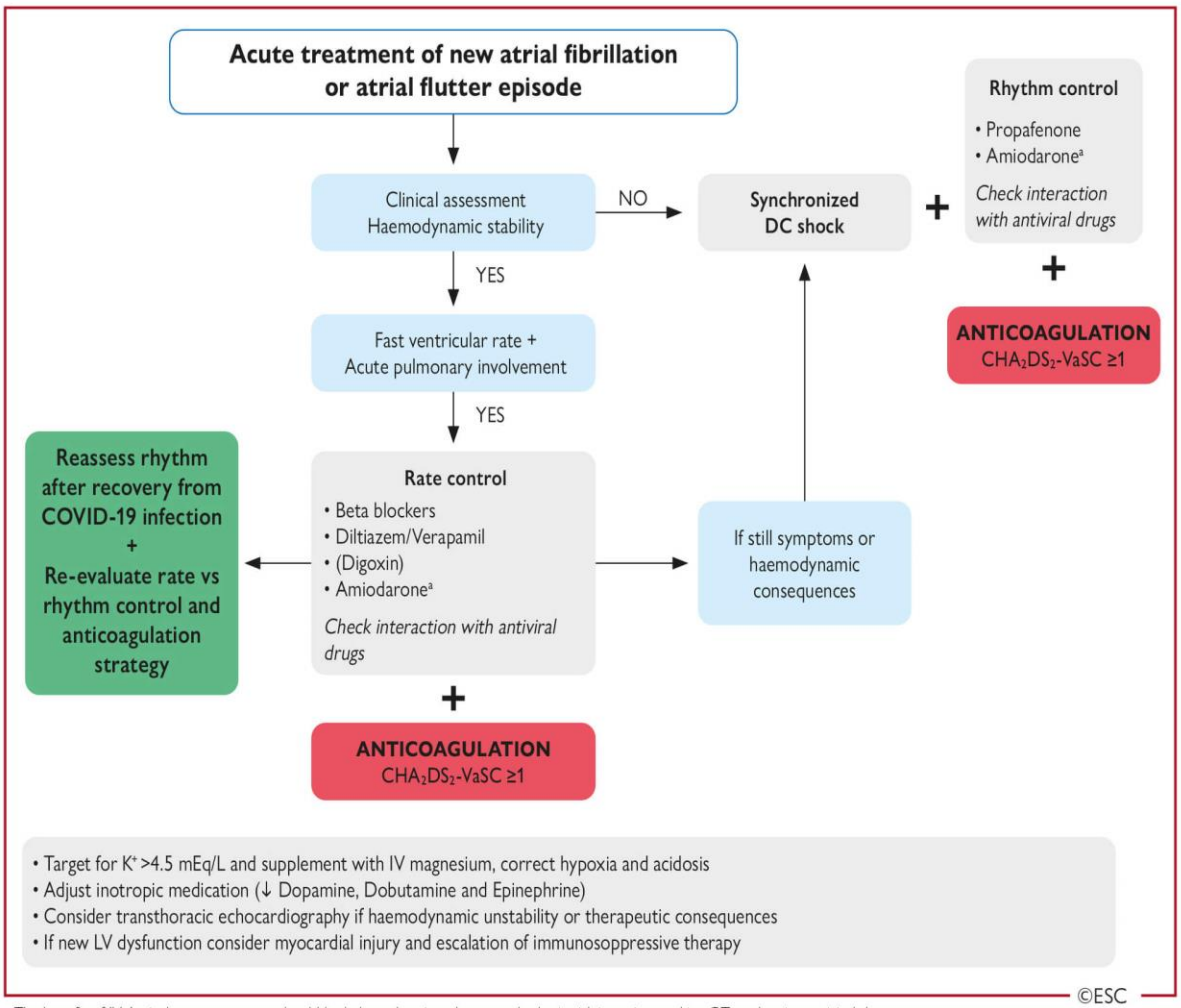
- Intravenous adenosine can probably be used safely for acute termination, but confirmatory data are lacking;
- Maintenance therapy with beta-blockers (or CCBs if beta-blockers are contraindicated) should be initiated with low threshold. Drug interaction with antiviral drugs should be evaluated, including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

Atrial Fibrillation and Flutter

There are no specific reports on the occurrence of AF during COVID-19 infection. It is likely that AF may be triggered by COVID-19 infection (fever, hypoxia, adrenergic tone), either new onset or recurrent. In patients with severe pneumonia, ARDS and sepsis, the incidence of AF during hospitalization is known to be high. Reportedly 23–33% of critically ill patients with sepsis or ARDS had AF recurrence and 10% developed new-onset AF.[101] 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. [55,34] In a recent report from Italy, among 355 COVID-19 patients who died (mean age 79.5 years, 30% women), retrospective chart review identified a history of AF in 24.5%.[18] This finding supports the estimates that especially older

patients admitted to the hospital (and ICU) with COVID-19 associated pneumonia, ARDS and sepsis frequently develop new-onset or recurrent AF, which may further complicate management. Specific precipitating factors in this setting are hypokalaemia and hypomagnesaemia (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 myocardial injury.[23]

Figure 16 Atrial tachyarrhythmias



[a]The benefit of IV Amiodarone treatment should be balanced against the proarrhythmic risk in patients taking QT-prolonging antiviral therapy.

Ventricular Arrhythmias

Although there are no reports on the incidence of ventricular arrhythmias in the general population of patients with COVID-19 infection, a recent single centre retrospective study from

Wuhan analyzed the occurrence and significance of malignant ventricular arrythmias in 187 hospitalized patients with confirmed COVID-19 infection. Among the 187 patients (mean age 58 ±14.7 years, 49% male), 43 (23%) patients died during hospitalization. Overall, 66 (35.3%) patients had underlying CVD including hypertension (32.6%), coronary heart disease (11.2%), and cardiomyopathy (4.3%), and 52 (27.8%) patients exhibited myocardial injury as indicated by elevated Troponin T levels. During hospitalization, malignant ventricular arrhythmias (defined as sustained VT or VF) occurred in 11 (5.9%) patients. VT/VF occurred more frequently in patients with elevated troponin levels (17.3% vs. 1.5%, $p < 0.001$).[25] These findings suggest that new-onset malignant ventricular arrhythmia is a marker of acute myocardial injury and may warrant more aggressive immunosuppressive and antiviral treatment. In patients with a history of CVD and ventricular arrhythmias, exacerbation of the known VT/VF may occur due to COVID-19 infection as trigger. Although reports are not available for COVID-19, a correlation between increased appropriate ICD therapies and influenza epidemic has been shown.[87]

Special considerations during the COVID-19 pandemic are depicted in Figure 17 and summarized below:

Bradyarrhythmias

In theory, exacerbation of known conduction system or sinus node disease or new-onset high degree AV block or sinus node dysfunction may occur in patients with COVID-19 infection, especially in case of myocardial involvement. Other mechanisms of AV block in COVID-19 are vagally mediated due to neuroinvasion, or hypoxia. A case of transient AV block in a critical COVID patient was recently published.[21] One experimental study from 1999 has shown that coronavirus-infected rabbits have ECG abnormalities including 2nd degree AV block secondary to myocarditis and HF.[21] 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 increased vagal tone.[20] Hypoxaemia should be ruled out.

A heart rate/temperature discordance was observed in patients with COVID-19:[10,] The heart rate at admission was about 80 beats per minute (bpm), slower than expected in these patients with fever. This has also been observed in other infectious disease such as typhoid fever.

Special considerations for permanent PM implantation in patients with COVID-19 are 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 (see above) and transient bradyarrhythmic side effects of antiviral therapy.

- Some treatments used for COVID-19 might increase the likelihood for AV block or bundle branch block, such as chloroquine (less with hydroxychloroquine) or fingolimod (Table 15). Some of these effects might become apparent only after many weeks;
- Therefore, recovered COVID-19 patients 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 10)
- In case of persistent 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;
    - After recovery from the COVID-19 infection the need for permanent PM implantation should be reassessed.

Arrhythmogenic and QTc Considerations of COVID-19 Therapies

Treatment strategies against SARS-CoV-2 potentially use a combination of several drugs exerting synergistic effects. Despite the lack of definitive evidence on their efficacy, drugs with suspected viricide effect that are being used 'off-label' include chloroquine/hydroxychloroquine, protease inhibitors (like lopinavir-ritonavir or, in a minority of cases, darunavir-cobicistat), remdesivir and azithromycin.[21] In specific cases, interferon and, for the ARDS glucocorticoids and/or tocilizumab, may also be administered.[22]

Chloroquine has been widely used as an antimalarial drug and in the treatment of rheumatological diseases like systemic lupus erythematosus and rheumatoid arthritis, and has been found to inhibit SARS-CoV-2 growth *in vitro*.[21-22] **Hydroxychloroquine** is an analogue of chloroquine with less gastric intolerance and less concerns for drug interactions. *In vitro*, hydroxychloroquine was found to be more potent than chloroquine in inhibiting SARS-CoV-2.[22] A recent small clinical study reported that SARS-CoV-2 positivity in nasopharyngeal secretions is significantly decreased at day 6 after inclusion (i.e. day 10 after symptom onset) in hydroxychloroquine-treated COVID-19 patients (n = 26) versus patients who received supportive care only (n = 16). However, several major limitations (small sample size; non-homogeneous groups with differences in viral loads, number of days since onset of symptoms and quality of follow-up; and rather late administration of the drug, close to the expected time of viral clearance), raise doubts about the significance of the findings.[21]The current evidence therefore does not imply yet a translation of (hydroxy)chloroquine *in vitro* activity to clinically relevant outcomes. Results of ongoing clinical trials of chloroquine/hydroxychloroquine efficacy in the treatment of SARS-CoV-2 should be awaited before definite recommendations are provided for or against the use of these drugs. One major concern with these drugs is the very rare risk of QTc prolongation and TdP/sudden death. A recent metanalysis 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).[22] However, during COVID-19 infection, the QT-related risk may be amplified by concomitant use of other QTc-prolonging drugs and/or electrolyte imbalances (hypokalaemia, hypomagnesaemia and/or hypocalcaemia). A second concern with chloroquine/hydroxychloroquine is the potential occurrence of conduction disturbances, although these are rare and appear to be linked mostly to long-term treatment (Table 15).

The protease inhibitor **lopinavir-ritonavir** has shown to be effective against SARS-coronavirus and MERS-coronavirus *in vitro* and in animal models.[20,103] A recent randomized controlled open-

label trial suggested that in hospitalized patients with severe COVID-19, lopinavir-ritonavir combined therapy does not provide additional benefit to standard of care.[95] The main criticism of this study is the delayed time from illness onset to treatment assignment (median 13 days). Importantly, no pro-arrhythmic major adverse events were described in either arm and there was only one QTc prolongation in the lopinavir ritonavir arm (no details on the degree or the existence of other concomitant QTc prolonging factors).[27] However, 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 15). When lopinavir-ritonavir is not available and/or the patient is intolerant, **darunavir-cobicistat** is used as an alternative.

In vitro and animal studies suggest that **remdesivir** (GS-5734) is effective against zoonotic and epidemic SARS-coronavirus and MERS-coronavirus.[22-23] Several randomized controlled studies are underway in the current SARS-CoV-2 epidemic. *In vitro* studies suggest a better efficacy of remdesivir compared to lopinavir-ritonavir.[30] An advantage of remdesivir is that no significant drug interactions have been described. However, there are no reports on its effect on QTc duration. Unfortunately, currently it is not widely available worldwide (only in clinical trials or for compassionate use from Gilead Sciences, Inc.).

The anecdotal evidence supporting the use of **azithromycin** (being a weak CYP3A4 inhibitor) comes from the above-mentioned open-label small non-randomized study of hydroxychloroquine treated COVID-19 patients (n = 26) versus patients who received supportive care only (n = 16). In 6 patients, the addition of azithromycin to hydroxychloroquine showed significant SARS-CoV-2 positivity reduction in nasopharyngeal secretions compared to hydroxychloroquine alone.[218] Azithromycin has in isolated cases been associated with QTc prolongation and TdP mainly in individuals with additional risk factors.[23] Two studies have evaluated the association of chloroquine and azithromycin for the prevention and treatment for malaria in Africa with 114 and 1445 individuals, respectively in the arm treated with the combination.[22] The association of chloroquine and azithromycin showed an acceptable safety profile.

Considerations on the Use of Anticoagulants in COVID-19 Patients

Many cardiac patients or patients with other CV history will have an indication for anticoagulation. Table 16 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 SmPCs 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 rephrase here also the conventional dose reduction criteria for NOACs, for those patients in whom oral treatment for stroke prevention in AF patients, can be continued. For more details, including the assessment of renal (and liver) function and other considerations in patients taking a NOAC, please see the 2018 EHRA Practical Guide on the use of NOACs in patients with

AF.[26] 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 mg and 2 x 110 mg. No pre-specified 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 15mg if CrCl < 50 mL/min.

Patient Information

There are many pending questions about the COVID-19 pandemic.[74] What is the full spectrum of disease severity? How 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? Knowledge is being accumulated very fast and our task is to deliver key information for patients with CVD.

- Patient information is of paramount importance during the COVID-19 pandemic when the allocation of medical resources is a matter of debate;[75]
- Pre-existing CVD has a direct impact on the risk of SARS-CoV-2 and survival;[21]
- The occurrence of SARS may lead to CV complications as well as treatments used to cure the COVID-19 disease;
- Unambiguous information to the population and the patients is key for a better control of the disease and the rapid development of specific treatment strategies.

Who is at Risk for Severe SARS-CoV-2?

There are several clinical features associated worse short-term outcome of SARS-CoV-2 manifestations.[54] These include asthma, age > 65-year-old, COPD, chronic HF, cardiac arrythmias, coronary artery disease. Female sex, statin therapy or ACE inhibitors appear to be independent protective factors. The effect of social background and ethnicity on survival needs some clarification. 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 be also 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 therefore should not been 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 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;[52,191]
- There are some treatments that may need to be adjusted when concomitant specific therapy for the COVID-19 disease is initiated.

Table 17 Concomitant conditions that may be associated with more severe course of SARS-CoV-2 infection. Many of these features are confounded by age

• Chronic pulmonary disease
• Stabilized heart failure (NYHA 3 or 4)
• Waiting list for cardiac sugery
• Immuno-deficiency or prior organ transplantation
• Hypertension
• Coronary artery disease
• Cerebrovascular disease
• Diabetes
• Severe overweight (>40 kg/m^2)
• Arrythmias
• Female sex
• ACE inhibitors
• Statin treatments

Interactions with Others, Healthy Lifestyle and Medical Advice during COVID-19 Pandemic

The following information is important for individuals with CVD:

- 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 seconds;
  - Cover the mouth or nose when you cough or sneeze with a tissue or use the inside of the elbow;
  - Avoid touching the eyes, nose and mouth;
  - To remove the virus, often clean surfaces like doorknobs or handles with a disinfectant;
  - Self-isolate in case of symptoms of fever, cough or a chest infection;
  - Stay home as much as possible;
  - Maintain physical activity to avoid VTE and maintain well-being.

Additionally, 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).[27] Isolation and physical restrictions may lead to inactivity and increased risk of VTE, in combination 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. Maintaining social network should be encouraged remotely.

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

Figure 20 Patient information during the COVID-19 pandemic - Part 1

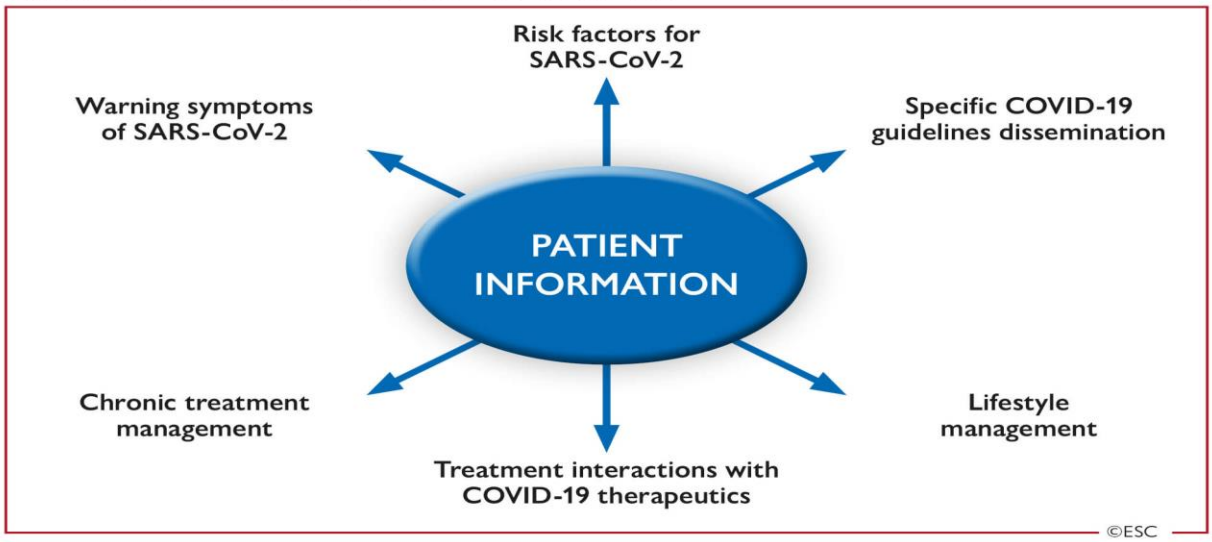
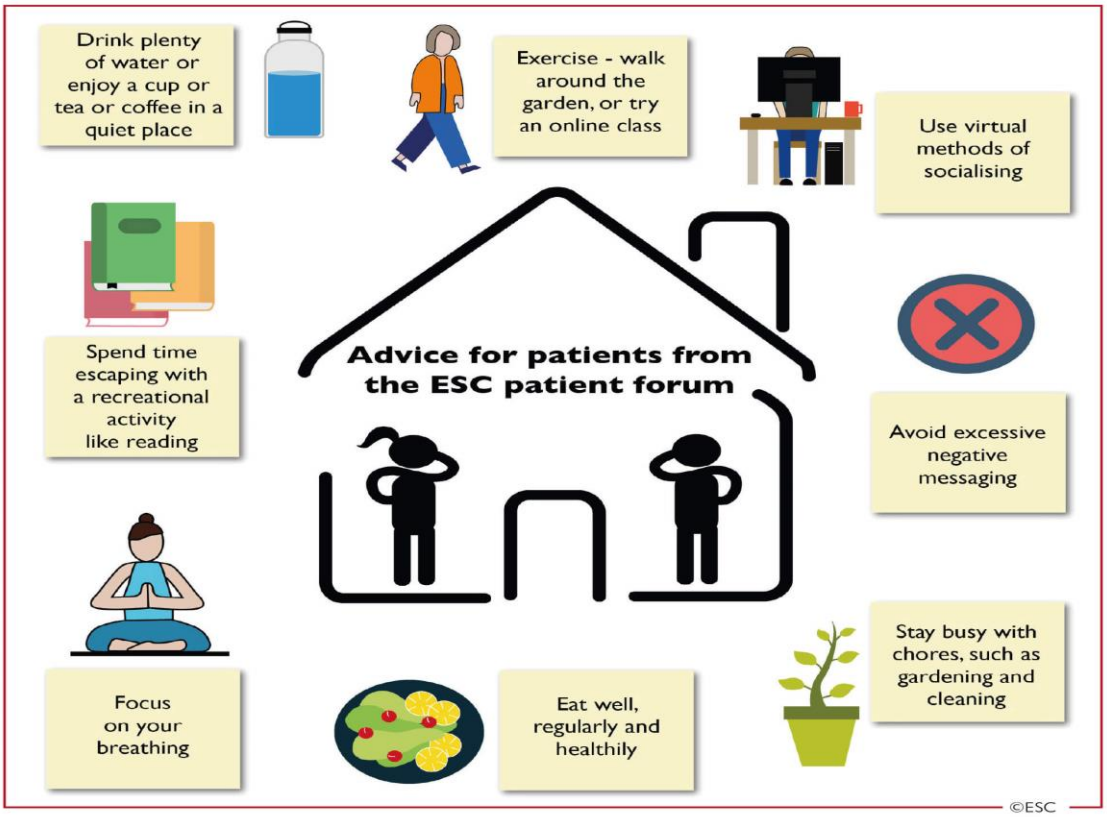


Figure 21 Patient information during the COVID-19 pandemic - Part 2



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