ESC
European Society of Cardiology

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic

The document is 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.

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List of abbreviations

Acronyms	Definition
AAA	Abdominal aortic aneurysm
AAD	Antiarrhythmic drugs
ACE2	Angiotensin-converting enzyme 2
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome (s)
ADAMTS17	ADAM metallopeptidase with thrombospondin type 1 motif, 17
AF	Atrial fibrillation
AGP	Aerosol generation procedure
AMI	Acute myocardial infarction
Ang	Angiotensin
ARB	Angiotensin receptor blocker
ARDS	Acute respiratory distress syndrome
AS	Aortic stenosis
ASD	Atrial septal defect
AV	Atrioventricular
AVA	Aortic valve area
AVB	Atrioventricular block
BAL	Bronchoalveolar lavage
BAV	Balloon aortic valvuloplasty
BNP	B-type natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
BS	Brugada syndrome
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome (s)
CCTA	Coronary computed tomography angiogram/angiography
CD209	Cluster of differentiation 209
CHA_2DS_2-VASc	Score for AF stroke risk (congestive HF, hypertension, age, diabetes and previous stroke/transient ischaemic attack – vascular disease [peripheral arterial disease, preceding MI, aortic atheroma])
CI	Confidence interval
CIED	Cardiovascular implantable electronic devices
CK	Creatine kinase
CMR	Cardiac magnetic resonance
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CrCl	Creatinine clearance
CRS	Cytokine release syndrome

Acronyms	Definition
CS	Cardiogenic shock
CT	Computed tomography
CTO	Chronic total occclusion
CV	Cardiovascular
CVD	Cardiovascular disease
CXCL10	C-X-C motif chemokine 10
CYP3A4	Cytochrome P450 3A4
DAPT	Dual antiplatelet therapy
DC	Direct current
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EP	Electrophysiology
ER	Emergency room
ERI	Elective replacement indicator
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FAERS	FDA adverse event reporting system
FFP2/FFP3	Filtering face-piece Class 2/Filtering face-piece Class 3 (respirator mask)
FoCUS	Focused cardiac ultrasound study
GRACE	Global Registry of Acute Coronary Events
HCP	Healthcare personnel, Healthcare professional
HF	Heart failure
HFA	Heart failure association
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
hs-cTn	High-sensitivity cardiac troponin
i.v.	Intravenous
ICA	Invasive coronary angiography
ICCU	Intensive cardiac care unit
ICD	Implantable cardiac defibrillator
ICU	Intensive care unit
IE	Infective endocarditis
Ig	Immunoglobulin
IL	Interleukin
ILR	Implantable loop recorder
INR	International normalized ratio
KDIGO	Global organization developing and implementing evidence-based clinical practice guidelines in kidney disease (Kidney Disease: Improving Global Outcomes)
LAA	Left Atrial Appendage
LAD	Left anterior descending (coronary artery)
LAFB	Left anterior fascicle block
LDH	Lactate dehydrogenase

Acronyms	Definition
LMWH	Low molecular weight heparin
LQTS	Long QT syndrome
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MCS	Mechanical circulatory support
MERS	Middle East respiratory syndrome
MI	Myocardial infarction
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NAAT	Nucleic acid amplification test
NGS	Next Generation Sequencing
NHC	Northwest Community Healthcare
NOAC	Non-vitamin K antagonist oral anticoagulant
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
NSTE	Non-ST-segment elevation
NSTE-ACS	Non-ST-segment elevation acute coronary syndromes
NSTEMI	Non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal B-type natriuretic peptide
NYHA	New York Heart Association
OD.	Once daily
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PAPR	Powered air-purifying respirator
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PET	Positron emission tomography
PFO	Patent foramen ovale
P-gp	P-glycoprotein
PM	Pacemaker
POC	Point of Care
POCUS	Point of care focused ultrasound
PPE	Personal protective equipment
PSVT	Paroxysmal supraventricular tachycardia
QT	QT interval (the interval from the QRS complex to the end of the T wave on an ECG representing ventricular depolarization and repolarization and indicating the time during which ventricular contraction and subsequent relaxation occurs)
QTc	Corrected QT interval
RAAS	Renin–angiotensin–aldosterone system
RAS	Renin–angiotensin system
RBBB	Right bundle branch block
RNA	Ribonucleic acid

Acronyms	Definition
ROR	Reporting odds ratio
rPA	Recombinant plasminogen activator
RR	Risk rate
RT-PCR	Reverse transcriptase polymerase chain reaction
s.c.	Subcutaneous
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAVR	Surgical aortic valve replacement
SCD	Sudden cardiac death
SLE	Systemic Lupus Erythematosus
SMR	Secondary mitral regurgitation
SOFA	Sequential Organ Failure Assessment
SPECT	Single photon emission computed tomography
STEMI	ST-segment elevation MI
STS	Society of Thoracic Surgeons
SVI	Stroke volume index
T1MI	Type 1 myocardial infarction
TAVI	Transcatheter aortic valve implantation
TdP	Torsades de Pointes
TEE	Transesophageal echocardiography
TISS	Therapeutic intervention scoring system
TMPRSS2	Transmembrane protein serine 2
TNK	Tenecteplase
tPA	Tissue plasminogen activator
TTE	Transthoracic echocardiogram/echocardiography
UFH	Unfractionated heparin
ULN	Upper limit of normal
US	United States
VF	Ventricular fibrillation
VHD	Valvular heart disease
VKA	Vitamin K antagonist
VT	Ventricular tachycardia
VTE	Venous thromboembolism
WHO	World Health Organization
WPW	Wolff-Parkinson-White (syndrome)

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. Owing to redistribution of health care resources, access to emergency treatment including reperfusion therapy may be affected depending on the severity of the epidemic at a local level. This is further aggravated by increasing concerns of delayed presentation of CV emergencies as patients are afraid to seek medical attention during the pandemic.

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

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

Key points

- 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

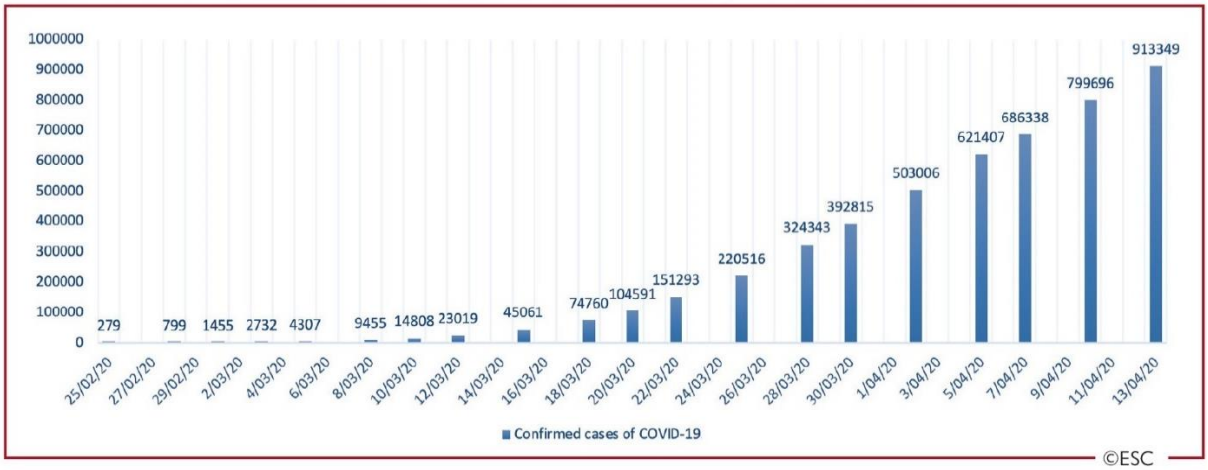
By 10 March 2020, 4296 persons world-wide had died from COVID-19 infection. By 7 May, 3.67 million had tested positive and more than 250 000 had died.[1] The overall case-fatality rate is very country-specific for COVID-19 infection and depending on the phase of the epidemic, testing, registration, demography, healthcare capacity and governmental decisions.[2]

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)



A large Chinese study analyzed 72 314 patient records which consisted of 44 672 (61.8%) confirmed cases, 16 186 (22.4%) suspected cases, and 889 (1.2%) asymptomatic cases.[4] Among confirmed cases in this study, 12.8% had hypertension, 5.3% diabetes and 4.2% CVD. [4] Strikingly, these numbers are lower than the prevalence of CVD risk factor in a typical Chinese population, but it is important to mention that these are not age-adjusted and 53% of cases had missing data on comorbidities.[5] A study including 5700 patients from New York City, Long Island, and Westchester County (United States of America (USA)) reported a similar message that hypertension (56.6%), obesity (41.7%), diabetes (33.8%), coronary artery disease (11.1%) and congestive heart failure (6.9%) were the most common comorbidities.[6] In comparison, the prevalence of hypertension, obesity and diabetes in the general population in the USA is respectively 45%, 42.4% and 10.5%.[7-9] In early retrospective analysis based on data from 138 patients in Wuhan, China, approximately 50% of patients with COVID-19 infection had one or more comorbidities.[10] Moreover, in patients admitted with a severe COVID-19 infection this proportion was as high as 72%.[10] It remains vague whether diabetes, hypertension and CVD are causally linked or associated due to age. However, an important message is the fact that patients who develop severe disease are more likely to be vulnerable because of comorbid disease, including CVD.

Ethnicity seems to be linked to susceptibility and outcomes of a COVID-19 infection.[11, 12] Data from the United Kingdom show that one third of patients admitted to an intensive care unit due to COVID-19 infection were from an ethnic minority background.[11, 13] Reports from the USA reveal the same message that ethnic minority groups have also been disproportionately affected by COVID-19 infections.[12] There are multiple potential mechanisms such socioeconomic, cultural, or lifestyle factors and genetic predisposition. Also, pathophysiological differences in susceptibility or response to infection such as increased risk of admission for acute respiratory tract,[14] an increased prevalence of vitamin D deficiency,[15] increased inflammatory burden, and higher prevalence of cardiovascular risk factors such as insulin resistance and obesity than in white populations.[11, 16]

Verity et al.[17] estimated that the case fatality ratio in China (adjusted for demography) was 1.38% but estimated case-fatality depends very much on the testing strategy of non-severe cases as many cases remain unverified. Case-fatality is highest in older age groups: The case fatality ratio was 0.32 in patients aged < 60 years of age in comparison with 6.4% in patients aged > 60 years.[17] In Italy case fatality ranged from 0% below age 30 years to 3.5% for age 60–69 years and 20% above age 80 years.[18] Higher mortality of a COVID-19 infection in older age groups was also revealed in an American dataset.[6] This underlines the fact that increasing age is an important risk factor for severe course of COVID-19 infections. Underlying CVD is also associated with higher risk for a severe COVID-19 infection. In a retrospective cohort study of 72 314 cases in China[19] patients with CV comorbidities had fivefold higher mortality risk (10.5%), however, without age adjustment. Multinational cohort analyses will give more insights in the prevalence and risk of CV comorbidities in COVID-19 infection. There are several potential mechanisms explaining why the course of the disease is more severe in patients with underlying CV risk factors and CVD.[20] These are described in sections 3 and 9.

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

Key points

- 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.[10]

Next to acute complications, COVID-19 infection may also be linked with an elevated long-term CV risk. It is well established that in patients with pneumonia, hypercoagulability and systemic inflammatory activity can persist for a long period.[2, 20] Moreover, follow-up studies of the SARS epidemic demonstrated that patients with a history of SARS-coronavirus infection often had hyperlipidaemia, CV system abnormalities or glucose metabolism disorders.[20-22] However, SARS was treated with pulses of methylprednisolone which could be the explanation for the long-term perturbation of lipid metabolism rather than a consequence of the infection itself.[24] Naturally, no long-term effects of a COVID-19 infection are known yet but these effects of a SARS-coronavirus infection justify surveillance of recovered COVID-19 infection patients.

3. Pathophysiology - Mechanisms of Disease in Relation to the Cardiovascular System

Key points

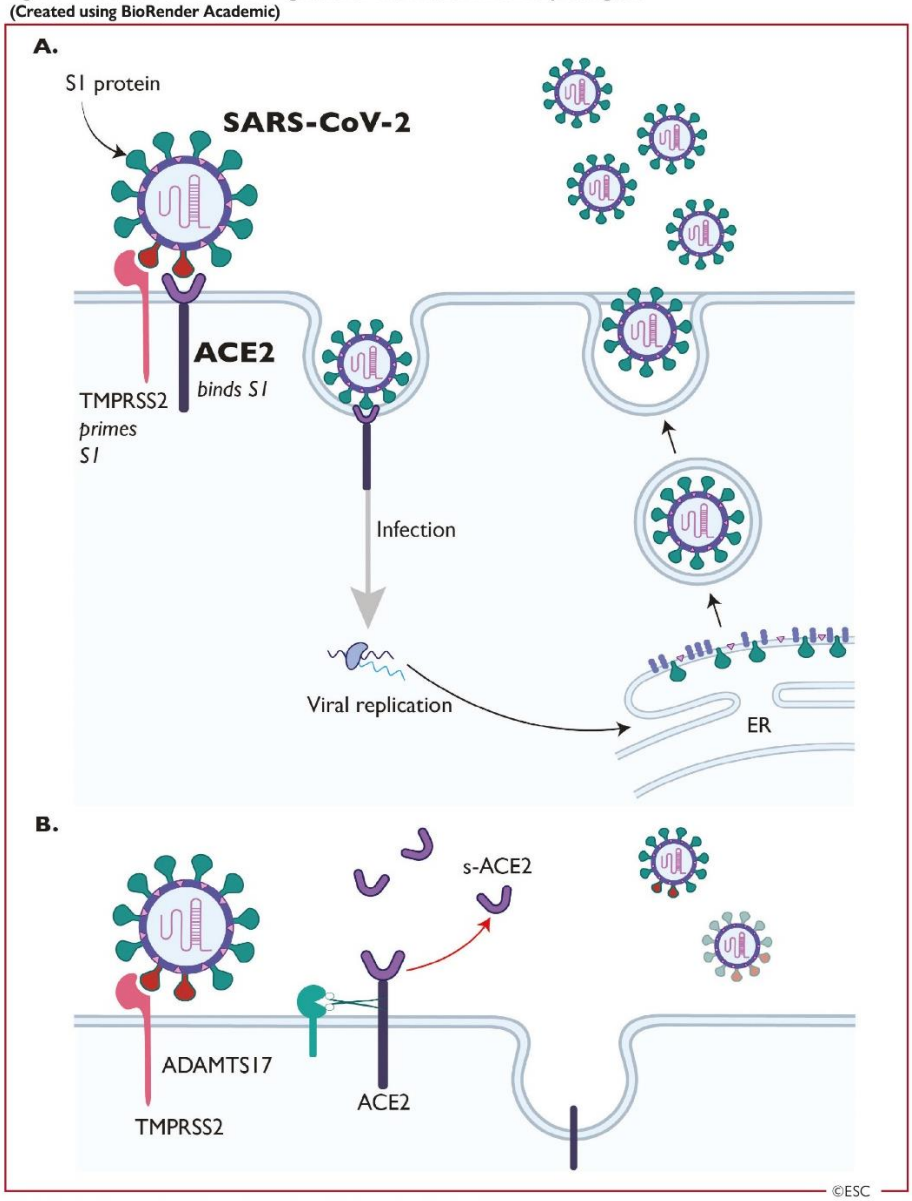
- The pathobiology of coronavirus infection involves SARS-CoV-2 binding to the host receptor angiotensin-converting enzyme 2 (ACE2) to mediate entry into cells;
- ACE2, which is expressed in the lungs, heart and vessels, is a key member of the renin angiotensin system (RAS) important in the pathophysiology 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.[34]

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] In the context of COVID-19, however, ACE2 is also involved in SARS through its function as the coronavirus receptor.[38] Binding of the SARS-CoV-2 spike protein to ACE2 facilitates virus entry into lung alveolar epithelial cells, where it is highly expressed, through processes involving cell surface associated transmembrane protein serine 2 (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, 42]

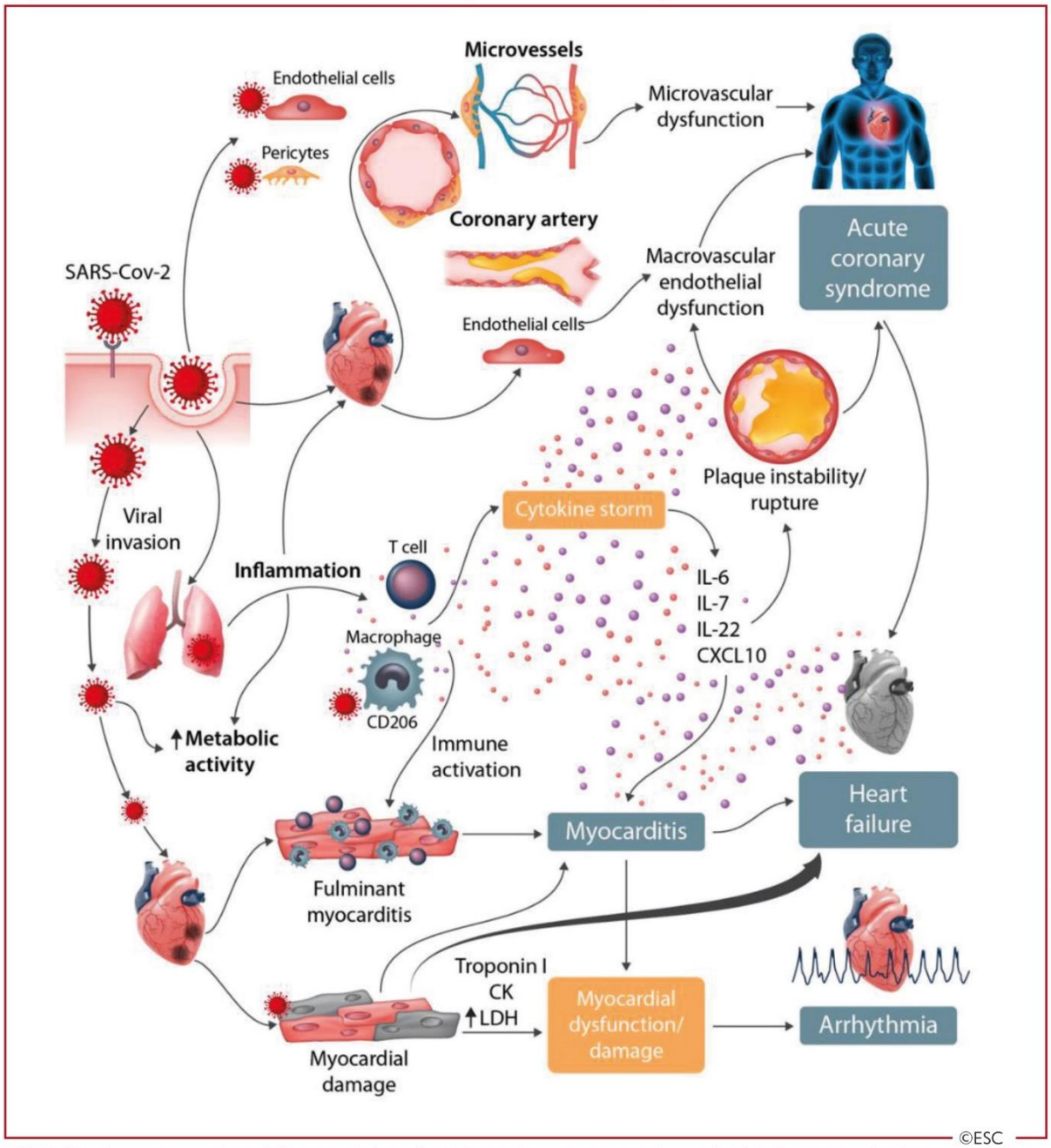
Figure 2 Critical role of ACE2 in the regulation of viral invasion in ACE2 expressing cells (Created using BioRender Academic)



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 anchors on trans-membrane 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 is of particular importance because this 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]

3.1. 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 suggested 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, 53] Recent observational study of over 8910 patients from 169 hospitals in Asia, Europe, and North America, did not show a harmful association of ACEIs or ARBs with in-hospital mortality,[54] while a Wuhan study demonstrated that in 1128 hospitalized patients use of ACEI/ARB was associated with lower risk of COVID-19 infection or serious complication or deaths from COVID-19 infection.[47, 54-60] The recent data are all-cause mortality compared with ACEI/ARB non-users.[60] This is in line with prior guidance from major CV Societies, that stated that patients on or ARBs should not stop their treatment.[51, 61]

3.2. 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.

3.3. 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).[64] 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).

Altered vascular permeability can result in non-cardiogenic pulmonary oedema and promotes ARDS as well as multi-organ dysfunction. High serum IL-6 levels are a common feature in CRS. IL-6 is a clinical predictor of mortality in COVID-19.[66] Thus IL-6 targeting may be permissive for use in COVID-19 to tackle the CRS. Finally, it has been shown that hypertension is associated with circulating lymphocytes in patients[67] and CD8 T cell dysfunction with development of CVD.[68] CD8 T cells are a pillar of antiviral immunity, thus their dysfunction can make the organism inefficiently target virally infected cells.

4. Strategies for Diagnosing SARS-CoV-2

Key points

- 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.

As evidenced by previous epidemics, including SARS and MERS, highly sensitive and specific laboratory diagnostics are essential for case identification, contact tracing, animal source finding, and efficient and rational containment measures.[69] Precise case identification is essential in order to isolate vulnerable individuals. Based on current epidemiological analysis, CVD conveys risk of a more severe outcome of COVID-19;[21, 44] therefore, testing should be particularly widely considered in CVD patients. Moreover, in similarity to influenza, efficient testing of carers and people in contact with high risk patients may allow protection of subjects with multiple comorbidities. The decision to test should be based on clinical and epidemiological factors and linked to an assessment of the likelihood of infection, in particular when availability of tests is limited. Available testing strategies are outlined below (Table 1).

While isolation of the virus itself using electron microscopy would be the most specific diagnostics, it requires biosafety level-3 facilities which are not available in most healthcare institutions. Serum antibody and antigen detection tests would be the easiest and fastest, but have not yet been validated, and there may be cross-reactivity with other coronaviruses, especially SARS-coronavirus. Furthermore, antibodies are not measurable in the initial phase of the infection. Therefore, real-time PCR remains the most useful laboratory diagnostic test for COVID-19 worldwide.[70, 71]

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

Comparative specificity and sensitivity of these tests needs to be carefully assessed, when more data is available. It is important to note that negative results of molecular testing (RT-PCR) do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions but must be combined with clinical observations, patient history, and epidemiological information. There are a number of factors that may lead to a negative result in an infected individual. These include poor quality of the specimen (small material), collection late or very early in the infection, poor handling/shipping as well as technical reasons inherent in the test such as virus mutation or PCR inhibition. Therefore, retesting is recommended after 48 hours in clinically suspected cases that test negative.

It is essential that adequate standard operating procedures are in use and that staff are trained for appropriate specimen collection, storage, packaging, and transport. This must be observed in order for testing to be reliable and safe for staff and patients.

The optimal testing material includes nasal swab rather than pharyngeal. In order to obtain a sufficiently deep swab, the sample must be obtained by experienced and trained staff. According to a comparative study using lung CT as comparator, the sensitivity of nasopharyngeal swab may be limited to 60–70%.[72] It has also been concluded that the test does not seem to change clinical decisions and diagnostic considerations in subjects with pretest probability exceeding 60–70% (e.g. subjects with positive epidemiological and clinical criteria fulfilled). This however does not indicate that such tests should not be performed to confirm infection, but it is important that the test is repeated if there is clinical suspicion of COVID-19 infection. Lung CT has a high sensitivity for diagnosis of COVID-19 in hospitalized patients who are RT-PCR positive. In a study undertaken between 06 January and 06 February 2020 in Tongji Hospital, Wuhan, China, in a population of 1014 patients – when using RT-PCR as a reference, the sensitivity of lung CT imaging for COVID-19 was 97%.[72] Importantly, 60–93% of patients had initial positive lung CT consistent with COVID-19 before the initial positive RT-PCR results.

Nucleic acid shedding is also an important tool to verify patient improvement, although 42% of patients showed improvement of follow-up lung CT scans before the RT-PCR results turning negative.[72] It is important, however, that nucleic acid shedding does not always indicate presence of live virus.

Widespread testing strategies included drive-through testing in South Korea. However, testing capacity may be insufficient. Thus testing priorities have been suggested by individual health systems such as one proposed by Centers for Disease Control for the United States (US) (Table 2). Sample pooling strategy has been proposed in relation to sample collection as the most cost-efficient tool for population-wide screening, for example at airports.

Table 2 Testing priorities for COVID-19 pandemic according to Center for Disease Control, US

PRIORITY 1 **Ensure optimal care options for all hospitalized patients, lessen the risk of nosocomial infections, and maintain the integrity of the healthcare system**
• Hospitalized patients • Symptomatic healthcare workers
PRIORITY 2 **Ensure that those who are at highest risk of complication of infection are rapidly identified and appropriately triaged**
• Patients in long-term care facilities with symptoms • Patients 65 years of age and older with symptoms • Patients with underlying conditions with symptoms • First responders with symptoms
PRIORITY 3 **As resources allow, test individuals in the surrounding community of rapidly increasing hospital cases to decrease community spread, and ensure health of essential workers**
• Critical infrastructure workers with symptoms • Individuals who do not meet any of the above categories with symptoms • Health care workers and first responders • Individuals with mild symptoms in communities experiencing high COVID-19 hospitalizations
NON-PRIORITY **Individuals without symptoms**

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

5.1. 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] 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.

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

In a recent report related to 138 confirmed COVID-19 cases, 41.3% were considered acquired infection from the hospital, and more than 70% of these patients were HCP.[78] Health care workers are in fact at increased risk for contracting the virus, as demonstrated by Wu and colleagues, who reported that in China 1716 of the 44 672 (3.8%) infected individuals were professionals (see later).[19]

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. Table 3 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.

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

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 (Figure 4).

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.

All HCP should be well-versed in proper techniques for donning and removing PPE including eye protection (Figure 5 and Figure 6).[77]

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]

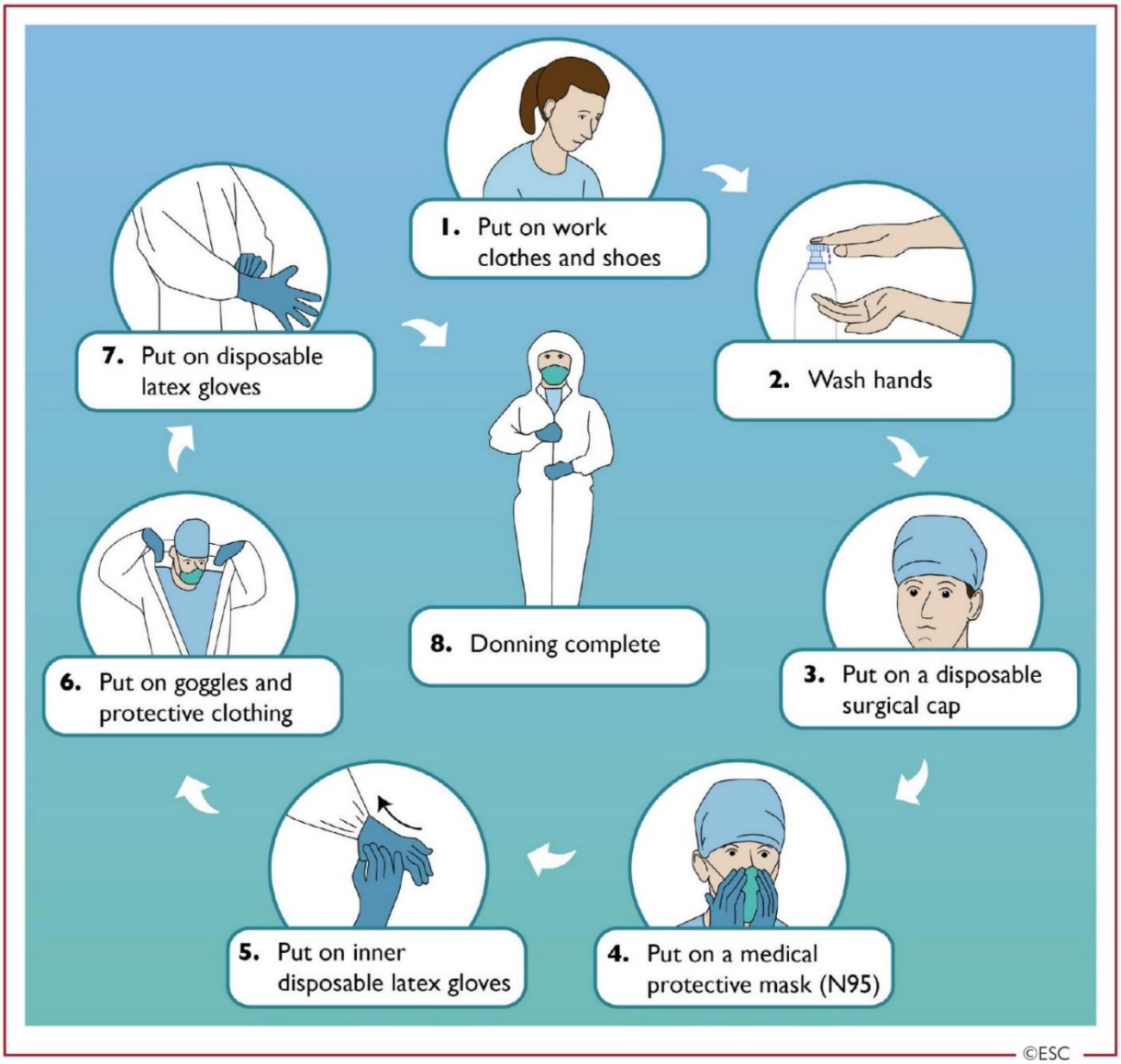
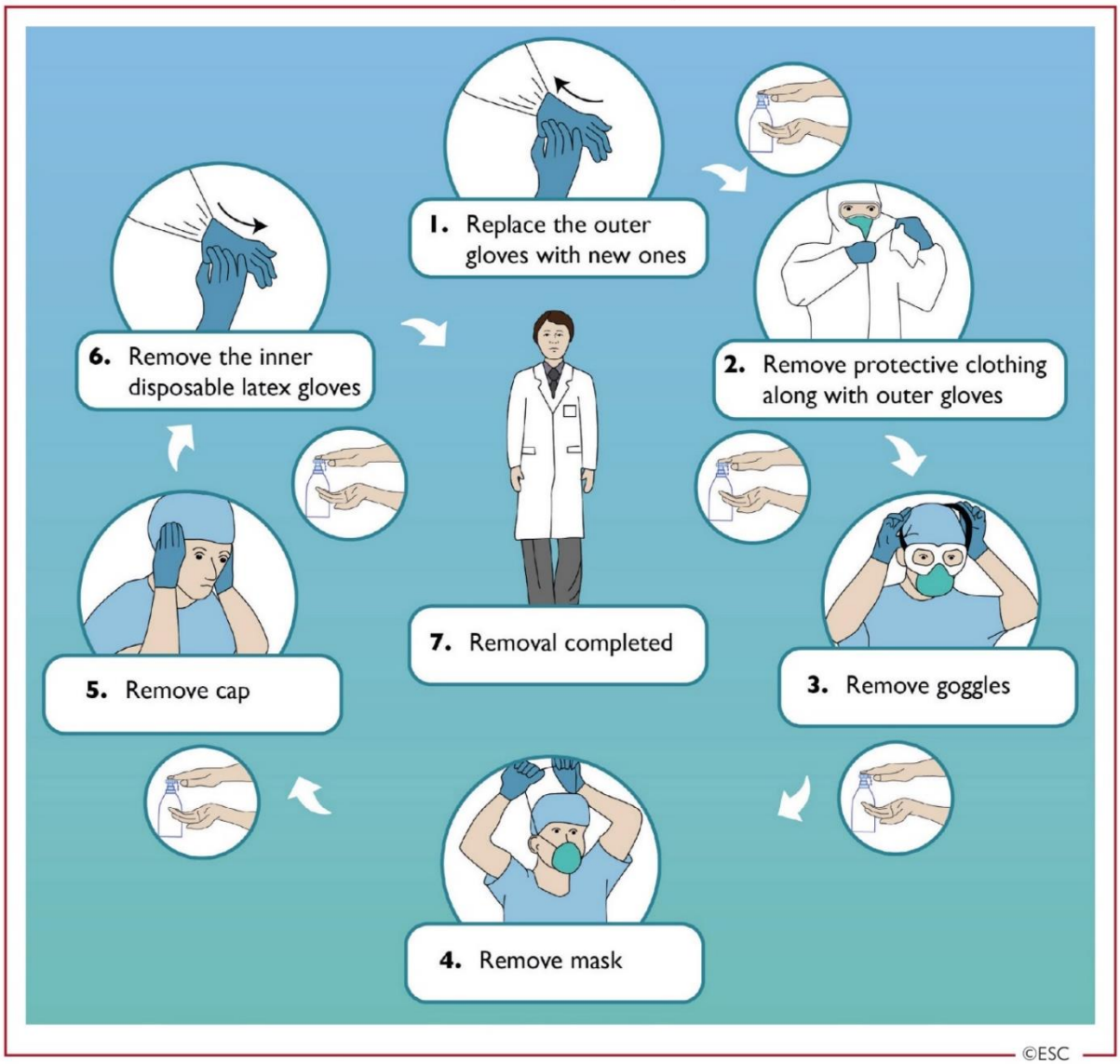


Figure 6 Guidance on removing personal protective equipment (PPE) to manage COVID-19 patients (modified from the "Handbook of COVID-19 Prevention and Treatment")[77]



5.2. Settings

5.2.1. 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).

5.2.2. 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.

5.2.3. 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).

5.2.4. 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.[76, 77]

5.2.5. Catheterization Laboratory

- HCP should be well-versed in proper techniques for donning and removing PPE including eye protection (Figure 5 and Figure 6).[77] 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.

5.2.5.1. 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).

5.2.5.2. 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).

5.2.6. Electrophysiology Laboratory

Most of the electrophysiology (EP) activity is being markedly reduced or suspended in areas that have been severely affected by COVID-19 outbreak. Residual EP activity should be maintained for selected categories of patients (Table 7 and Table 13).

Protection of the HCP:[83]

- EP laboratories exclusively dedicated to patients potentially infected with SARS-CoV-2 are not readily available in most institutions but should be exploited whenever possible;
- All patients with clinical indication for an EP procedure should undergo a nasopharyngeal swab immediately after admission;
- In case of haemodynamic instability and possible COVID-19 case (Table 3), the procedure should be performed with Level II protection measures (Table 5).
- In critical conditions such as syncope and complete atrioventricular (AV) block, patients should immediately be transferred to the EP laboratory and undergo pacemaker (PM) implantation under Level II protection measures (Table 5). After the procedure, these patients should be transferred to a dedicated COVID-19 area until screening for possible SARS-CoV-2 infection is performed;
- In case of two negative results within 48 hours and absence of suspicious symptoms of COVID-19 infection, the planned procedure may be performed using standard protective tools;

Patients with SARS-CoV-2 positive test:

- In haemodynamic stability, ablation procedures should be deferred using intravenous (i.v.) antiarrhythmic drugs (AADs) as indicated by the underlying arrhythmia;
- Patient access to and departure from a "joint" EP laboratory should be operated using the pertinent internal paths;
- The number of operators should be limited to the essential. Ideally, one nurse, one operator, one assistant at the console and one anaesthesiologist, when indicated;
- No specific instructions are due with regard to the type of implant techniques and implantable devices that, however, should have remote control technology;
- Cleaning and sanitization of the EP laboratory should be performed after each procedure.

5.2.7. Transesophageal Echocardiography, Continuous Positive Airway Pressure and Orotracheal Intubation Patients

The major issue is that the viral load in the airway is probably very high and very contagious.[84] This poses significant risks for HCP performing non-invasive ventilation by CPAP or invasive ventilation with orotracheal intubation. Accordingly, a high level of vigilance is necessary to prevent contracting the infection when managing patients using CPAP, when intubation is performed or the transesophageal echocardiogram (TEE) probe is inserted.

- Patients undergoing TEE should be tested for SARS-CoV-2 status;
- In case of two negative results within 48 hours and absence of suspicious symptoms of COVID-19 infection, the planned procedure may be performed using standard protective tools.

In patients with positive SARS-CoV-2 test or unknown status:

- A "point-of-care" focused ultrasound (POCUS) exam may be performed at the bedside in SARS-CoV-2–positive patients to avoid TEE and the associated infection risk for HCP;
- In case of invasive ventilation and CPAP, a Level III protection should be used, whereas for TEE a Level II protection may be sufficient (Table 5).

5.3. Patients

Key points

- 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.[20] 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.[86]

Beyond telemedicine 'home care' and 'mobile clinics' are currently proposed as a way to prevent unnecessary movement of patients towards hospitals, provided that nurses and physicians wear the appropriate PPE. This solution could prevent clinical instability of many cardiac diseases (i.e. chronic HF), assure patient adherence to long-term treatment and contribute to a 'community-centred' form of care that might be more advantageous than a purely 'patient-centred' care model, where only infected, hospitalized patients consume most of the available resources of the healthcare system.[87]

When CV patients temporarily access the hospital facilities for diagnostic or therapeutic reasons they should always protect themselves by systematically wearing surgical masks, practicing social distancing and appropriate washing/cleaning their hands with alcoholic solutions, which should be provided by the hospital staff.[88] Patients should also be protected by HCP donning surgical masks, depending on the local community prevalence of COVID-19.

Figure 7 How do I protect myself?

6. Triage Systems (Reorganization and Redistribution)

6.1. Overriding Principles of Triage

Key points

- 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.

Patient triage is of paramount *importance* when medical services are overwhelmed by a pandemic and healthcare resources are limited. This is particularly true for the COVID-19 epidemic, whose outbreak is currently seriously challenging the healthcare systems across the world. Some peculiar aspects of this pandemic, potentially affecting triage of cardiac patients, should be outlined:

- Initial symptoms of a COVID-19 infection such as breathlessness, chest pain, or asthenia may mimic the early manifestations of a cardiac disease and therefore require a tight collaboration of different professionals and specialists, in order to assign any single patient to the correct diagnostic work up process as soon as possible. Also, COVID-19 patients might abruptly develop acute cardiac complications (such as ACS or pulmonary embolism [PE])[89] and come to the hospital for this reason. In this case a prompt management of both diseases could also contribute to a better outcome;
- In each institution, an explicit diagnostic algorithm for suspected COVID-19 infection is important to inform triage. Patients with possible/probable or confirmed COVID-19 infection (Table 4) should be triaged as COVID-19 infected;
- In particular, critically ill patients for acute CV condition (STEMI patients, out-of-hospital cardiac arrest [OHCA] patients), should quickly access medical or interventional treatment according to the current evidence-based guideline recommendations. Therefore, they should be presumed as SARS-CoV-2 positive, until proven otherwise. Accordingly, HCP should wear adequate PPE, particularly in the triage phase (Table 4). Recommendations made by the WHO state that contact precautions (by means of appropriate face masks, eye glasses, hydro repellent lab coats and gloves) are necessary since the very early triage phase.
- Physicians should triage cardiac patients requiring a highly intensive level of care who have a concomitant suspected or confirmed COVID-19 infection based on local protocols that take into consideration ethical issues and resource availability.[90]

6.2. Hospital and Ambulance Networks

Key points

- 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.

Hub centres are committed to provide acute reperfusion to all patients requiring an urgent PCI. Patients with STEMI or high-risk NSTEMI should be triaged by the emergency medical services team and timely transported to hub centres, if feasible. As a general rule we recommend that the number of catheterization laboratories available for primary PCI should not be reduced during the pandemic, to avoid an increase in door-to-balloon time, to diminish the risk of infection during transfer for both professionals and/or patients, and to unload the health care system. Regional STEMI networks should adapt to dynamic changes of the pandemic in every region according to local medical and logistic resources. As an example, in Lombardy, Italy, a system of specialized COVID-19 referral hospitals has been defined at the start of the virus epidemic, reducing by more than 60% the number of previous referral centres with 24 hour/7 day capacity to perform a primary PCI.[91] Active shifts have been also assigned to interventional cardiologists, in order to satisfy the foreseen increased number of STEMI or NSTEMI patients arriving at the hospital.[92]

The ambulance networks also need to be reorganized in order to bring the patients straight to the COVID-19 referral hospital, skipping the spoke centres from where a secondary transportation could be difficult to arrange and time-consuming. The major objective of this rearrangement is primarily to allow for a timely treatment of the acute CVD, despite the unavoidable epidemic-related delays. It is also functional to secure patients to COVID-19-dedicated hospitals or to hospitals with isolated COVID-19 dedicated facilities when patients with acute CVDs are highly suspect for COVID-19 infection. China has been the first country to receive specific recommendations for a transport work programme directly by the country Health Authorities.[93]

6.3. Emergency Department

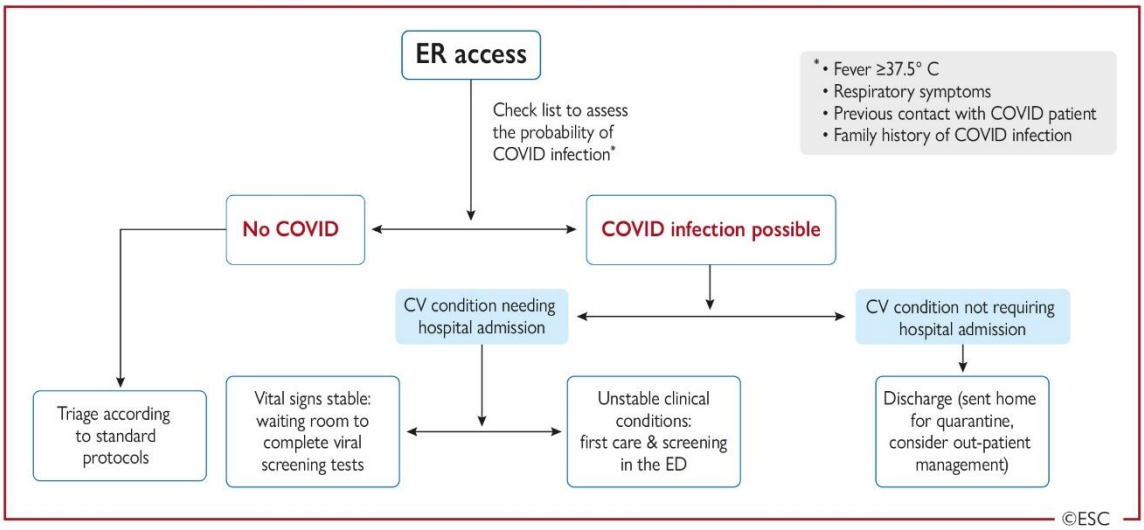
Key points

- 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.

In countries highly affected by the COVID-19 pandemic EDs have been re-organized to provide possible COVID-19 patients with dedicated access areas and isolated facilities from their first arrival to the hospital. Local protocols for rapidly triaging patients with respiratory symptoms should be issued with the aim of differentiating patients with CVDs from COVID-19 patients. In China for example patients with no geographical or family history of virus infection, fever, respiratory symptoms, fatigue or diarrhoea were considered ‘COVID-19 unlikely’ and their CVD was usually treated with standard protocols.[94]

A check-list should be adopted to quickly differentiate patients with possible or probable COVID-19 infection from non-infected patients (Table 3 and Table 4). Patients with mild, stable diseases should be discharged from the ED as soon as possible (Figure 8), with the suggestion to stay at home in quarantine if a COVID-19 infection is suspected or confirmed.

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



Conversely, patients in need of hospital admission for acute CVD with concomitant possible/probable SARS-CoV-2 infection (Table 4) should rapidly undergo testing and be managed as SARS-CoV-2 infected until they have two negative tests within 48 hours. Patients in need of hospital admission not suspected of SARS-CoV-2 infection can be managed according to standard of care.

6.4. Intensive Care Unit and Intermediate Care Unit

Key points

- 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.

ICU beds are mainly devoted to complicated COVID-19 patients in need of intensive care, who frequently present with underlying CVD and poor prognosis.[19, 95] Provided that in a pandemic situation the ethical value of maximizing benefits is recognized as the most relevant to drive resource allocation,[96] this might invariably disadvantage patients with advanced age and more severe CVD who will not be prioritized for advanced care provision.

Acute CV patients who tested negative (and without clinical suspicion for) COVID-19 infection, should be accurately identified and admitted, if feasible, to dedicated areas ICUs or ICCUs free from COVID-19 patients ('clean' ICUs or ICCUs), particularly in COVID-19 referral hospitals. If a fully 'clean' facility is not available, because of overwhelming numbers of COVID-19 patients, it should be guaranteed that airborne isolation rooms are set up in the facility, effectively separating patients with COVID-19 infection from all the others to minimize their infective risk. Such organization should also allow for adequate protection of HCP and well-defined pathways to and from the isolated rooms, in order to contain the spread of infection.[97]

Intermediate care units (also identifiable as ICCUs level II or I according to the Association for Acute Cardiovascular Care position paper[98]) share the same problems of ICUs, being usually equipped with CPAP machines for non-invasive ventilation. The same solutions already discussed for ICUs are therefore also applicable to intermediate care units. Triaging CV patients in need of CPAP from COVID-19 patients with pneumonia is mandatory, but still isolated rooms for COVID-19 positive CV patients (with acute HF for example) different from rooms for COVID-19 negative CV patients are very much needed.

7. Diagnosis of Cardiovascular Conditions in COVID-19 Patients

7.1. Clinical Presentation

7.1.1. Chest Pain

Key points

- 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.

7.1.2. Dyspnoea, Cough, Respiratory distress

Key point

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

7.1.2.1. 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, 65]

7.1.2.2. Cough

Cough is present in 59.4–81.1% of patients with COVID-19, irrespective of disease severity.[34, 99] Unproductive (dry) cough is more frequent, whereas sputum production is present in 23.0–33.7%.[10, 34, 65, 80]

7.1.2.3. 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.[100] Among 1099 adult inpatients and outpatients in China, ARDS occurred in 3.4%,[80] but in hospitalized patients, the rates are significantly higher (19.6–41.8%).[10, 34, 99] 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, 66, 80, 99, 100]

7.1.3. Cardiogenic Shock

Key points

- 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.

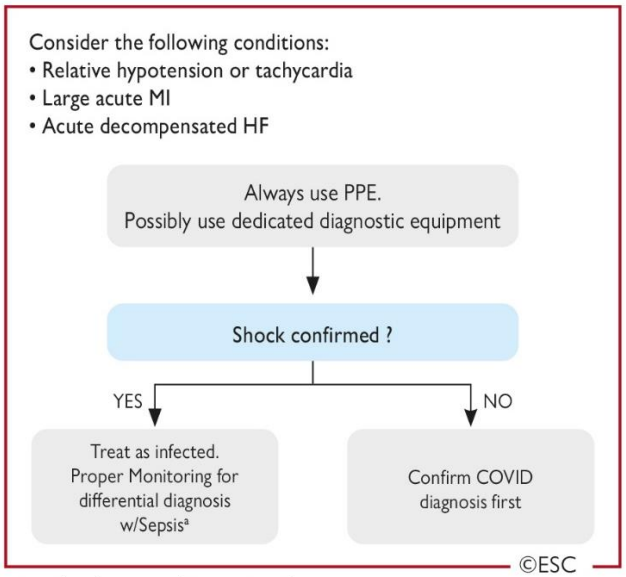
An early, accurate, and rapid diagnosis of CS in patients with confirmed or suspected COVID-19 is essential.[101] The exact incidence of CS in these patients is unknown. However, the median duration between onset of symptoms and admission to ICU in critically ill COVID-19 patients has been 9–10 days, suggesting a gradual respiratory deterioration in most patients.[102] 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:

- The proper level and type of monitoring, in addition to the haemodynamic status of the patient, should depend upon available local resources. Importantly, key diagnostic testing in patients with suspected CS, including electrocardiogram (ECG), bedside echocardiography, and urgent/emergent coronary angiography, should be integrated into local diagnostic protocols (with dedicated and/or protected equipment whenever possible) to ensure both the best deliverable care and a minimal risk of viral transmission to other patients and health care providers;
- Anecdotal clinical experience[44, 104] and experimental evidence indicating that > 7.5% myocardial cells have positive ACE2 receptor expression,[42] the target through which SARS-CoV-2 invades human cells, suggest that myocarditis may complicate COVID-19. This diagnosis should be considered as a potential cause of CS.

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.

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

Key points

- 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. In a study of 138 hospitalized patients with COVID-19 in Wuhan, arrhythmia was reported in 16.7% of total patients and in 16 of 36 patients admitted to the ICU (44%), although the authors did not further specify its type.[10] In a subsequent publication from the same institution, ventricular tachycardia (VT)/ventricular fibrillation (VF) was reported as a complication of the COVID-19 disease in 11 of 187 patients (5.9%), with a significantly higher incidence in patients with elevated troponin T.[25] However, the largest observational study from China, with 1099 patients from 552 hospitals, did not report any arrhythmia.[80] Hypoxaemia and a systemic hyperinflammation status may lead to new-onset atrial fibrillation (AF), although there are no published data so far. However, important consideration should be given to rhythm management (drug interactions with COVID-19 treatment) and anticoagulation.

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.

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

Key points

- 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.[105-108] Moreover, for influenza epidemics it has been demonstrated that there is a consistent rise in autopsy-confirmed coronary deaths.[109] Fatal AMIs have also been observed in the short term after coronavirus associated SARS.[110]

Notably, recent data from China suggest that myocardial injury during COVID-19 infection – as indicated by elevated troponin levels – represent one predictor of a higher risk of CV complications and an adverse clinical outcome.[25, 26] Moreover, an increased rate of thromboembolic events has been observed in the context of COVID-19 infection.

7.2. Electrocardiogram

Key points

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

So far no specific ECG changes have been described in patients with SARS-CoV-2 infection. Therefore, we have to assume that the overall minimal level of myocardial injury associated with the infection (see the following section on biomarkers) does not translate into characteristic ECG manifestations in the majority of patients, although ST-segment elevation in the setting of myocarditis have been described.[61] As a consequence, the same ECG diagnostic criteria for cardiac conditions apply in patients affected by SARS-CoV-2 infection and in the general population. Little is known about COVID-19 infection and arrhythmias. One report on 138 patients described an arrhythmia (not further specified) in 16.7% and the prevalence increased to 44.4% in the 16 patients who were admitted to the ICU.[10] For considerations of arrhythmia and corrected QT interval (QTc) prolongation of COVID-19 therapies see section 10.1.

7.3. Biomarkers

Key points

- 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.

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

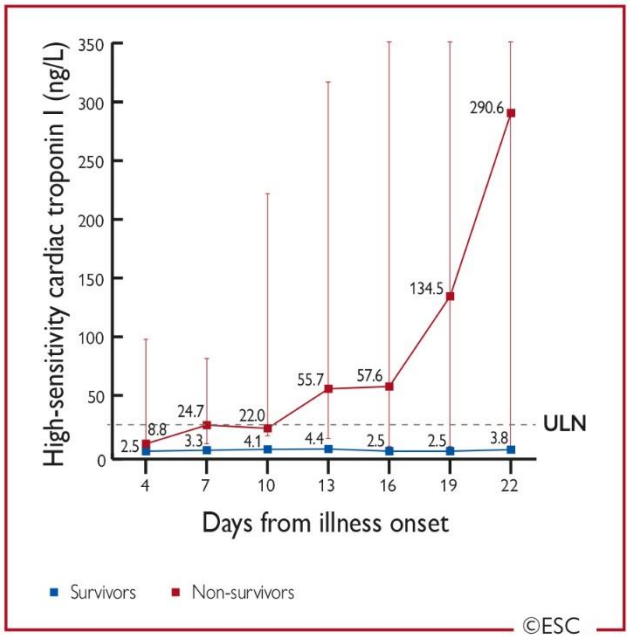
7.3.1.1. Cardiac Troponin I/T

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, 111] 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, 66, 89, 111-113]

Cohort studies from patients hospitalized with COVID-19 in China showed that 5–25% of patients had elevations in cardiac troponin T/I, and this finding was more common in patients admitted to the ICU and among those who died.[24-26, 66, 111] Concentrations remained in the normal range in the majority of survivors. In non-survivors, troponin levels progressively increased in parallel with the severity of COVID-19 and the development of ARDS (Figure 10).[24, 26, 34, 66, 111]

Figure 10 Temporal changes in high-sensitivity cardiac troponin I concentrations from illness onset in patients hospitalised with COVID-19

Differences between survivors and non-survivors were significant for all time points shown. ULN denotes upper limit of normal (adapted from Zhou et al.[34])

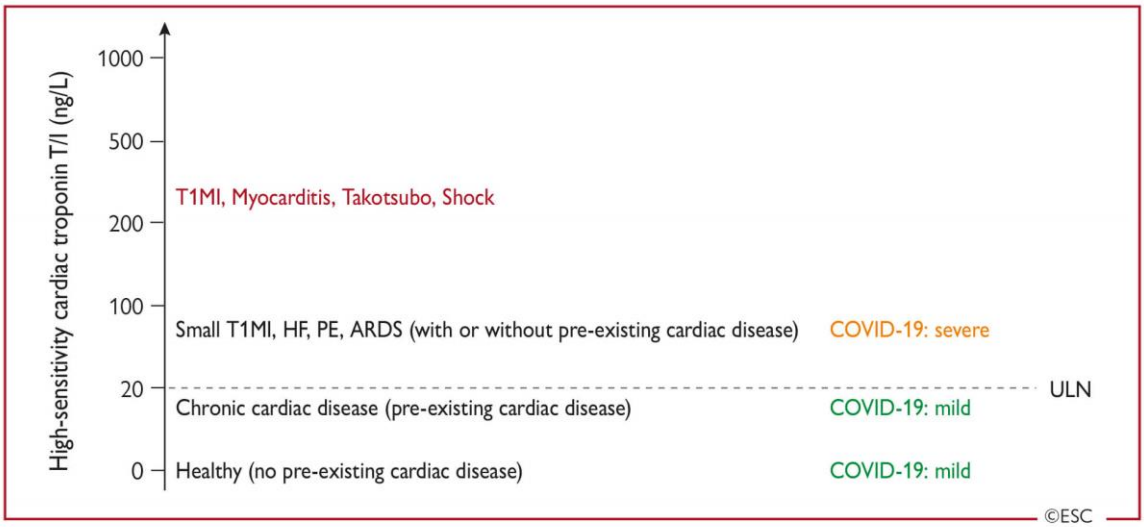


Mild elevations in cardiac troponin T/I concentrations (e.g. < 2–3 times the ULN), particularly in an older patient with pre-existing cardiac disease, do NOT require work-up or treatment for T1MI, unless strongly suggested by angina chest pain and/or ECG changes (Figure 11). Such mild elevations are in general well explained by the combination of possible pre-existing cardiac disease AND/OR the acute injury related to COVID-19.

Figure 11 High-sensitivity cardiac troponin (hs-cTn) T/I concentrations should be interpreted as quantitative variables.

In non-critically-ill patients with COVID-19, mild elevations (e.g. up to 3-times the ULN) elevations are in general well explained by the combination of possible prior cardiac disease AND the acute cardiomyocyte injury related to COVID-19. Even higher concentrations indicate the presence of specific acute cardiac disease such as T1MI, myocarditis, or takotsubo syndrome.

ULN denotes upper limit of normal and is assay-specific, HF denotes heart failure, PE denotes pulmonary embolism, ARDS denotes acquired respiratory distress syndrome, T1MI indicates type 1 myocardial infarction.



Marked 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, 89, 111] 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, 113, 114]

7.3.1.2. 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, 115-117] While experience in patients with COVID-19 is limited, very likely the experience from other pneumonias can be extrapolated to COVID-19.[26, 115-117]

As quantitative markers of haemodynamic stress and HF, the concentrations of BNP/NT-proBNP in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease AND/OR the acute haemodynamic stress related to COVID-19.[26, 115-117] At least to some extent, the release of BNP/NT-proBNP seems to be associated with the extent of right ventricular haemodynamic stress.

7.3.1.3. 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.[118] 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.[84] Although the D-dimers have a lower specificity for the diagnosis of acute PE, 32–53% of patients still have a normal D-dimer and the vast majority has D dimers below 1000 ng/ml.[10, 34, 80] Therefore, recommended diagnostic algorithms combing pre-test probability assessment and D dimer tests can be used in case of suspected acute PE.[119] In particular, algorithms applying a pre-test probability dependent D-dimer threshold may yield a decent specificity.[120-122]

7.3.2. Potential Mechanisms Underlying the Biomarker Elevation

The potential mechanisms underlying myocardial injury in those with COVID-19 infection are not fully understood. However, in keeping with other severe inflammatory and/or respiratory illnesses, direct ('non-coronary') myocardial injury is most likely the cause. Myocarditis, septic shock, tachycardia, severe respiratory failure, systemic hypoxaemia, Takotsubo syndrome or T1MI triggered by COVID-19, are alternative causes. Direct myocardial involvement mediated via ACE2, cytokine storm, or hypoxia induced excessive intracellular calcium leading to cardiac myocyte apoptosis have been suggested as alternative mechanisms.[2, 48, 123] As quantitative biomarkers of haemodynamic myocardial stress and HF, intracardiac filling pressures and end-diastolic wall stress seem to be the predominant triggers of the release of BNP/NT-proBNP.[115-117]

7.3.3. 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.[113] 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.[113, 124-126] 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.[113, 124-126]

Similarly, BNP/NT-proBNP should be measured whenever on clinical grounds HF is suspected.[26, 115-117] In patients who are not critically ill, rule-in cut-offs for HF maintain high positive predictive value even in patients with pneumonia.[26, 115-117] 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.[26, 115-117]

It is a matter of ongoing debate whether cardiac troponin T/I should be measured as a prognostic marker in patients with COVID-19. The strong and consistent association with mortality observed in the currently available reports of patients hospitalized with COVID-19, with some evidence suggesting cardiac troponin T/I even as an independent predictor of mortality, should be seen in favour of this approach.[25, 26, 34, 111] On the other hand, at this point in time, based on three arguments we consider a more conservative approach even more appropriate.[26, 34, 66, 89, 111-113] First, beyond cardiac troponin T/I other routinely available clinical and laboratory variables have also emerged as strong predictors of death in COVID-19 including older age, higher Sequential Organ Failure Assessment (SOFA) score, D dimers, IL-6 and lymphocyte count. It is unlikely that cardiac troponin T/I provides incremental value to a full model. Second, there is a recent risk of inappropriate diagnostic and therapeutic interventions triggered based in cardiac troponin T/I concentrations measured for prognostic purposes. Third, in patients with COVID-19 as well as with other pneumonias or patients with ARDS, at this point in time, no specific therapeutic intervention can be justified based on the use of cardiac troponin T/I as a prognostic marker.[26, 34, 66, 89, 111-113]

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.

7.4. Non-Invasive Imaging

Key points

- 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.

Non-urgent or elective cardiac imaging should not be performed routinely in patients with suspected or confirmed COVID-19 infection. Accordingly, non-urgent or elective exams should be postponed until the COVID-19 infection has ceased (Table 6).[127, 128]

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.

7.4.1. Transthoracic and Transesophageal Echocardiography

Key points

- 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.

Echocardiography can be performed bedside to screen for CV complications and guide treatment. POCUS, FoCUS and critical care echocardiography are probably the preferred modalities to image patients with COVID-19. Limited evidence exists for the use of lung ultrasound to differentiate ARDS (single and/or confluent vertical artefacts, small white lung regions) from HF.[129] The presence of dilated right ventricle and pulmonary hypertension may indicate contrast CT to rule out PE. In COVID-19 infected patients, echocardiography should focus solely on the acquisition of images needed to answer the clinical question in order to reduce patient contact with the machine and HCP.

It should not be forgotten that the risk of infection remains in the reading rooms and therefore the material used should be also frequently sanitized.

7.4.2. Computed Tomography

Key points

- 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.

Cardiac CT should be performed when there is a potential impact on clinical management, including evaluation of symptomatic suspected CAD, acute symptomatic heart valve dysfunction, left ventricular assist device (LVAD) dysfunction, PE, urgent structural intervention.[130] Cardiac CT is preferred to TEE to rule out the presence of intracardiac thrombus. In patients with acute chest pain and suspected obstructive CAD, CCTA is the preferred non-invasive imaging modality since it is accurate, fast and minimizes the exposure of patients. In patients with respiratory distress, lung CT is recommended to evaluate imaging features typical of COVID-19 and differentiate from other causes (HF, PE).[94] However, it should not be used to screen for or as a first-line test to diagnose COVID 19 and should be reserved for hospitalized patients.[131] A dedicated CT scanner for patients with suspected or confirmed COVID-19 is preferred. As in other imaging modalities, local standards for prevention of virus spread and protection of personnel should be followed.

7.4.3. Nuclear Cardiology

Key points

- 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.[132] The use of PET-CT can be limited to patients with suspected endocarditis of prosthetic valves or intracardiac devices when other imaging modalities are inconclusive or to avoid the performance of a TEE which is associated with larger risk of spreading. Single photon emission computed tomography (SPECT) or PET may also be used for diagnosing ischaemia in patients with suspected obstructive CAD when CCTA is not appropriate or available.

7.4.4. Cardiac Magnetic Resonance

Key points

- 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.[133]

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.[133] 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.

The role of CMR in COVID-19 patients is currently not clear. Accepted diagnostic indications for CMR should be considered as appropriate in these patients, but should not be performed unless clinically necessary and after a reconsideration of best suited imaging technique.[128]

Another important attention is the use of CMR contrast in patients with COVID-19. Renal function might be decreased in patients with COVID-19 and might contradict a clinically urgent CMR scan.

One indication for an acute CMR might be suspicion of acute myocarditis, which has been reported in patients with COVID-19.[134] Typical symptoms might be elevated troponins, ventricular dysfunction and/or severe arrhythmias that cannot be explained by other diagnostics and imaging methods.[20]

7.4.5. 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 mask (that could strongly affect his/her exercise capacity). This problem is further increased since rooms of outpatient clinics are rarely large and well aerated. Performance of exercise testing is discouraged in COVID-19 suspect or positive patients and, in general, in every patient in COVID-19 epidemic or potentially epidemic areas. Alterative diagnostic methods for CAD not requiring exercise should be used as an alternative to exercise testing whenever possible.

There remain conditions where exercise testing is necessary. These mainly concern patients with heart failure. Cardiopulmonary exercise testing remains the method of choice for the assessment of exercise capacity, a well-known prognostic index, and for the indication to heart transplantation in patients with heart failure. In addition, exercise testing is proposed as the method of choice for the diagnosis of heart failure with preserved ejection fraction (HFpEF) in patients with breathlessness and intermediate scores for HFpEF diagnosis. A low-level exercise may be, however, sufficient in these cases.[135]

7.5. Differential Diagnosis

Key points

- 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.

8. Categorization of Emergency/Urgency of Invasive Procedures

The rearrangement of the healthcare service required to face the COVID-19 pandemic has posed a series of relevant issues on prioritization of cardiac invasive procedures.[136] Different regions in Europe and worldwide differ substantially in terms of local healthcare resources, epidemic density of the COVID-19 outbreak, changes of the epidemic over time and therefore access to healthcare services other than COVID-19 care. These differences have a wide range of implications for national/regional healthcare services, national health care authorities and in-hospital redistribution of resources. Regions (also within the same country) may be categorized into three groups according to the degree of involvement in the epidemic, with subsequent different implications for the healthcare system as summarized in Table 7.

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

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:

- To increase capacity for COVID-19 patients;
- 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;
- 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.

In this context, a strategy is needed to identify patients who are in a condition allowing to postpone procedures and those who are not. An obvious concern is to maintain the standard-of-care and timely access of patients with ACS including AMI to reperfusion therapy. In patients with chronic coronary syndromes (CCS), principles of prioritization can be based on risk stratification, taking into account prognostic implications of symptoms and the presence of known critical disease of the left main stem or of the proximal left anterior descending (LAD) coronary artery at prior coronary angiogram or at CCTA.[137] Similarly, patients with decompensated, symptomatic, severe aortic stenosis (AS) scheduled for transcatheter aortic valve replacement should be prioritized.[138] Table 8 summarizes a categorization of invasive cardiac procedures according to urgency that may be implemented at areas affected by the COVID-19 outbreak.

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

Clinical condition	EMERGENCY (do not postpone)	URGENT (perform within days)[a]	LOWER PRIORITY (perform within <3 months)[a]	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 cm^2, mean transvalvular gradient >60 mmHg, symptoms with minimal exertion) • TAVI/SAVR in symptomatic patients with low-flow low-gradient AS (AVA <1.0 cm^2, 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 cm^2, mean transvalvular gradient >40 mmHg) • TAVI/SAVR with symptomatic paradoxical low-flow low-gradient aortic stenosis (AVA <1.0 cm^2, 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

[a]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

9.1. Non-ST-Segment Elevation Acute Coronary Syndromes

The management of patients with NSTE ACS should be guided by risk stratification.[113] 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).

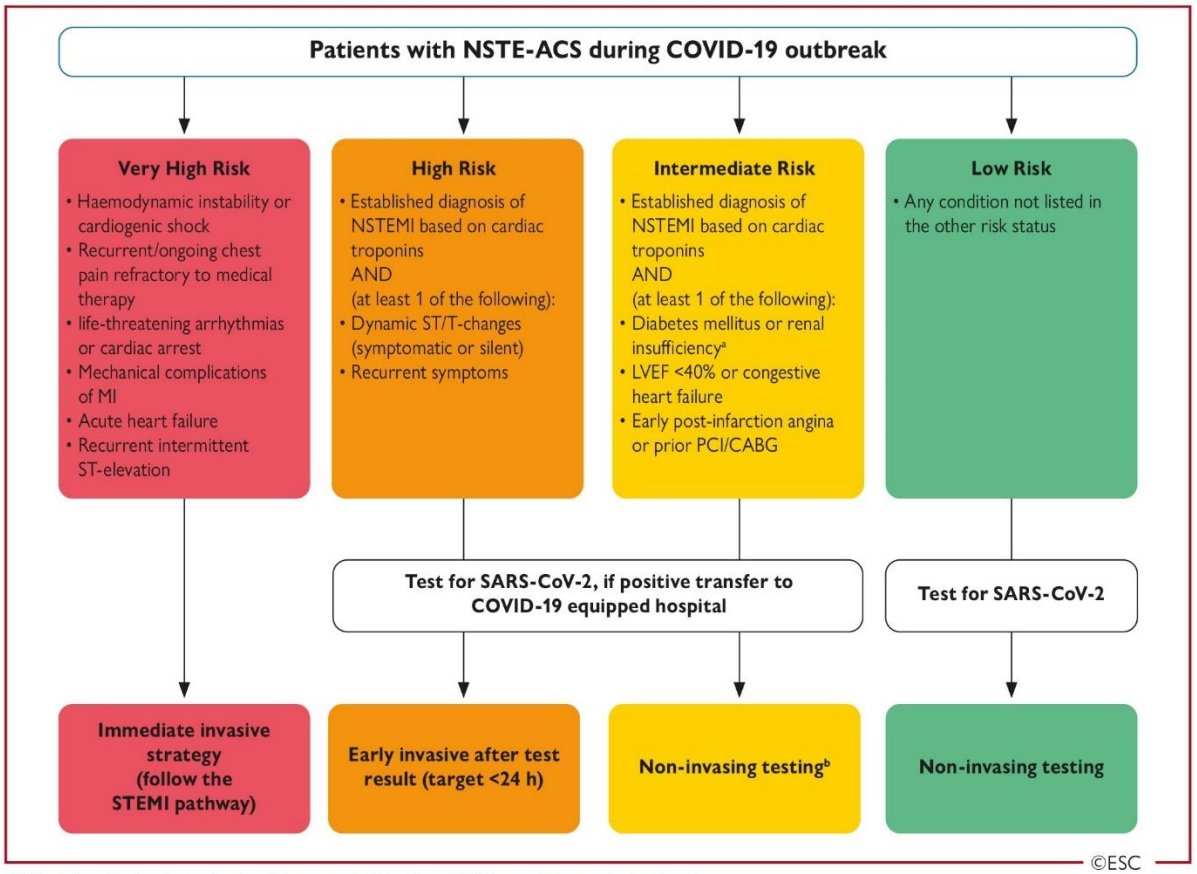
Patients with Troponin rise and no acute clinical signs of instability (ECG changes, recurrence of pain) might be managed with a primarily conservative approach. Non-invasive imaging using CCTA may speed-up risk stratification, avoid an invasive approach[139] allowing early discharge.

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.

9.2. 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.[114] Concurrently, the safety of HCP should be ensured.[136] 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:

1. The maximum delay from STEMI diagnosis to reperfusion of 120 minutes should remain the goal for reperfusion therapy under the following considerations:
    a. Primary PCI remains the reperfusion therapy of choice if feasible within this time frame and performed in facilities approved for the treatment of COVID-19 patients in a safe manner for healthcare providers and other patients;
    b. Primary PCI pathways may be delayed during the pandemic (up to 60 minutes – according to multiples experiences) due to delays in the delivery of care and the implementation of protective measures;
    c. If the target time cannot be met and fibrinolysis is not contraindicated, fibrinolysis should then become first line therapy;
2. As SARS-CoV-2 test results are not immediately available in STEMI patients, any STEMI patient should be considered potentially infected;
3. All STEMI patients should undergo testing for SARS-CoV-2 as soon as possible following first medical contact irrespective of reperfusion strategy, at the latest upon admission to the ICU post primary PCI. Until the result of the test is known, all precautionary measures should be taken to avoid potential infection of other patients and HCP;
4. Consider immediate complete revascularization if indicated and appropriate in order to avoid staged procedures and reduce hospital stay;
5. All physicians involved in the management of patients with STEMI should be familiar with indications, contraindications and dosage of fibrinolysis and adhere to established administration protocols (Table 9 and Table 10).

Specific pathways for management of STEMI patients are illustrated in Figure 13. It is suggested to perform left ventriculography during catheterization of any ACS patients to reduce the need for echocardiography and shorten hospital stay.

The treatment of the non-culprit lesions should be managed according to patients' clinical stability as well as angiographic features of those lesions. In the presence of persistent symptomatic evidence of ischaemia, subocclusive stenoses, and/or angiographically unstable non-culprit lesions, PCI during the same hospitalization should be considered. Treatment of other lesions should be delayed, planning a new hospitalization after the peak of the outbreak.[114]

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

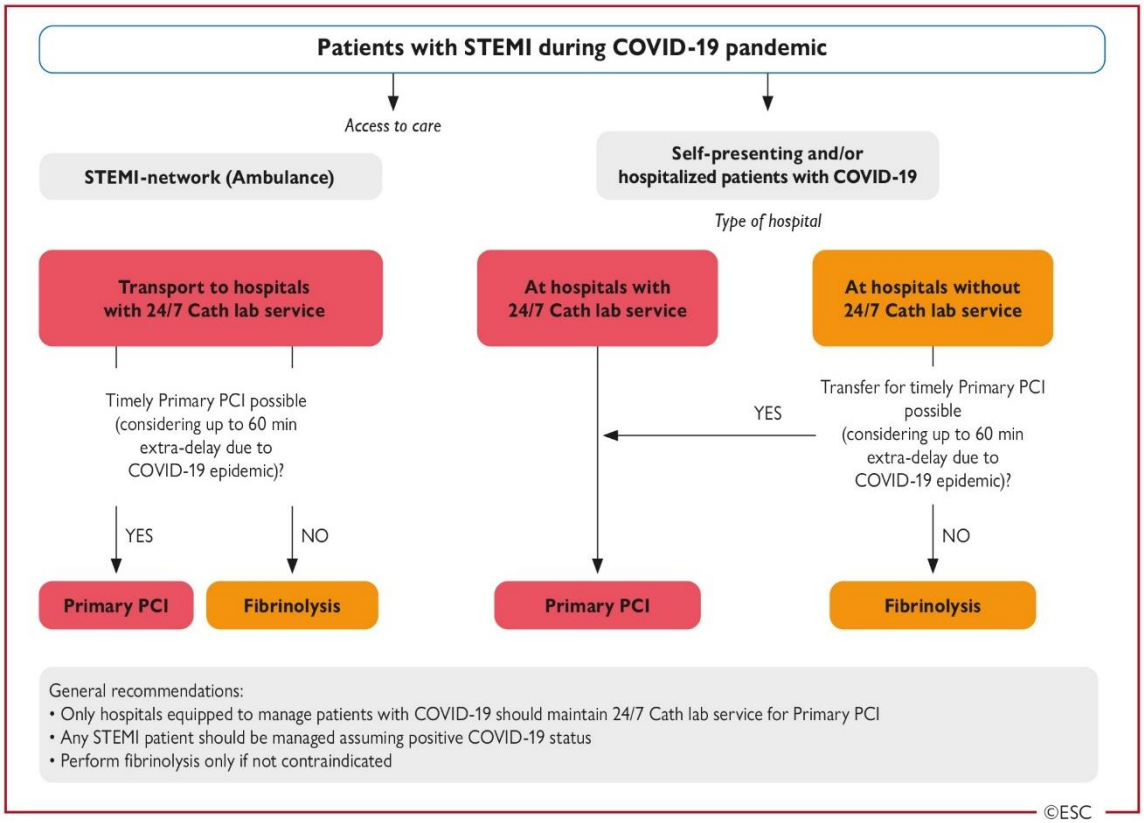


Table 9 Recommendations for fibrinolytic therapy (Extracted from[114])

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.

9.3. Cardiogenic Shock

Key points

- 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.[101, 114, 137, 140, 141] 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:

a. 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;
b. 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;
c. 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.

Triage strategies, based on current evidence and a previously established critical care triage protocol developed by working groups for use during a worldwide influenza pandemic,[142] are summarised in Table 11 and Table 12. Specific recommendations are provided for patients with and without concomitant infection in Figure 14. Two scenarios will be considered:

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

The infection should be suspected according to recently defined epidemiological and clinical criteria.[143]

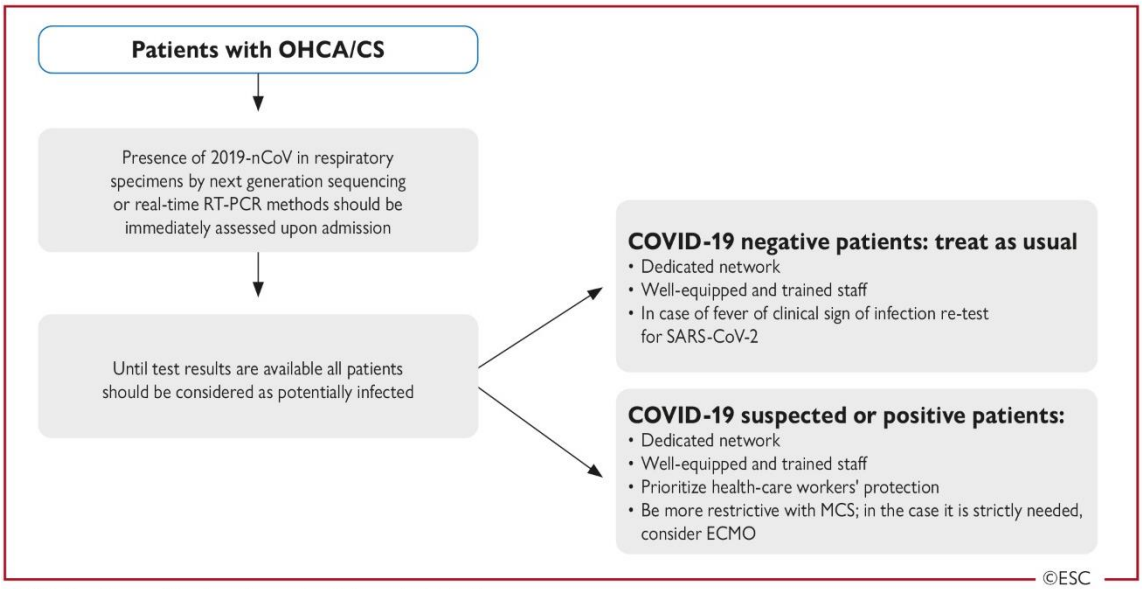
Table 11 Detailed inclusion and exclusion criteria for triage in intensive care unit (ICU) upon admission
(modified from Christian et al)[142]

Inclusion criteria:
• Requirement for invasive ventilator support. • Requirement for hemodynamic support with vasoactive agents (noradrenaline-equivalent dose >0.1 µg/kg/min) or mechanical support. • Requirement for renal replacement therapy. *If at least 1 criterion is fulfilled, check for exclusion criteria.*
Exclusion criteria:
• Patients' end of life decision preferences. • Unwitnessed cardiac arrest, witnessed cardiac arrest, not responsive to electrical therapy, recurrent cardiac arrest. • Metastatic malignant disease. • End-stage neurodegenerative disease. • Severe and irreversible neurological event or condition. Chronic condition: - patients with NYHA class IV heart failure not eligible to left ventricle assist device or heart transplantation - GOLD group D COPD - Cystic fibrosis or pulmonary fibrosis with baseline PaO_2 <55 mmHg - Liver cirrhosis, Child-Pugh score >7 - End-stage kidney disease on dialysis with refractory symptoms despite active medical management treatment. • Severe dementia. • Estimated survival <12 months. *If not even one criterion is met and ICU beds are not available, check for additional exclusion criteria.*
Additional exclusion criteria to be checked if no ICU beds are available:
• Severe trauma. • Severe cerebral deficits after stroke. • Moderate dementia. • Estimated survival <24 months. • Chronic condition: - Home oxygen therapy - Liver cirrhosis with refractory ascites or encephalopathy > stage I • Age >80 years • Age >70 years and at least one criterion: - Cirrhosis - Stage III chronic kidney disease KDIGO - NYHA class >II heart failure • Patients aged >60 years with NYHA class III heart failure without acute treatable cardiac disease and/or LVEF <30% even if eligible to left ventricle assist device or heart transplantation. *If neither of these criteria is fulfilled, consider to withdraw ICU support from patients who arrived earlier to save those with better prognosis (Table 12).*

Table 12 Criteria for little or no likelihood of benefit with ICU treatment (occurrence of at least 1 criterion)

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

Figure 14 Management of patients with cardiogenic shock (CS)/out-of-hospital cardiac arrest (OHCA) during COVID-19 pandemic



ECMO = ExtraCorporeal Membrane Oxygenation; MCS = mechanical circulatory support.

9.4. 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.

9.4.1. Practical Considerations on Medical Therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been identified as a potential risk factor for serious clinical presentation of SARS-CoV-2 infection.[144] Potential impact of chronic aspirin therapy has been questioned. However, at the low dose administered in CCS, aspirin has very limited anti-inflammatory effect. Therefore, CCS patients should not withdraw aspirin for secondary prevention.

Statin therapy has been variably associated with favourable outcomes in patients admitted with influenza or pneumonia.[145, 146] On the other side, patients with COVID-19 have been sometimes reported to develop severe rhabdomyolysis or increased liver enzymes.[147] In these latter cases, it may be prudent to temporarily withhold statin therapy.

For CCS patients treated with antihypertensive drugs please refer to section 9.7.

9.4.2. Non-Invasive Testing

Non-invasive testing in patients with CCS is tailored upon different clinical presentations.[148] In regions with high rate of SARS-CoV-2 infection, evaluation of asymptomatic CCS patients with non invasive testing should be postponed in order not to expose these patients to an unnecessary risk of infection or overload the health care systems.

For symptomatic patients with suspected CAD and a pre-test probability of 5–15%, functional imaging for detection of myocardial ischaemia or CCTA are normally recommended as initial tests to diagnose CAD. In regions with critical situation and medical system overloaded by the COVID-19 pandemic, CAD screening even in symptomatic patients should probably be postponed in the majority of patients. Yet, if necessary, depending upon local availability and expertise, CTA should be preferred (section 7.4).

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

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

9.4.3. Invasive Assessment and Revascularization

Symptomatic patients with very high clinical likelihood of obstructive CAD are generally referred to ICA without prior non-invasive diagnostic testing.[148] However, even in these patients, medical treatment should be attempted first in order to reserve ICA with possible ad-hoc revascularization only in case of clinical instability, especially in regions were healthcare systems are heavily overloaded by patients with COVID-19.[149] Revascularization (either by PCI or coronary artery bypass graft [CABG]), can be postponed in most CCS patients. However, in hospitals whose ICUs are dedicated to or overloaded with high numbers of patients with COVID-19, the impact on CABG deferral might be even more pronounced. Priority is given to keep ICU beds available for COVID-19 patients requiring critical care. Therefore, healthcare systems might identify COVID-19-free hospitals serving as hubs for selected CCS patients in whom invasive and surgical procedures cannot be postponed. In these latter patients, SARS-CoV-2 infection should be ruled out by nasopharyngeal swab/tracheobronchial aspiration and/or CT scan before hospital admission. Alternatively, in selected patients, hybrid revascularization CABG/PCI or even full-PCI can be considered by the heart team based on patient's clinical conditions and local situation (see Table 13).

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.

9.5. 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.[150]

9.5.1. Acute Heart Failure

Key points

- Acute HF may complicate the clinical course of COVID-19, particularly in severe cases;
- Underlying mechanisms of acute HF in COVID-19 may include 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]

In 21 patients admitted to an ICU for severe COVID-19, 7 (33.3%) patients developed dilated cardiomyopathy, characterized by globally decreased LV systolic function, clinical signs of CS, elevated creatine kinase (CK), or troponin I levels, or hypoxaemia, without a past history of systolic dysfunction.[89] An analysis of mortality causes in COVID-19 patients (150 hospitalized/68 dead) revealed that myocardial damage/HF and combined respiratory failure/myocardial damage/HF were responsible for 7% and 33% of fatal cases, respectively.[66]

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

1. Acute myocardial injury (defined as serum hs-cTn I elevation > 99th percentile of the ULN or new abnormalities in ECG or echocardiography) occurs in 8% of COVID-19 patients.[150] It may be caused by ischaemia, infarction or inflammation (myocarditis). In patients with severe infection, evidence of acute myocardial injury is present in 22.2–31%.[10, 34, 65] A meta analysis of four studies (n = 341) suggested that in patients with severe infection, hs-cTn I was significantly higher at admission (mean standardized difference 25.6 ng/L) compared to those with non severe course.[151] In addition, troponin levels remained high in non-survivors throughout the clinical course and increased with illness deterioration.[34] A history of HF was more frequently noted in patients with, compared to those without, acute myocardial injury (14.6% vs. 1.5%).[26] Acute myocardial injury was also more frequently associated with significantly elevated NT-proBNP levels (median 1689 pg/mL);[26]
2. ARDS, hypoxaemia, acute kidney injury, hypervolaemia, stress-induced cardiomyopathy and a profound systemic inflammatory activation (‘cytokine storm’), characteristic of severe infection and multiorgan dysfunction, could also contribute to acute HF or exacerbation of chronic HF in COVID-19;
3. Sustained/repetitive cardiac arrhythmia may also lead to deterioration in cardiac function. Cardiac arrhythmia has been described in 16.7% of all hospitalized COVID-19 patients and in 44.4% of patients requiring intensive care admission.[10]

9.5.2. Myocarditis

Key points

- 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] One published case involved a 38-year-old male presenting with chest pain, hypotension, bilateral pneumonia with pleural effusions and ST segment elevation, but with normal CT coronary angiogram.[104] Echocardiography demonstrated dilatation 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 successfully recovered after receiving high-dose parenteral glucocorticoid anti inflammatory therapy and immunoglobulin, along with other therapeutic measures.

9.5.3. Chronic Heart Failure

Key points

- 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.

9.5.3.1. Prevention of SARS-CoV-2 Infection

During the COVID-19 outbreak, patients with chronic HF should be advised to closely follow protective measures aimed at preventing disease transmission (e.g. self-isolation, social distancing, frequent hand washing, use of hand sanitizers and wearing a face mask in public spaces). Ambulatory stable HF patients (with no cardiac emergencies) should refrain from hospital visits.

9.5.3.2. Diagnostic Hints

Routine clinical methods, ECG (arrhythmias, myocardial ischaemia, myocarditis) and chest X-ray (cardiomegaly, COVID-19 pneumonia) can provide a diagnostic clue. Due to the relatively low sensitivity of chest X-ray to detect COVID-19 pneumonia, patients with a high degree of clinical suspicion (tachypnoea, hypoxaemia), but with ambiguous chest X-ray findings, should be referred to chest CT.[152] Laboratory findings, such as increased erythrocyte sedimentation rate, fibrinogen and C-reactive protein, and lymphocytopenia, may suggest COVID-19 pneumonia. TTE is very important, not only to evaluate pre-existing LV dysfunction in HF, but also to assess patients suspected of having SARS CoV 2-associated myocarditis.[153] During all medical procedures, an attention should be given to prevent viral transmission to HCP.

9.5.3.3. Chronic Heart Failure Treatment

SARS-CoV-2 utilizes the ACE2 receptors for cell entry and some data indicate that ACEIs and ARBs may upregulate ACE2,[154] thus hypothetically increasing the susceptibility to the infection. Recently, a case series of 12 patients with COVID-19-associated ARDS, demonstrated that plasma Ang II levels were markedly elevated and linearly associated with viral load and lung injury.[33] This has led to a suggestion that ARB treatment could have a beneficial effect in curbing the Ang II-mediated lung injury. Clearly, further research in required to resolve the controversies regarding the role of ACEI/ARB in COVID-19.

There is currently no clinical evidence of an association between ACEI/ARB treatment and the susceptibility to infection, or the clinical course. Withdrawal of medical treatment in HF patients may increase the risk of worsening HF.[155] Available data do not support discontinuation of ACEI/ARB and it could be recommended that HF patients continue guideline-directed medical therapy, including beta blockers, ACEI, ARB, or sacubitril/valsartan, and mineralocorticoid receptor antagonists, irrespective of COVID-19.[156]

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

9.5.3.4. 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.

9.5.4. Left Ventricular Assist Device and Heart Transplantation

Key points

- LVAD patients have greater susceptibility to the infection, and strict preventive measure should be applied to avoid it;
- Heart transplant recipients may be at a higher risk of severe COVID-19 disease or prolong viral shedding, hence tight adherence to preventive measures should be advised to avoid infection;
- Limited data exists about the presentation and prognosis of COVID-19 in heart-transplant recipients. However, variable clinical outcomes in solid organ recipients in earlier coronavirus outbreaks (SARS and MERS),[157, 158] suggest that hospitalization, close monitoring and appropriate treatment of COVID-19 heart-transplant patients should be recommended.

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

The susceptibility to the infection and the clinical course of COVID-19 in heart transplant recipients is not known. Recently, two cases (one mild, another more severe) of COVID-19 have been described in heart transplant recipients in China.[159] Importantly, the presenting symptoms were similar to those of immunocompetent individuals, including fever, elevated inflammatory markers (e.g. C-reactive protein), lymphocytopenia and chest CT demonstrating bilateral ground-glass opacities. The treatment of the patient with more severe infection included temporary discontinuation of baseline immunosuppressant medications and institution of high-dose glucocorticoids, immunoglobulins and fluroquinolone antibiotics, along with other treatment measures. Of note, both patients recovered and remained rejection-free.

Yet another report of 87 heart transplant recipients from China, indicated that high-degree adherence to preventive measures (see above), resulted in a low rate of possible infection and transition to manifest illness (e.g. 4 patients were reported to have airway tract infection and 3 of them had a negative SARS-CoV-2 test result, whilst 1 patient was not tested).[160] Importantly, all patients fully recovered after treatment.

9.6. Valvular Heart Disease

Key points

- 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).

Although VHD has not been explicitly linked to increased morbidity and mortality in early COVID-19 case series, up to 40% of the patients admitted to the ICU had pre-existing congestive HF.[89] VHD mainly affects the elderly and the symptoms of disease progression (mainly dyspnoea) may mimic those of lung infection or infiltration. In addition, VHD may aggravate the course of COVID-19 infection and complicate haemodynamic management of the systemic inflammatory response (cytokine storm),[161] ARDS, and any superimposed bacterial septicaemia (observed in up to one third of ICU patients).[65]

Elective surgical and transcatheter interventions for VHD consume significant health care resources and many (or all, according to circumstances) may be inappropriate during the pandemic given the immense pressure on acute and intensive care facilities. However, patients with severe VHD must remain under close telephone surveillance and be encouraged to report progressive symptoms. Concentration of resources on the treatment of pandemic victims guides decisions with the overall aim of avoiding shortage of ICU beds and ventilators. Prioritization of valve interventions should therefore balance the immediate and short-term prognosis of individual patients against available resources and the risk to patients and HCP of acquiring in-hospital infection. In this respect, use of less invasive procedures (particularly transcatheter aortic valve implantation [TAVI] via transfemoral approach performed under conscious sedation and/or local anaesthesia), may present an opportunity to minimize ICU and hospital stay. The need for clinical decision making by Heart Teams remains of paramount importance and use of telemedicine (or other means of virtual communication) is essential if face-to-face meetings are difficult (or impossible) during the acute phase of the pandemic.

9.6.1. Management of Aortic Stenosis

Key points

- 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,[162, 163] LVEF, pulmonary hypertension,[164] and elevated biomarkers (natriuretic peptides or troponin).[165-167] Mortality of patients with severe symptomatic AS who are treated conservatively is high, reaching 50% at 1 year and 70–80% at 2 years.[168] Deferring surgical aortic valve replacement (SAVR) or TAVI by several months may therefore affect prognosis.

In the context of the COVID-19 pandemic, the Heart Team should undertake systematic individual risk assessment based on objective criteria that determine disease progression. Priority should be given to patients with syncope or HF (New York Heart Association [NYHA] Class III/IV), high or very high transvalvular gradients and those with reduced LV function Table 8, whereas a watchful waiting strategy is more appropriate in those with minimal or no symptoms. TAVI (or balloon aortic valvuloplasty) may be considered in haemodynamically unstable patients (COVID-19 positive/negative). However, the potential benefits of valve intervention in a critically ill COVID-19 positive patient (no cases reported to date) should be carefully weighed against the likelihood of futility given the > 60% mortality of COVID-19 positive patients admitted to ICU.[169]

All cases should be discussed by the Heart Team and indications for TAVI extended to intermediate[170, 171] and selected low-risk patients.[172, 173] Increased use of transfemoral TAVI (when feasible) may allow optimal utilization of resources by avoiding general anaesthesia and intubation, shortening (or preventing) ICU stay and accelerating hospital discharge and recovery.[174]

9.6.2. Management of Mitral Regurgitation

Key points

- 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),[175] others may develop unstable HF syndromes that are refractory to medical treatment, particularly in the context of acute infection.[176]

In the context of the COVID-19 pandemic, priority should be given to the treatment of patients with acute primary MR complicating AMI or IE, and those with severe primary or SMR who remain symptomatic despite guideline-directed medical and device treatment and seem likely to require hospital admission. All other patients should be managed conservatively.[175-178]

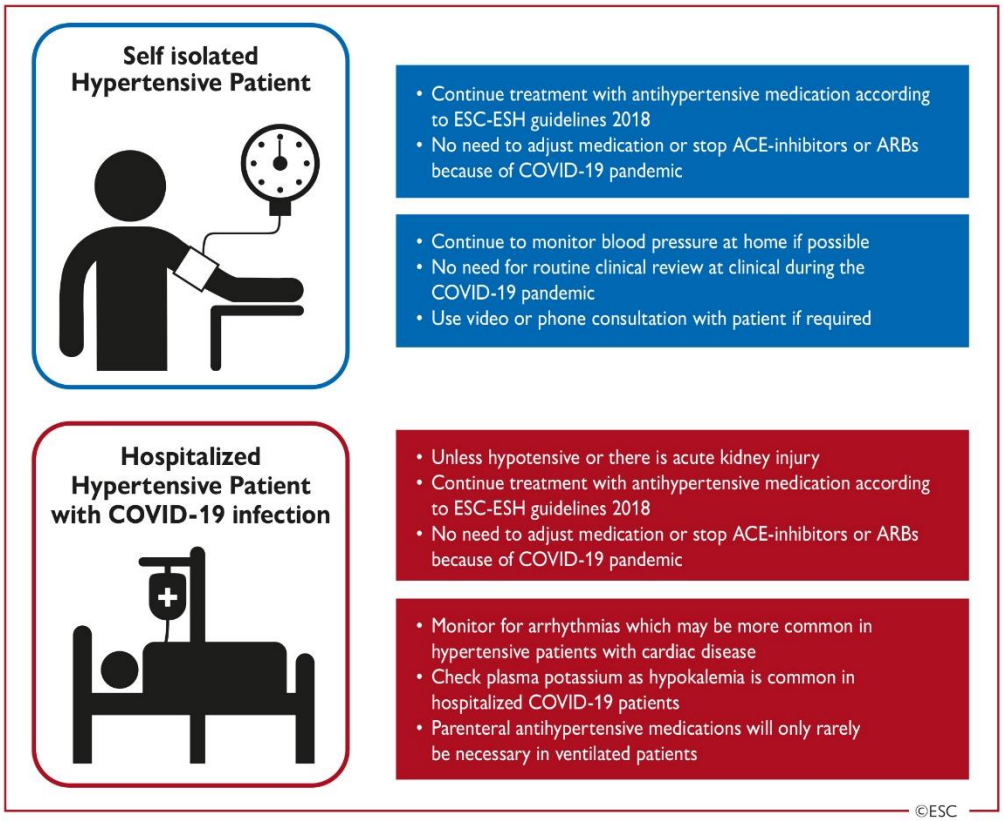
Transcatheter mitral edge-to-edge repair may be considered in anatomically suitable high-risk or inoperable patients with acute MR (excluding those with IE) or highly selected patients with decompensated primary MR or SMR refractory to guideline-directed medical and device treatment. Despite a low risk of complications requiring ICU admission,[179] the procedure requires general anaesthesia (in distinction to transfemoral TAVI) and prolonged echocardiographic guidance, thereby exposing interventionists and anaesthetists to the risk of COVID-19 transmission. Use of temporary circulatory support (intra-aortic balloon pump or Impella) should be restricted to patients with a good prospect for recovery in the context of available ICU resources.

9.7. Hypertension

Key points

- 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, or the risk of developing severe complications from 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.

Figure 15 Hypertension management in the COVID-19 context



9.7.1. 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, 80, 99, 180] 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.

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 other unmeasured confounders.[47] 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.

9.7.2. Antihypertensive Treatment with Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers

RAS blockade with ACEIs or ARBs are the foundation of antihypertensive therapy in the current ESC-ESH Guidelines for the management of arterial hypertension (2018).[181] The recommended treatment of hypertension for most patients is combinations of an ACEI or ARB with a calcium channel blocker (CCB) or thiazide/thiazide like diuretic.[181]

Concern has been expressed that treatment with ACEIs or ARBs might increase the risk of infection, or developing the severe consequences of infection with COVID-19.[21, 46, 182] This concern originates from a hypothesis that links the observations that COVID-19 invades cells by binding to the enzyme ACE2 which is ubiquitous and expressed on the surface of alveolar cells in the lung.[39, 41, 183] In some animal studies, but not all, ACEIs or ARBs have been shown to increase ACE2 levels mainly in cardiac tissue.[49, 184, 185]

Importantly, there have been no studies showing that RAS-blocking drugs increase ACE2 levels in human tissues and no studies in animals or humans showing that RAS-blocking drugs increase ACE2 levels in the lung, or that the level of ACE2 expression in the lung is rate limiting for COVID-19 infection.

Moreover, there have been no studies in humans demonstrating an independent link between RAS blocker use and the development of severe complications of COVID-19 infection, after adjustment for age and other comorbidities. Recently a series of observational cohort studies have been published which consistently show that treatment with RAS blockers does not increase the risk of COVID-19 infection, or increase the risk of severe complications or death from COVID-19 infection.[54-60] In one study, there was even a substantial reduction in risk of severe complications or death from COVID-19 infection in patients with diabetes mellitus.[56] These recent findings are very important and provide reassurance to patients and their doctors that prior speculation about the safety of RAS blockers in the context of COVID-19 infection has not been proven.

Indeed, studies in animal models of infection with influenza or coronaviruses have suggested that ACE2 is important in protecting the lung against severe injury and that RAS-blocking drugs are also protective against severe lung injury due to these viruses.[186-188] Human studies of RAS-blockade or recombinant ACE2 to prevent respiratory decompensation in COVID-19 infected patients have been suggested, planned or are ongoing.[189, 190]

In summary, there is currently no evidence to suggest that ACEIs or ARBs increase the risk associated with COVID-19 infection and there is no reason why these drugs should be discontinued due to concern about COVID-19 infection. Treatment of hypertension when indicated, should continue to follow the existing ESC-ESH guideline recommendations.[191]

9.7.3. 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.[181]

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

9.7.4. 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[193] and early reports suggests is also prominent in hospitalized COVID-19-infected patients.[194] 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.

9.8. Acute Pulmonary Embolism – Prevention and Diagnosis

Key points

- 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.

Although solid evidence is unavailable to date, a number of case reports suggest that the incidence of PE in patients with COVID-19 infection may be high.[195-197] Taking this into account, together with COVID-19-associated systemic inflammation, coagulation activation, hypoxaemia and immobilization, anticoagulation at standard prophylactic doses should be considered for all patients admitted to the hospital with COVID-19 infection.

Patients with COVID-19 infection often present with respiratory symptoms and may also report chest pain and haemoptysis.[80] These symptoms largely overlap with the presentation of acute PE which may cause underdiagnosis of this relevant complication.[198] Unexpected respiratory worsening, new/unexplained tachycardia, a fall in BP not attributable to tachyarrhythmia, hypovolaemia or sepsis, (new-onset) ECG changes suggestive of PE, and signs of deep vein thrombosis of the extremities should trigger a suspicion of PE. It is recommended to only order diagnostic tests for PE when it is clinically suspected, although it is recommended to keep a low threshold of suspicion. The specificity of D-dimer tests may be lower in patients with COVID-19 compared to other clinical settings. Even so, it is still advised to follow diagnostic algorithms starting with pre-test probability and D-dimer testing, especially when pre-test probability dependent D-dimer thresholds are being used.[120-122] This may help to rationalize the deployment of resources and personnel for transporting a patient to the radiology department with all the associated isolation precautions. In the clinical scenario of a patient with COVID-19, who has just undergone CT of the lungs but the findings cannot explain the severity of respiratory failure, CT pulmonary angiography may [or should] be considered before leaving the radiology department.

When acute PE is confirmed, treatment should be guided by risk stratification in accordance with the current ESC guidelines.[119] Patients in shock should receive immediate reperfusion therapy. Haemodynamically stable patients may be treated with either unfractionated heparin (UFH), low molecular weight heparin (LMWH) or a NOAC, depending on the possibility of oral treatment, renal function and other circumstances. When choosing the appropriate drug and regimen (parenteral versus oral) for initial, in-hospital anticoagulation, the possibility of rapid cardiorespiratory deterioration due to COVID-19 should be taken into account. Of note, some of the investigational drugs for COVID-19 may have relevant interactions with NOACs. In particular, this may be the case for lopinavir/ritonavir via Cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (P-gp) inhibition. In such cases, the bleeding risk may be elevated and NOACs should be avoided. Because close monitoring is necessary which may contribute to spreading of the infection, vitamin K antagonists (VKAs) should only be considered in special circumstances such as the presence of mechanical prosthetic valves or the antiphospholipid syndrome.[119]

9.9. Arrhythmias

Key points

- 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.

Very few data are available on antiarrhythmic management specifically in COVID-19 patients. Therefore, this text reflects a consensus based on limited evidence. This text will be updated if more information becomes available.

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

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

Several national societies and health services including the Heart Rhythm Society, National Health Service (UK) and the Cardiac Society of Australia and New Zealand have issued similar local recommendations to achieve these goals and guide the management of patients with cardiac arrhythmias and cardiac implantable devices during the COVID-19 pandemic.[199-201] Below, we review considerations for implantable cardiac device monitoring and follow-up, elective and urgent EP procedures and treatment options of cardiac arrhythmias during the COVID-19 pandemic.

9.9.1. Monitoring and Follow up of Patients with Cardiac Implantable Devices

- Remote interrogation (patient-initiated or automatic prescheduled transmissions) or remote monitoring (i.e. automatic daily or alert-triggered transmissions) should be utilized as much as possible to replace routine device interrogation visits to hospitals, clinics and practices. In-person office visits should be replaced by remote contact by telephone or internet by the treating physician, using the device information obtained through remote interrogation or monitoring:
    - For patients who are **followed-up already through remote interrogation/monitoring**, deferring in-office evaluation is usually possible. This may have psychological implications, as patients may feel that a delay of their regular check-up may prejudice the integrity of their device. Reassurance on these issues therefore is important when they are called to postpone their visit;
    - For patients **not followed-up via remote interrogation/monitoring**, activating it usually requires an in-office visit for registering transmitters, obtaining consent from the patients, and/or activating the feature. This puts the patient at risk for an infection and can be time consuming to the hospital, where resources may already be stretched. However, initiating remote interrogation/monitoring without the patient coming to the office or hospital may be an option for Boston Scientific and Abbott devices (PM and ICD) and for newer Medtronic devices using BlueSync, since remote monitoring is programmed ON as default on these cardiovascular implantable electronic devices (CIEDs). Legacy Medtronic devices can be initiated at home by the patient for remote interrogation, but alert-based monitoring of non-BlueSync Medtronic ICDs requires in-office programming on. Also for Biotronik CIEDs, remote monitoring needs an in-office programming ON of the CIED, unless that has been done at the time of implant as is customary in some countries and centers. When the CIED is ready, for all manufacturers the patient only needs to plug in the transmitter device

at home, which then activates automatically (Biotronik; Abbott), after a single push on a button (Boston Scientific or BlueSync Medtronic), or after a series of actions with a removable wand (legacy Medtronic) that can be guided over the phone. Manufacturers point to the restrictions by privacy regulation (like General Data Protection Regulation) to directly send transmitters to the patients' home and should provide devices to the hospital which has to ship these in a second step;

- Remote interrogation/monitoring may require hospital re-organization which may preclude large scale transitioning from an outpatient setting to a telemetry-based model during hectic COVID-19 times during which hospital operations are already stretched;
- Device patients for whom a scheduled in-office visit needs to be postponed can also be reassured that major alterations of device integrity will be signaled by an auditory alarm. Patients should be instructed to contact their center if they notice an alarm;
- Patients without new symptoms or alarms should be rescheduled for device follow-up after the pandemic;
- Urgent in-hospital or ambulatory device interrogations may be needed for patients with suspected new and severe lead dysfunction; battery depletion especially in PM-dependent patients; malignant arrhythmia detection; appropriate or inappropriate ICD therapy delivery if this cannot be sufficiently managed by remote interrogation/monitoring;
- All patients should be screened for symptoms, or exposure to confirmed COVID-19 infection prior to admission:

    - In patients **without** suspected or confirmed COVID-19 infection:
        - Interrogation should preferably use wireless communication, minimizing direct contact, while maintaining safe distance and using appropriate PPE;
        - Interrogation should be performed in separate designated non-infected areas (see section 5);
    - In patients **with** suspected or confirmed COVID-19 infection:
        - Local hospital protocols for the use of a dedicated single set of programmers with appropriate storage in designated areas, cleaning before and after use, single use wand protection and the use of appropriate PPE (Section 5) are recommended. Interrogation should preferably use wireless communication, obviating direct contact.

9.9.2. Considerations for Electrophysiological and Implantable Device Procedures

The categorization of EP procedures in the context of COVID-19 is depicted in Table 14. In summary, all elective ablation and cardiac device implantation procedures should be postponed, and antiarrhythmic medications should be reviewed and intensified if necessary, to allow control of symptomatic arrhythmia recurrences during the COVID-19 pandemic period.

Urgent EP procedures in patients without suspected or confirmed COVID-19 infection should be performed in a designated non-infected catheterization laboratory area, while limiting direct contact with personnel, and with the appropriate use of PPE (Section 5) during the procedure. In patients with suspected or confirmed COVID-19 infection, the procedure should be performed in a designated catheterization laboratory area, while limiting direct contact with personnel, and with the appropriate use of PPE (Section 5) during the procedure. If intubation is required, this should be performed outside the EP laboratory to avoid contamination.

The hospital stay and all ancillary procedures (ECG, echocardiography) should be reduced to minimum and be performed after clinical reassessment of their necessity.

Table 14 Categorization of electrophysiological procedures in the context of COVID-19

	URGENT PROCEDURES (perform within days)	SEMI-URGENT PROCEDURES (perform within weeks, < 3 months)	NON-URGENT/ELECTIVE PROCEDURES (can be postponed for ≥ 3 months)	PERSONAL PROTECTION LEVEL
CATHETER ABLATION	• VT/VF ablation for electrical storm • AF or A flutter ablation for AF/A flutter causing tachycardiomyopathy or syncope • WPW syndrome with fast preexcited AF and or syncope and/or cardiac arrest	• VT ablation for medically refractory recurrent VT • AF/A flutter ablation for medically refractory AF/A flutter with repeated ER visits • Medically refractory SVT with repeated ER visits	• PVC ablation • PSVT ablation • AF/A flutter ablation • EP testing	Level II/III protection
CARDIAC IMPLANTABLE ELECTRONIC DEVICE (CIED)	• Urgent PM implantion for symptomatic high-degree AV block or sinus node dysfunction with long asystolic pauses • Urgent secondary prevention ICD implantation for cardiac arrest or VT • ICD/PM battery replacement for imminent or actual EOL in PM dependent patients • Lead revision for symptomatic malfunction • Lead extraction for infection	• ICD/PM battery replacement for ERI • Primary prevention ICD in very-high risk of lifethreatening ventricular arrhythmias	• Primary prevention ICD • CRT implantation • CIED upgrade • Lead extraction in patient without infection • Lead revision for asymptomatic malfunction	Level II/III protection
CARDIOVERSION/ OTHER EP PROCEDURES	• Highly symptomatic medically refractory new onset of AF/A flutter	• Symptomatic medically refractory AF/A flutter	• LAA closure • ILR implantation • Tilt table testing • Ambulatory rhythm monitoring	Level II/III protection

9.9.3. Management of Cardiac Arrhythmias in Patients with COVID-19 Infections

The incidence and type of cardiac arrhythmias as a direct consequence of COVID-19 infection is currently unknown. In a single centre retrospective study including 138 patients hospitalized with COVID-19 pulmonary infection in Wuhan, China, cardiac arrhythmias occurred in 23 patients (16.7%) and acute cardiac injury in 10 (7.2%) patients (defined as troponin rise, or new ECG and echocardiographic abnormalities). Cardiac arrhythmias were considered a major complication and occurred more frequently in patients who were transferred to the ICU as opposed to the patients treated on the general ward (16 [44%] of 36 patients vs. 7 [6.9%] of 102 patients, $p < 0.001$, respectively).[10] However, the type and duration of arrhythmias was not specified in this report.

In general, the acute treatment of arrhythmias should not be significantly different from their management in non-COVID-19 patients and should be in line with the current ESC, European Heart Rhythm Association and related guidelines.[202-208]

9.9.3.1. Tachyarrhythmias

9.9.3.1.1. 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 (see Section 10).

- 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 (see Section 10);
- After the COVID-19 pandemic, the indication for catheter ablation should be reassessed.

9.9.3.1.2. Atrial Fibrillation and Flutter

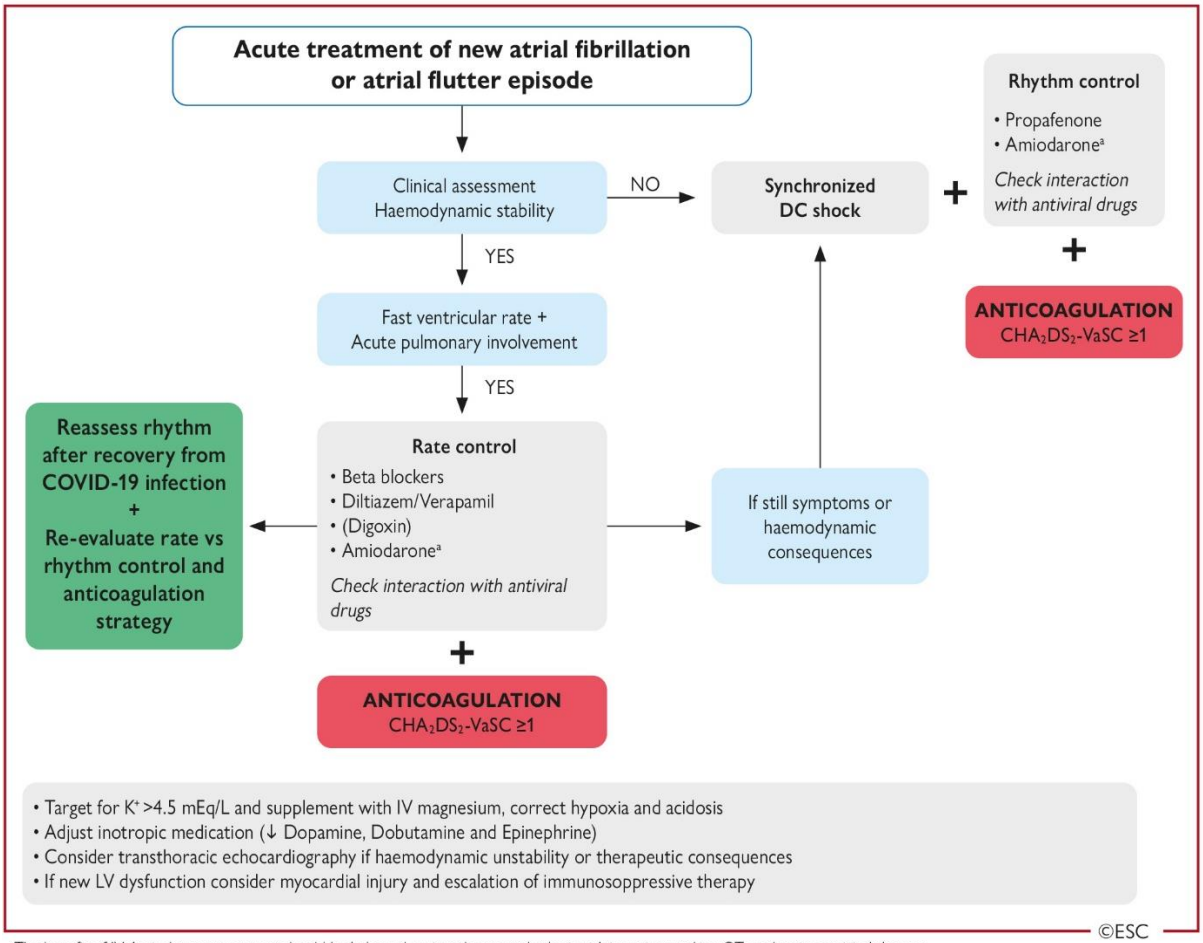
There are no specific reports on the occurrence of AF during COVID-19 infection. It is likely that AF may be triggered by COVID-19 infection (fever, hypoxia, adrenergic tone), either new onset or recurrent. In patients with severe pneumonia, ARDS and sepsis, the incidence of AF during hospitalization 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.[202, 209-211] 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.[202, 209-211] 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.[202]

As in all patients with AF, treatment goals have to consider ventricular rate control, rhythm control and thromboembolic prophylaxis. Specifically in the context of COVID-19 infection, the following considerations should be made (Figure 16):

- In patients with haemodynamic instability due to new-onset AF and atrial flutter, electrical cardioversion should be considered. This however needs to be balanced versus the need for more equipment and personnel at the side of the patients, and the possible need for intubation (with the risk of increased viral aerosol creation);
- In critically ill patients with haemodynamic instability due to new onset AF/atrial flutter, i.v. amiodarone is the choice of antiarrhythmic medication for rhythm control, however its combination with hydroxychloroquine and/or azithromycin should be preferably avoided. If it is used, the benefit of the treatment should be balanced against proarrhythmic risk due to QT prolongation (see section 10, Table 15);

- In patients with severe acute respiratory insufficiency, cardioversion is unlikely to provide sustained benefit without concomitant intensified treatment of the underlying hypoxaemia, inflammation and other reversible triggers such as hypokalaemia and hypomagnesaemia, metabolic acidosis, catecholamine infusion, volume overload, increased sympathetic tone and bacterial superinfection;
- In hospitalized patients under antiviral treatment with new-onset or recurrent AF/atrial flutter but without haemodynamic instability, discontinuation of AADs is preferred (especially sotalol and flecainide, but likely also amiodarone and propafenone) and initiation of rate control therapy with beta-blockers (or CCBs unless contraindicated, with or without digoxin; beware drug interactions) is preferred to allow safe antiviral medication use is a reasonable therapeutic option. Spontaneous cardioversion to sinus rhythm may occur within few hours to days in a proportion of stable COVID-19 patients with recent onset AF and mild to moderate clinical presentation without pronounced inflammation;
- In hospitalized patients with new-onset atrial flutter, rate control may be more challenging than AF. If the patient remains symptomatic or there are haemodynamic consequences, electrical cardioversion may be considered;
- Anticoagulation for the prevention of AF-related stroke or systemic embolism should be guided by the CHA2DS2-VASc score (and not AF clinical type or current rhythm status). Therapeutic anticoagulation should be considered in male and female patients with CHA2DS2-VASc score ≥ 1and ≥ 2, respectively, and is indicated in male and female patients with CHA2DS2-VASc score ≥ 2and ≥ 3, respectively;
- The need for an echocardiogram should be balanced against the need for close contact between HCP and patient, and contamination of equipment. Only when considered mandatory for immediate therapeutic management in the critically ill patient, it can be used to asses LV function and pericardial and myocardial involvement. TTE is in general preferred to TEE to avoid aerosol generation. If possible, TTE should be deferred until after convalescence;
- Similarly, TEE should be obviated by early start of anticoagulation in new-onset AF, or continuation in newly admitted COVID-19 patients with antecedent AF;
- Drug-drug interactions including antiviral, antiarrhythmic and anticoagulation drugs should be considered before administration.(see section 10, Table 15 and Table 16).
- After recovery from the COVID-19 infection, 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.

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.

9.9.3.1.3. 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.[212]

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

- In unresponsive patients without breathing, the local Basic and Advanced Life Support protocol should be followed. During basic life support, ventilation is not performed, only cardiac compressions, to avoid the risk of ingestion of aerosols. For Advanced Life Support, only HCP with full PPE are eligible to perform intubation;
- In patients with VF, asynchronous defibrillation, and in patients with haemodynamically unstable VT, synchronized electrical cardioversion should be performed;
- In patients with sustained monomorphic VT:

    - Electrical cardioversion should be considered in patients taking QT prolonging combination antiviral drugs, especially in case the patient is already ventilated;
    - Intravenous procainamide (if available) or lidocaine, could be considered in patients taking QT prolonging combination antiviral drugs and if the haemodynamic status permits;
    - Intravenous amiodarone could be considered in patients with known structural heart disease and impaired LV function; however, its action is slow for conversion of VT, and combination with hydroxychloroquine and azithromycin should be preferably avoided due to QTc effects. The benefit of treatment should be balanced against the increased proarrhythmic risk due to QT prolongation (see section 10, Table 15).

- In critically ill patients with COVID-19 infection and recurrent sustained VT and recurrent VF ('VT storm'), i.v. amiodarone is the antiarrhythmic medication of choice. However, its combination with hydroxychloroquine and/or azithromycin should be preferably avoided and the benefit of treatment should be balanced against the increased proarrhythmic risk due to QT prolongation (see section 10, Table 15)
- Intravenous lidocaine may be considered as a safer but less effective alternative to amiodarone, especially if underlying myocardial ischaemia is suspected:

    - Addition of sympathetic blockade (e.g. esmolol) should be considered;
    - Intubation (with all the risk of viral spreading associated), sedation and ventilation may be considered to abort VT storm;
    - Temporary PM implantation for overdrive termination may be considered, balancing the possible therapeutic benefit against the invasiveness of the lead placement with risk for personnel. In the absence of a functional cardiac catheterization laboratory, floatation guided temporary wire insertion may be considered in case of emergency;

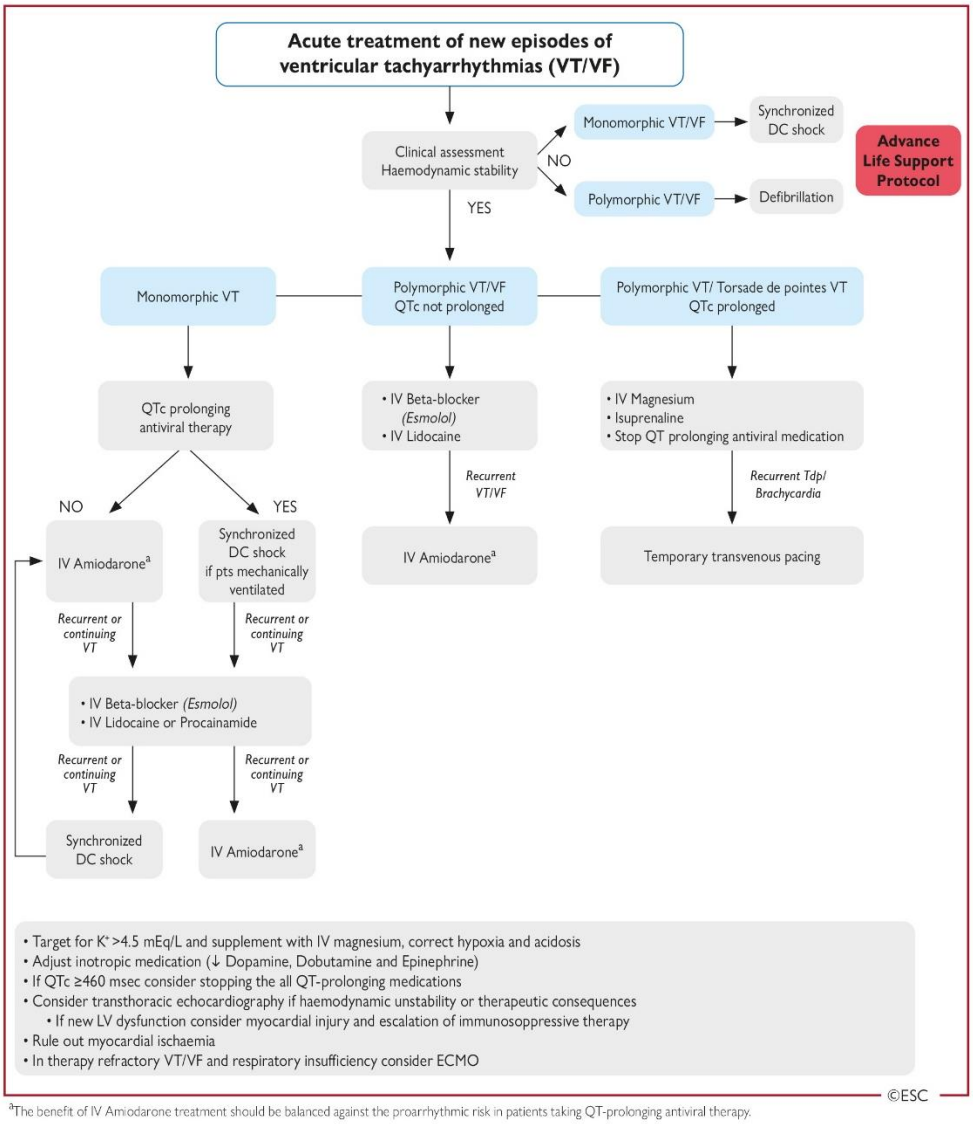
- In patients with severe acute respiratory insufficiency, correction of underlying reversible triggers should be considered as hypoxia, hypovolaemia, electrolyte abnormalities as hypokalaemia and hypomagnesaemia, metabolic acidosis, catecholamine infusions, volume overload, increased sympathetic tone, tamponade, pneumothorax, ischaemia, bacterial superinfection and proarrhythmic drugs;
- Special attention should be paid to the prevention of TdP VT in the setting of COVID-19 infection;

    - TdP is a polymorphic VT associated with QT prolongation and triggered by QT prolonging antiviral drugs (hydroxychloroquine and azithromycin), especially in combination with AADs (especially sotalol), electrolyte disturbances ((in particular K+ and Mg2+), kidney dysfunction, and/or bradycardia, especially in females and in patients with LV hypertrophy or diminished LV function;
    - Therapy of TdP VT consists of:

- Withdrawal of all QT prolonging drugs;
- Normalizing potassium level (target > 4.5 mEq/L);
- Intravenous magnesium supplementation;
- Increasing heart rate, by withdrawing bradycardic agents, and if needed by i.v. isoproterenol or temporary pacing (balancing benefit against the invasiveness of the lead placement with risk for personnel). Isoproterenol is contraindicated in the setting of congenital long QT syndrome (LQTS);

- Polymorphic VT without QT prolongation is not TdP but usually signals ischaemia or acute myocardial injury;
- Echocardiography should be considered in all patients with new malignant ventricular arrhythmias not related to QT prolongation, to assess ventricular function and myocardial involvement;
- After recovery from the COVID-19 infection the need for secondary prophylactic ICD, catheter ablation, or wearable defibrillator (in case of suspected transient cardiomyopathy due to myocarditis) needs to be evaluated.

Figure 17 Ventricular tachyarrhythmias



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

9.9.3.1.4. Channelopathies

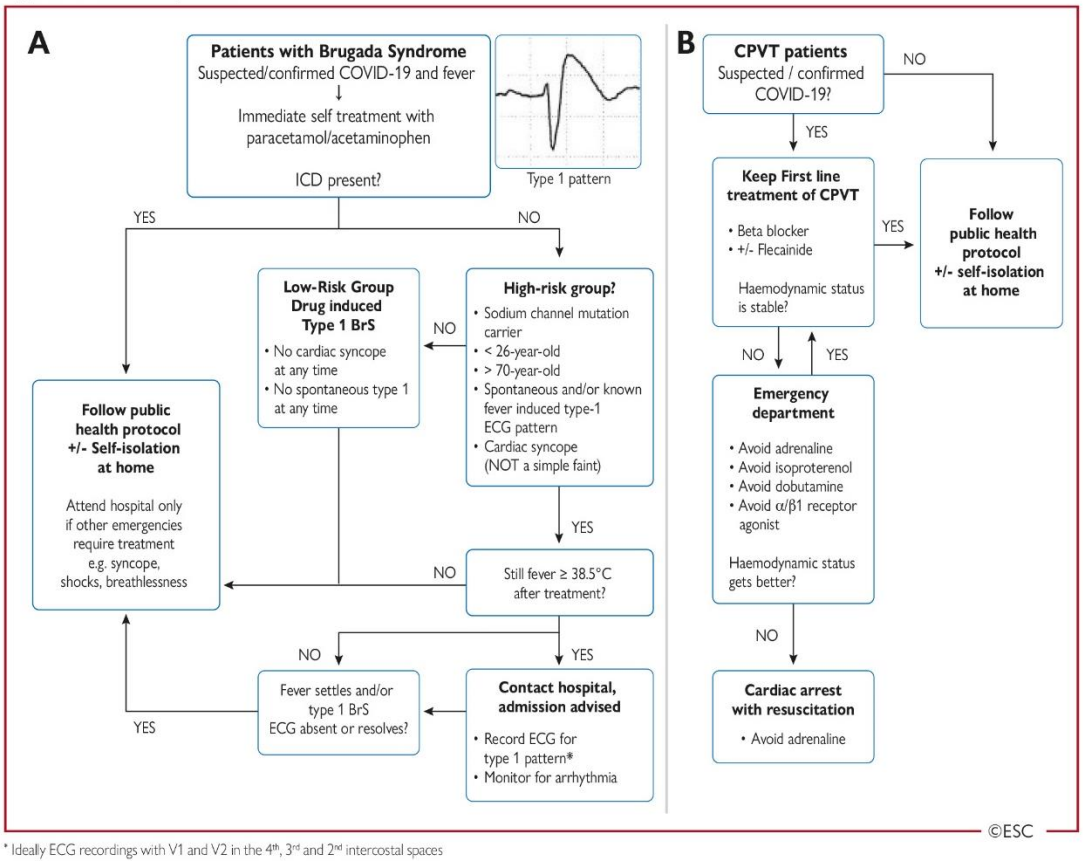
There are no specific reports on the occurrence of COVID-19 infection in patients with channelopathies. However, COVID-19 infection may occur in patients with known congenital LQTS, Brugada syndrome (BS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and short QT syndrome, with a risk of pro-arrhythmia. The specific interactions of these channelopathies and COVID-19 has been reviewed in a recent review.[213]

Special considerations in congenital LQTS with COVID-19 infection is the combination of antiviral drugs (hydroxychloroquine and azithromycin) and stress factors (electrolyte disturbances and kidney dysfunction) that may further prolong QTc. The QTc should be monitored as closely as safe and practicable. All unnecessary QT prolonging drugs should be stopped, and if QTc > 500 ms or if QTc increases by ≥ 60 ms from baseline, then the safety of QT prolonging antiviral drugs should be reviewed and serum potassium levels should be kept at > 4.5 mEq/L. (Section 10, Figure 19);

In BS with COVID-19 infection, the main concern is fever-triggered malignant ventricular arrhythmia. Therefore, in all COVID-19 patients with BS, fever should be aggressively treated with paracetamol. As shown in a recently published case-report, COVID-19-induced fever may lead to symptomatic BS.[214] ECG monitoring should be considered if antipyretic therapy is ineffective and the temperature remains > 38.5ºC in higher risk BS patients (Figure 18, Panel A).

In patients with CPVT and COVID-19 infection, beta-blockers and flecainide should be continued with monitoring of drug interactions with antiviral drugs (see section 10, Table 15) and in critically ill patients, catecholamine infusions should be administered with great caution, requiring permanent monitoring (Figure 18, Panel B).

Figure 18 Channelopathies



* Ideally ECG recordings with V1 and V2 in the 4th, 3rd and 2nd intercostal spaces

9.9.3.2. 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.[215] One experimental study from 1999 has shown that coronavirus-infected rabbits have ECG abnormalities including 2nd degree AV block secondary to myocarditis and HF.[216] 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.[202] Hypoxaemia should be ruled out.

A heart rate/temperature discordance was observed in patients with COVID-19:[10, 102] 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.

10. Treatment of SARS-CoV-2 infection

Key points

- There is a scarcity of evidence regarding the efficacy and risk of different treatment strategies in patients with COVID-19 disease;
- In all patients undergoing antiviral treatment, it is of major importance to correct modifiable predisposing factors to QTc prolongation: electrolyte imbalances, concomitant unnecessary drugs and bradycardia;
- Baseline ECGs may not be needed in all before starting antiviral treatment, especially if recent prior ECGs are available and no clinical indication (like unexplained syncope). This saves HCP time and reduces nosocomial spread;

- On-treatment ECGs are recommended to rule out significant prolongation of QTc (> 500 ms, or by > 60 ms versus baseline);
- Resource allocation will need to be adjusted locally depending on availability and demand. According to the context, it is worth exploring alternative ECG monitoring methods (e.g. monitoring leads, smartphone-enabled mobile ECG, handheld devices);
- In COVID-19 patients with an indication for oral anticoagulant therapy, renal and liver function and drug-drug interactions between oral anticoagulant and COVID-19 therapies should be considered in order to minimize the risk of bleeding or thromboembolic complications;
- In NOAC-eligible patients (i.e. those without mechanical prosthetic heart valves, moderate to severe mitral stenosis or antiphospholipid syndrome), NOACs are preferred over VKAs owing to their better safety and fixed dosing without the need for laboratory monitoring of anticoagulant effect (hence no direct contact), notwithstanding the importance of proper NOAC dosing and adherence to treatment;
- Whereas apixaban, rivaroxaban or edoxaban can be given as oral solutions or crushed tablets (via enteral tubes), severely ill COVID-19 patients may be switched to parenteral anticoagulation, which has no clinically relevant drug-drug interactions with COVID-19 therapies (with the exception of azithromycin, which should not be co-administered with UFH).

10.1. 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.[217-220] In specific cases, interferon and, for the ARDS glucocorticoids and/or tocilizumab, may also be administered.[221]

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*.[218-220] **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.[220] 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.[218] 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).[222]

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.[223-226] 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.[227] 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).[227] 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.[228-230] 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.[230] 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.[231, 232] 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.[233, 234] The association of chloroquine and azithromycin showed an acceptable safety profile.

For a detailed overview of all known direct or indirect (through drug-drug interactions) arrhythmological effects of experimental pharmacological therapies in COVID-19 patients, see Table 15.

Table 15 Arrhythmological considerations of novel experimental pharmacological therapies in COVID-19 infection

	HR	AV CONDUCTION	QRS INTERVAL	QTC INTERVAL	TDP RISK	AAD DRUGS INTERACTIONS	COMMENTS
CHLOROQUINE	Mild ↓	Mild ↑ Δ_{PR}= 14.8 ms[235]	Mild ↑ Δ_{QRS}= 9.9 ms[235]	Moderate ↑ Δ_{QTc}= 27- 51 ms [235-237] ↑ Δ_{QTc} in 14.2% of pts [238]	Very-low risk of TdP (72 cases of VF/VT/TdP/LQTS in FAERS registry)	**SEVERE**[a] Amiodarone, Flecainide, Mexiletine, Sotalol, Dofetilide **MODERATE**[b] Disopyramide, Propafenone, Quinidine, Digoxin **MILD**[c] Metoprolol, Nebivolol, Propranolol, Timolol, Verapamil	- Very low risk of cardiotoxicity during chronic therapy is reported[239, 240] - In a study in SLE it was negatively associated with AVB (P = 0.01) as was its longer use (6.1 ± 6.9 vs. 1.0 ± 2.5 years, P = 0.018)[238-241] - Proarrhythmia occurs mostly with overdosage or in chronic therapy (> years)[242] - Proemetic effect is common - Risk of retinopathy, myo/neuropathy during chronic therapy is reported
HYDROXY-CHLOROQUINE	Mild ↓ [239, 240, 243]	Mild ↑	Mild ↑	Moderate ↑ Δ_{QTc}= 25 ms [239, 240]	Very-low risk of TdP (222 cases of VF/VT/TdP/LQTS in FAERS registry)	See Chloroquine	- Very low risk of cardiotoxicity during chronic therapy is reported[239, 240] - Proarrhythmia occurs mostly with overdosage or in chronic therapy (> years)[242] - Less cardiotoxicity reported than with Chloroquine[242] - In a study of pregnant women with Ro/La antibodies, AVBs were more frequent in those not using hydroxychloroquine[244]
AZITHROMYCINE	Mild ↓ [245]	Mild ↑ [245]	Mild ↑ [245]	Moderate-Severe ↑ Δ_{QTc}= 5-32 ms [245-247]	Low risk of TdP Cumulative incidence SCD = 64.6/1 million[248] ROR for Tdp = 4.76 compared to other medication (2.81-7.98)[232] RR for SCD or VT= 3.40 compared to no macrolide use [248-250]	**SEVERE**[a] Amiodarone, Dysopiramide, Dofetilide, Flecainide, Propafenone, Sotalol **MODERATE**[b] Beta-blockers, Digoxin	In a study during treatment days 1 to 5, patients receiving azithromycin had significantly increased risk of serious arrhythmia (HR = 1.77; 95% CI, 1.20-2.62) compared with patients receiving amoxicillin[251, 252]
LOPINAVIR/ RITONAVIR	NR	Moderate↑ Δ_{PR}= 33.5 ms[235]	Mild ↑ Δ_{QRS}= 7 ms[253]	Moderate ↑ Δ_{QTc}= 20 ms[235]	Low risk of TdP (27 cases of VF/VT/TdP/LQTS in FAERS registry) HR for Tdp 1.02 (0.26-3.24)[246]	**SEVERE**[a] Amiodarone, Dronedarone, Disopyramide, Dofetilide, Flecainide, Sotalol **MODERATE**[b] Lidocaine, Mexiletine, Propafenone, Quinidine, Digoxin, All Beta-blockers, Ca^{2+} blockers	Cases of AV block are reported
TOCILIZUMAB	No ECG changes described[254]				Unknown	**MILD**[c] Amiodarone, Quinidine	
FINGOLIMOD SIPONIMOD	Moderate-Severe ↓ Δ_{HR}= -23 bpm[255]	Mild-moderate ↑	Unknown	Mild ↑	Unknown	**MODERATE**[b] Beta-blockers, Ca2+ blockers, Ivabradine, Amiodarone, Flecainide, Propafenone	Reported risk of rare, transient and benign bradycardia and AV conduction abnormalities[256]; - In a study of 3591 patients, 31 patients (0.8%) developed bradycardia (<45 bpm), 62 patients (1.6%) had second-degree Mobitz I and/or 2:1 AV blocks[257] - In study of 5573 patients new-onset first-degree AVB was experienced by 132 (2.4%) in-home and 74 (0.5%) in-clinic patients, and Wenckebach (Mobitz type I) second-degree AVB by four (0.07%) and nine (0.1%) patients, with no cases of third-degree AVB[258] - In study of 66 patients with MS fingolimod lead to an increase of vagal activation which persisted even after 14 months of treatment[255]
REMDESIVIR	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Very limited preclinical data showed safety[259]
INTERFERON ALFACON-1	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Limited data: cases of hypotension, arrhythmia, and cardiomyopathy reported
RIBAVIRIN	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	No cardiac side effect
METILPRED-NISOLONE	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	- May cause electrolyte disturbance - High dose intravenous prednisolone might cause acute sinus bradycardia[260] or in MS patients sinus tachycardia, bradycardia and rarely AF and VT[261]

AAD drugs-interactions:
[a]these drugs should not be co-administered.
[b]Potential interaction (need dose adjustments/close monitoring).
[c]Weak intensity interaction (need dose adjustments/close monitoring unlikely to be required).

AAD = antiarrhythmic drugs; AF = Atrial fibrillation AV = atrio-ventricular; AVB = AV block; CI = Confidence interval; FAERS = FDA Adverse Event Reporting System; HR = Heart rate; HR = Hazard ratio; LQTS = Long QT Syndrome; MS = Multiple Sclerosis; NR= Not reported; OR = Odd Ratio; ROR = Reporting Odd Ratio; RR = risk rate; SCD = Sudden cardiac death; SLE= Systemic Lupus Erythematosus; TdP = Torsade de Pointes; VF = Ventricular fibrillation; VT = Ventricular tachycardia.

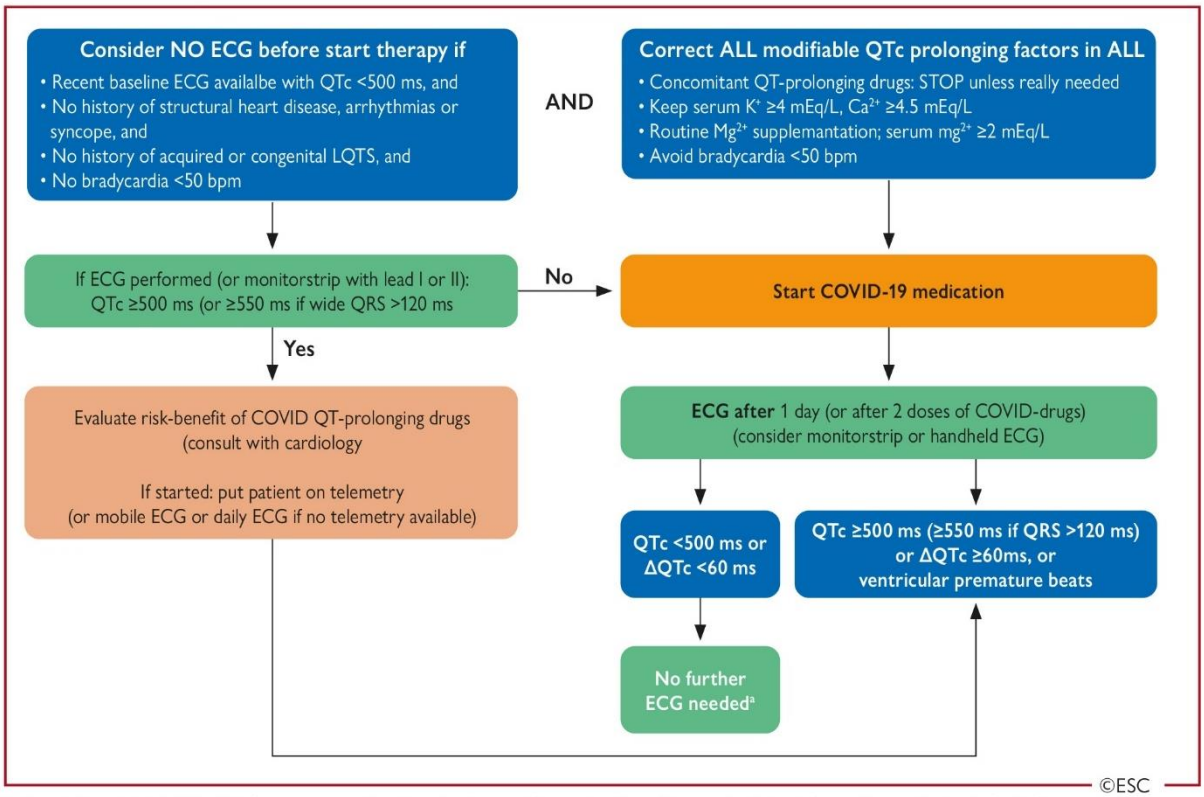
10.1.1. QTc Evaluation to Prevent Drug-Induced Pro-Arrhythmia

QTc prolongation by some drugs can theoretically lead to polymorphic VT (TdP). This is however a very rare complication, and the consideration has to be balanced versus the anticipated benefit of therapy for the COVID-19 patient. Figure 19 provides a practical flow chart for the management of patients to prevent TdP, for guidance on the timing and repetition of ECG recording, and on QTc measurements that would alter therapy. Other guidance flowcharts have been published.[213, 262] Briefly, the following steps are required to reduce the risk of drug induced TdP:

1. Identify risk factors associated with QTc prolongation;
    - Non-modifiable risk factors: congenital LQTS, known QT prolongation on QT prolonging drugs, female sex, age > 65 years, structural heart disease (ACS, uncompensated HF, hypertrophic cardiomyopathy), renal impairment, liver impairment;
    - Modifiable risk factors: hypocalcaemia, hypokalaemia, hypomagnesaemia, concomitant use of QTc-prolonging medications and bradycardia;
2. Identify and correct modifiable risk factors in all patients. Serum potassium should be kept at the high end (≥ 4.5 mEq/L);[263]
3. Perform a baseline ECG (12-lead or single strip depending on resource availability). Patients with a baseline QTc ≥ 500 ms are at risk of developing TdP or sudden death. The risk-benefit of treatment in this group should be carefully assessed. In some patients with a recent ECG showing normal QTc and no evidence of major CV alterations due to COVID-19, one may consider **not** to take a baseline ECG since every ECG exposes HCP and may contaminate equipment;
4. Perform an ECG once on treatment. If the patient has a QTc ≥ 500 ms or shows a ΔQTc ≥ 60 ms, consideration should be given to either switching to a drug with a lower risk of QTc prolongation, reducing the dose administered, or continuing the treatment plan. Close surveillance of the QTc (preferably including telemetry for arrhythmia monitoring) and electrolyte balance are mandatory.

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

Figure 19 QTc management



[a]As long as the patient is clinically stable (e.g. no pronounced vomiting, diarrhoea, signs/symptoms of heart failure or deterioration of respiratory or other organ function).

10.1.2. Technical Aspects of QT Measurements

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

A standard 12-lead ECG may not always be easy to obtain, given the enormous burden of increasing numbers of COVID-19 patients on healthcare providers. Enhanced use of modern handheld ECG devices should be considered in order to reduce traditional ECG recording as much as possible to preserve resources and limit virus spread. In a recent study, the QTc in lead-I and lead-II derived from a standard 12-lead ECG was compared with a rhythm strip from a handheld ECG device in 99 healthy volunteers and 20 hospitalized patients in sinus rhythm treated with dofetilide or sotalol.[264] QT on the handheld device had an excellent agreement with standard 12-lead ECG both in the normal range and in patients with QT prolongation.[264] This handheld ECG device (KardiaMobile 6L Alivecor) had a high specificity for detecting a QTc > 450 ms and should thus be considered as an effective outpatient tool for monitoring patients with prolonged QTc. Recently, KardiaMobile6L received expedited approval from the FDA for QT monitoring and can thus be used in COVID-19 patients treated with QT prolonging drugs such as chloroquine or hydroxychloroquine.

10.2. 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.[265] 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.

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

- Administration in a crushed form (e.g. via a nasogastric tube) does not alter the bioavailability of apixaban, edoxaban and rivaroxaban;[266-268]
- Apixaban can be given as oral solution or via nasogastric or gastric tube on an empty stomach (food impairs bioavailability of the crushed tablets);[269]
- Rivaroxaban tablet can either be crushed and mixed in water or apple puree and taken orally, or suspended in water and given via nasogastric tube (enteral tubes must not be distal to the stomach) followed by food;[267]
- Dabigatran capsules must not be opened, as it would result in a 75% increase in the drug bioavailability.[269]

Table 16 Interactions of anticoagulant drugs with COVID-19 therapies

	NOACs					VKAs			LMWH, UFH			
Anticoagulants / COVID-19 therapies	DABIGATRAN ETEXILATE	APIXABAN	EDOXABAN	RIVAROXABAN	Comments	WARFARIN	ACENOCOUMAROL	PHENPROCOUMON	ENOXAPARIN	FONDAPARINUX	DALTEPARIN	HEPARIN
CHLOROQUINE[20, 270, 271]	↑	↑	↑	↑	Any NOAC may be used (with caution)							
HYDROXYCHLOROQUINE[20, 270, 271]	↑	↑	↑	↑								
AZITHROMYCINE[20, 70, 272]	↑		↑	↑	If CrCl <30 mL/min dabigatran should be avoided. If renal function is impaired CrCl <50 mL/min) rivaroxaban should be used with caution.	↑						↑*
ATAZANAVIR[270, 271, 273]	↑[d] ↑[c]	↑[d] ↑[c]	↑[a]	↑[d] ↑[c]	Reduced dose edoxaban (30 mg OD) may be used with caution	↑		↑				
LOPINAVIR/RITONAVIR[20, 270, 271, 273]	↔ or ↓	↑[b]	↑[a]	↑	Dabigatran may be used with caution (should be avoided if CrCl <30 mL/min)	↓	↓	↓↑				
RIBAVIRIN[20, 270, 271, 273]					Any NOAC may be used (with caution)	↓						
REMDESIVIR[20, 270, 271]												
FAVIPIRAVIR[270]												
BEVACIZUMAB[270]												
ECULIZUMAB[270]												
TOCILIZUMAB[20, 270, 271]		↓		↓		↓	↓	↓				
FINGOLIMOD[20, 270]												
INTERFERON[20, 270]												
PIRFENIDONE[20, 270]												
METHYLPREDNISOLONE[20, 270]						↓						↓
NITAZOXANIDE[270, 271]						↑	↑	↑				

CrCl = Creatinine clearance; LMWH = Low molecular weight heparin; NOAC = Non-vitamin K antagonist oral anticoagulant; OD = Once daily; UHF = Unfractionated heparin; VKA = Vitamin K antagonist.

Grey light colour: No information found. ***Green colour:*** No clinically significant interaction is expected, or potential interaction is likely to be of weak intensity, not requiring additional action/monitoring or dose adjustment. ***Yellow colour:*** Potential interaction which may require additional monitoring (e.g., more frequent INR monitoring if on VKAs). ***Orange colour:*** Potential interaction which may require a dose adjustment. ***Red colour:*** The drugs should not be co-administered.

↑ Potential increased exposure to the anticoagulant drug. ↓ Potential decreased exposure to the anticoagulant drug. ↔ No significant effect on the exposure to the drug.

[a]The EMA product label for edoxaban advises the consideration of dose reduction from 60 mg once daily to 30 mg once daily with concomitant use of strong P-glycoprotein inhibitors.
[b]The US product label for apixaban proposes the use of apixaban at reduced dose (2.5 mg twice daily) if needed.
[c]No data on the safety/efficacy of use of NOACs when co-administered with atanazavir are known; if their use is deemed indicated, one should consider monitoring plasma level of the NOACs in this unknown condition, in line with the recommendation that was made in the last EHRA Practical Guide.[265]
[d]There is an overall agreement that the use of NOACs is not recommended when atanazavir is given in combination with its enhancers ritonavir or cobicistat.
*Azithromycin increases the effect of heparin by decreasing its metabolism.[270]

11. Patient Information

There are many pending questions about the COVID-19 pandemic.[274] 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.

Key points

- Patient information is of paramount importance during the COVID-19 pandemic when the allocation of medical resources is a matter of debate;[275]
- 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.

11.1. 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.

11.2. 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. These treatments are initiated during hospital admission and potential drug-drug interactions are summarized in Table 17 and Table 18.

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

Table 18 Potential interactions of drugs used to cure COVID-19[a]

Drugs used to cure COVID-19	Interactions	Action
Chloroquine and hydroxychlorokine	Betablokers QT prolonging drugs	Monitor ECG
Methylprednisolone	Warfarin	Monitor INR
Antiretroviral drugs	Warfarin	Monitor INR
	Statins	Start with low dose of rosuvastatin or atorvastatine
	NOACS	Avoid apixaban and rivaroxaban
	Antiarrythmics	Use QT prolonging or low dose digoxin with caution

[a]These medications will be administered during hospital admission. For full list of potential drug-drug interactions we refer to tables 15 (Section 10.1) and 16 (Section 10.2).

11.3. 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).[276] 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

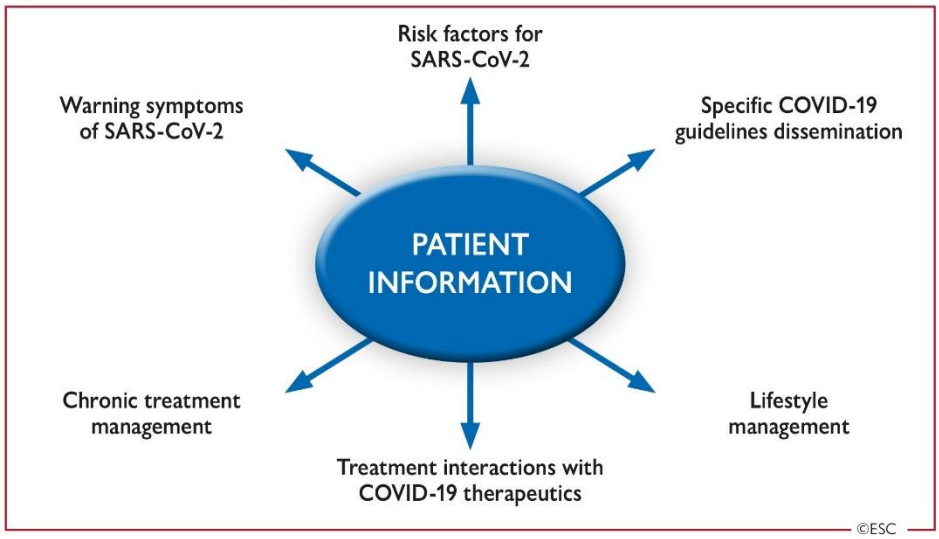
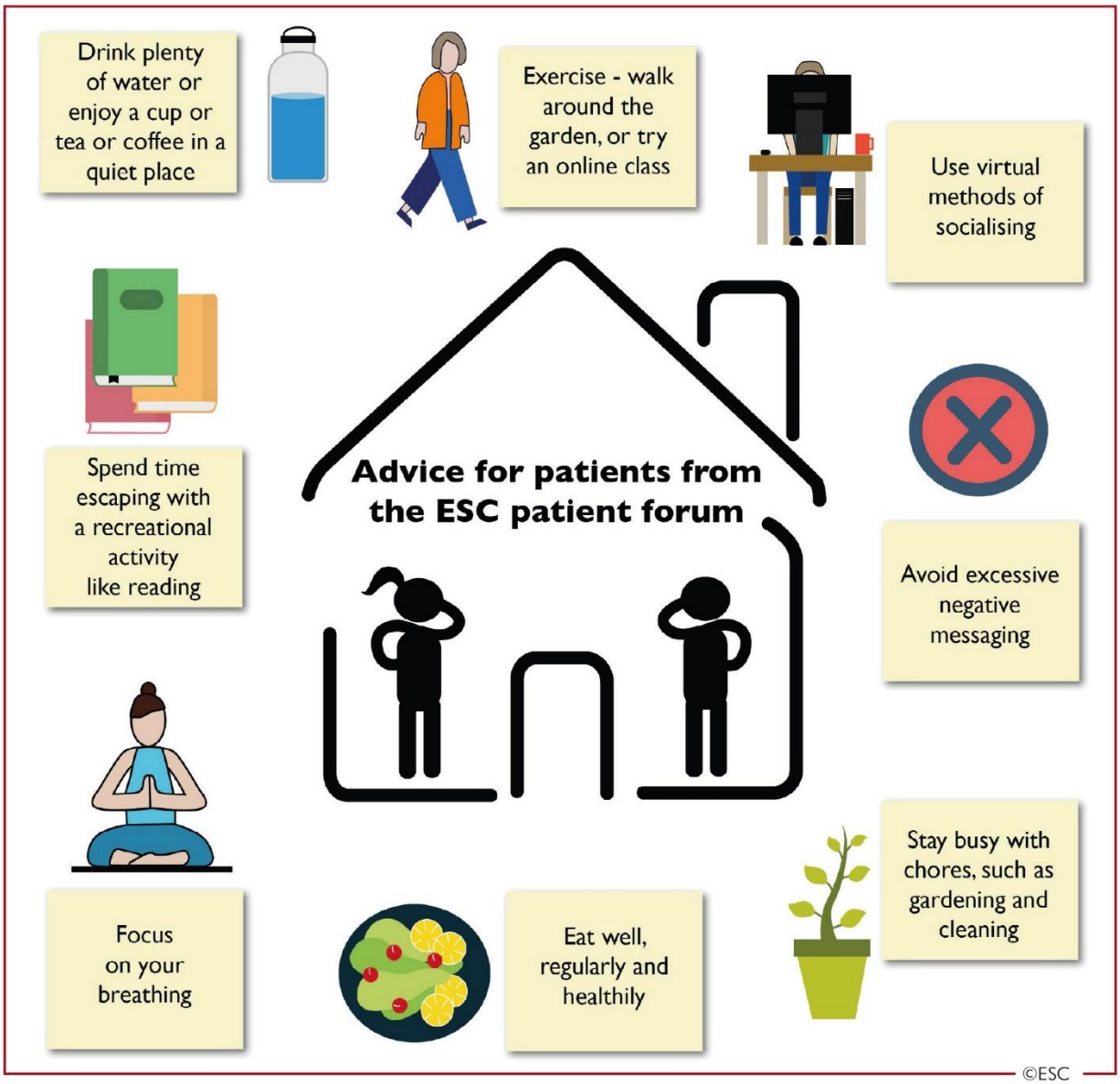


Figure 21 Patient information during the COVID-19 pandemic - Part 2



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