

# Guidance for Health Care Providers on Management of Cardiovascular complications in patients suspected or confirmed with COVID 19 virus infection

Thomas Alexander, Viji Samuel Thomson, Amit Malviya, Bishav Mohan, GS Wander, Harikrishnan S, Sandeep Seth, Srinivas Reddy, S Arulraj, Siddharth Shah, Shashank Joshi, Mangesh Tiwaskar, Milind Nadkar, Kamlesh Tewary

**As cardiovascular health professionals, this guidance document has been brought out to help fellow physicians manage patients during the COVID-19 pandemic.**

## INTRODUCTION

The current coronavirus disease (COVID-19), a rapidly evolving pandemic, is a relatively unique infection unlike the earlier severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS) epidemics demonstrating a much greater infectivity though a lower case-fatality rate. The clinical manifestations are continuously being evaluated and management strategies rapidly evolving, including specific antiviral medications. This document summarises the current understanding of the cardiovascular complications of this infection and discusses the current pathophysiological mechanisms and management. However, it must be emphasised that a full understanding of the disease process is yet incomplete and as more information becomes available, this document will be updated to reflect new knowledge.

This document highlights the management of cardiovascular complications. However, detailed protocols for the diagnosis, triage, isolation, and management of COVID-19 patients with cardiovascular complications and/or cardiovascular patients with COVID-19 should be developed together with other medical specialties involved in management of these patients – intensivists, pulmonologists etc.

**Scope of the Problem:** The clinical manifestations of COVID-19 are dominated by respiratory symptoms followed by gastrointestinal symptoms; however, a significant percentage of patients have severe cardiovascular complications that can impact the course of the illness. In addition, some patients with underlying cardiovascular diseases (CVDs) show an increased mortality. Early case reports from the Chinese Centres for Disease Control indicate that patients with underlying comorbid conditions have an increased risk for contracting COVID-19 and have a worse prognosis. This is significantly worsened with increasing age. Depending on the report, between 25% and 50% of COVID-19 patients have pre-existing co-morbid conditions. Case fatality rates have varied significantly between countries and for different age groups. Estimates vary between 0.25% and 3%. Patients with co-morbidities have higher mortality than the average population.

- Cancer: 5.6%
- Diabetes: 7.3%
- Hypertension: 6.0%
- Cardiovascular disease: 10.5%
- Chronic respiratory disease: 6.3%

**Cardiac Manifestations of the Covid 19 Infection:** Myocardial injury associated with the SARS-CoV-2 occurred in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, which mainly manifested as an increase in high-sensitivity cardiac troponin I (hs-cTnI) levels. The levels of biomarkers of myocardial injury were significantly higher in patients admitted to the ICU. Furthermore, more than 50% of patients who died demonstrated abnormally elevated Troponin levels.

About 90% of inpatients with pneumonia demonstrated elevated D-dimer concentrations indicative of heightened coagulopathy and manifested increased mortality.

Mechanisms of these effects include systemic pro-inflammatory cytokine responses that directly contributes to plaque rupture through local inflammation, induction of procoagulant factors and haemodynamic changes which predispose to ischaemia and thrombosis. In addition, among the confirmed cases of SARS-CoV-2 infection reported by the National Health Commission of China (NHC), some patients present with cardiovascular symptoms.

ACE2 is involved in heart function and has been identified as a functional receptor for corona viruses, including SARS-CoV and SARS-CoV-2. SARS-CoV-2 invades alveolar epithelial cells, resulting in respiratory symptoms which are more severe in patients with coexisting cardiovascular diseases. This could be associated with increased secretion of ACE2 in these patients compared with healthy individuals. This has also led to concerns regarding the role of ACE-I and ARB's.

## GENERAL MANAGEMENT AND SPECIFIC SUBSETS:

Guideline-directed, medications given to cardiovascular disease (CVD) patients during a widespread outbreak is critical and these include statins, beta blockers, ACE inhibitors and anti-platelet agents

Early identification and isolation of cardiovascular patients with COVID-19 symptoms from other patients is critically important. It is prudent to advise all cardiovascular patients of the potentially increased risk and to encourage additional, reasonable precautions in terms of isolation and social distancing. Acute viral infections have multiple short-term effects on the cardiovascular system:

- Increased risk of Acute coronary syndrome
- Myocarditis or worsening of previously stable LV dysfunction leading to heart failure
- Arrhythmias related to acute inflammation, ACS or LVF
- Shock

It is important to triage COVID-19 patients with underlying cardiovascular, diabetic, renal, respiratory or other comorbid conditions for prioritised treatment. In addition, careful thought should be given to manage specific subsets

1. Myocarditis: It is important to note that recent reports suggest that acute cardiac injury is present in about 7% of patients with COVID-19 and may represent either type 2 MI or myocarditis. Importantly, myocarditis can be caused by direct infiltration of the virus but can also be secondary to severe hypoxia and the "cytokine storm" mounted in response to the systemic infection. Some of these manifestations might be, in part, attributable to metabolic disarray, hypoxia, neurohormonal or inflammatory stress.

Diagnosis of Myocarditis among COVID-19 patients is made by:

- Elevated troponin-I or T (Trop I/Trop T)
- N-terminal brain natriuretic peptide (NTBNP) or BNP
- Sinus tachycardia and no ST segment elevation on electrocardiogram. Extensive QRS/ST-T wave changes predict poor prognosis
- Malignant tachyarrhythmias - ventricular tachycardia or fibrillation and AV blocks indicate extensive myocardial involvement and indicate prognosis
- Enlarged left ventricle with low left ventricular ejection fraction (LVEF) and global LV dysfunction on Echocardiography.

Management of myocarditis includes standard heart failure medications, ventilatory support and ECMO. Isolated case studies with prednisolone has shown benefit but is not recommended.

2. Acute Coronary Syndrome: Efforts should be made to try to differentiate between these Type 1 MIs vs. Type 2 acute coronary syndromes, with deferral of invasive management in the former, especially if the patient is hemodynamically stable. The classic symptoms and presentation of AMI may be overshadowed in the context of coronavirus infection, resulting in under or overdiagnosis.

Diagnosis of ACS should not be based only on elevated troponin levels since these can be significantly elevated in these patients even without ACS. A diagnosis should be based on

- History
- Serial Troponin levels
- ECG
- Echocardiogram – to correlate with segmental wall motion abnormality
- Combined CT Coronary Angiogram (If feasible) at the time of routine CT scan being done for patient management.

Reperfusion therapy in ACS should take into consideration the clinical presentation, staff availability, risk involved for medical personnel and the availability of high dependency beds in a hospital. Patients with coronary artery disease and may be at particular risk as a result of coronary plaque rupture secondary to virally induced systemic inflammation, and

- Standard pharmacological therapy (aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors) should be continued or optimised in all these patients.
- Pro-coagulant effects of systemic inflammation may increase the likelihood of stent thrombosis and potent anti-platelet therapy may be advisable

Current recommendations for ACS management would include – For confirmed COVID 19 infections

- STEMI: Low risk STEMI patients, consider thrombolysis as the treatment of choice. Cardiac catheterisation should be considered only for rescue PCI.
- STEMI: High risk STEMI patients. The risks to the treating personnel should be considered before deciding on primary PCI. If PPE is available and the hospital call lab personnel are well versed in its use, then consider primary PCI. In all other situations, thrombolysis should be the treatment of choice
- NSTEMI/Unstable Angina: Conservative management

For patients with suspected COVID-19 infection presenting with ACS, the current recommendation is

- STEMI: Thrombolysis should be the reperfusion strategy of choice, like that in patients with confirmed COVID 19 cases (Preferably Tenecteplase or Reteplase)
- NSTEMI/Unstable Angina: Conservative management until the confirmatory test results are available.

Patients with COVID-19 can have significant thrombocytopenia. This should be considered when deciding the revascularisation strategy (Lippi et al. DOI: 10.1016/j.cca.2020.03.022)

3. Shock: The dominant clinical presentation of COVID-19 is acute respiratory illness, which may lead to ARDS and is manifested as hypoxemia and ground-glass opacities on CT scan. However, similar features may be seen in patients with cardiogenic pulmonary edema due to myocarditis, ACS or worsening of previous LV dysfunction. Therefore, it is important consider cardiogenic or mixed etiology as the cause of respiratory manifestations in COVID-19.

Preliminary studies suggest that older age, comorbidities (especially diabetes and cardiovascular disease including hypertension), lower lymphocyte count, higher D-dimer level, and possibly cardiac injury are risk factors to consider for cardiogenic origin.

In many clinical situations, Echocardiography and serum brain natriuretic peptide (BNP) can help clarify the diagnosis and help differentiate ARDS and cardiogenic shock.

Management strategies

- Assess volume status
- Fluid resuscitation – restrictive rather than liberal and utilise crystalloids over colloids
- For adults with COVID-19 and shock, use Norepinephrine as the first-line vasoactive agent, followed by vasopressin or epinephrine.
- Titrate fluid/vasopressors to maintain MAP of 60-65mmHg
- Addition of Dobutamine should be considered in the presence of LV dysfunction and a MAP above 70mmHg.
- In refractory shock, steroids and ECMO may be considered.

Note: In patients with Corona virus infection there is marked lymphopenia and patient who succumbed to infection had very low lymphocyte counts. ECMO can result in reduction in some subsets of lymphocyte population. Hence lymphocyte counts should be closely monitored. In a small series of patients on ECMO the mortality reported was 83%. (Lancet Respir Med 2020; https://doi.org/10.1016/S22132600(20)301193)

4. Thromboembolic disease: There have been case reports of abnormal coagulation parameters in hospitalized patients with severe COVID-19 disease. In a multicentre retrospective cohort study from China, elevated D-dimer levels were strongly associated with in-hospital mortality.

Endothelial dysfunction with concomitant vascular inflammation may contribute to the hypercoagulable state in such patients. In the setting of critically ill COVID-19 patients who demonstrate clinical deterioration as evidenced by hypoxia or hemodynamic instability, thromboembolic disease should be considered as an additional possibility and investigated with evaluation of D-dimer levels or venous doppler studies.

Case reports of COVID-19 infected patients show increased venous thromboembolism (VTE). Furthermore, in patients with severe infection, clots have been noted in the small vessels of all organs including lung, heart, liver and kidney. This could contribute to worsening of the clinical condition.

The optimal thromboprophylaxis regimen for patients hospitalized with COVID-19 related illness is not known and there is no data on the use of NOAC's.

Current management strategies could include

- Unfractionated or LMW heparin
- Patients with recent stenting may benefit from intensification of the DAPT (substitute clopidogrel with Prasugrel/Ticagrelor)
- 5. Heart Failure: It is important to closely monitor patients for heart failure. This could result from myocarditis as well as HF exacerbation. New-onset atrial fibrillation as a cause for heart failure has also been reported.

The important management strategies include

- Guideline-directed medical therapy should be optimized in CVD patients. This includes the continuation of ACEI and ARB
- Optimise volume status with less aggressive fluid resuscitation for hypotension
- Atrial fibrillation to be managed medically or if hemodynamically unstable, cardioverted. For both AF and VT/VF, amiodarone can be used as per existing guidelines.
- 6. Systemic Hypertension: Following reports that systemic hypertension may be associated with increased risk of mortality in hospitalized COVID-19 infected subjects, there has been concern expressed regarding the potential adverse effects of angiotensin converting enzyme inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARBs). The concern arises from the observation that, like the coronavirus causing SARS, the COVID-19 virus binds to a specific enzyme called ACE2 to infect cells, and ACE2 levels are increased following treatment with ACE-I and ARBs. This has resulted in some patients or their doctors inappropriately stopping these medications prescribed for hypertension or heart failure.

The safety concerns of ACE-I or ARB treatment in relation to COVID-19 does not have a sound scientific basis as of now. On the contrary, animal studies suggest that these medications might be protective against serious lung complications in patients with COVID-19 infection. Based on current data and in view of the overwhelming evidence of mortality reduction in cardiovascular diseases, ACE-I and ARB therapy should be initiated or maintained in patients irrespective of SARS-CoV2. Withdrawal of RAAS inhibition or a switch to alternate drugs at this point is not recommended.

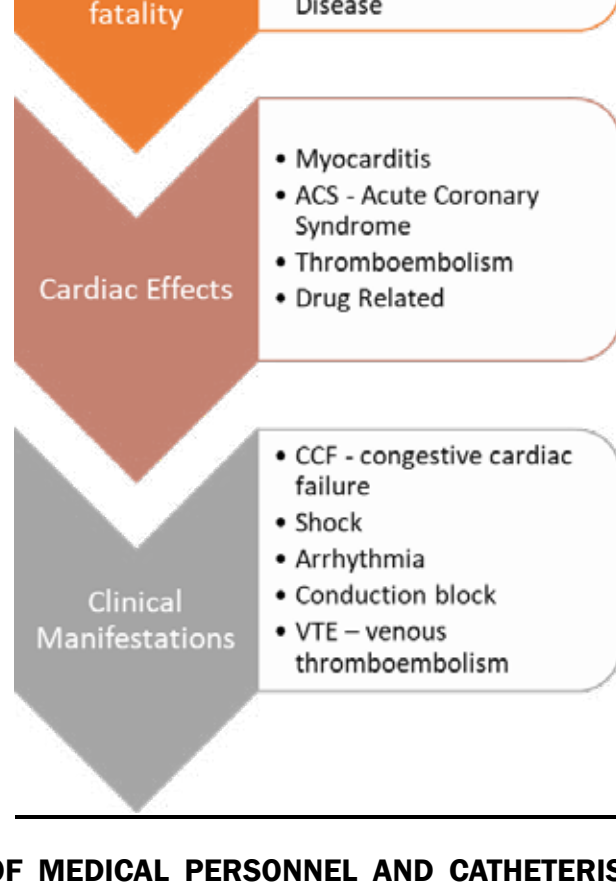
7. Drug Therapy and COVID-19: Interactions and Cardiovascular Implications

Antiviral Therapy	Ribavirin	Lopinavir/Ritonavir	Chloroquine/Hydroxychloroquine
How it works	Inhibits replication of RNA and DNA viruses.	Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A metabolism increasing levels of lopinavir.	Alters endosomal pH required for virus/cell fusion.
CV Drug Class Interactions	Anticoagulants	Antiplatelets Anticoagulants Statin Antiarrhythmics	Antiarrhythmics
CV Adverse Effects	Unknown	Altered cardiac conduction: QTc prolongation, high degree AV block, torsade de pointes	Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy Altered cardiac conduction: AV block, bundle branch block, torsade de pointes, ventricular tachycardia/fibrillation

The Indian Council of Medical Research (ICMR) has advised Hydroxychloroquine prophylaxis in health care workers involved in the care of suspected or confirmed COVID 19 infected patients and contacts of confirmed cases. Furthermore, HCQ is also one of the medications being evaluated as treatment in these patients. Since it is likely that there could be many patients on this medication a detailed table of drug interaction and precautions is also included.

Drug	Interactions and effects.	Action to be considered
1. <b>Antibiotics</b>		
<b>Macrolides (Azithromycin etc)</b>	QT prolongation and arrhythmias	Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor
<b>Quinolones (Ciprofloxacin etc)</b>	QT prolongation and arrhythmias	Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor
2 <b>Anti-arrhythmic drugs (Amiodarone, procainamide, quinidine, amiodarone, sotalol)</b>	QT prolongation and arrhythmias	Avoid co-prescription, always weigh the risks and benefit and seek expert opinion if needed.
3 <b>Anti-diabetic drugs including Insulin</b>	HCQ lowers blood sugar levels.	May need to monitor blood sugar levels and may need to reduce dose of anti-diabetic drugs
4 <b>Betablockers (Metoprolol, Carvedilol, Bisoprolol etc)</b>	HCQ increases drug levels of BB interfering with its metabolism at higher doses	Can be continued, but this monitoring may be needed
5 <b>Digoxin</b>	HCQ increases Digoxin levels at high doses.	Can be continued, but monitoring may be needed

8. Summary:



## SAFETY OF MEDICAL PERSONNEL AND CATHETERISATION AND ECHOCARDIOGRAM LABORATORY PROTOCOL

The cardiovascular care team (including physicians, nurses and technicians) may have limited training and experience with the acute management of viral epidemic disease. The increased transmission of COVID-19 to healthcare workers suggests that routine infectious disease mitigation precautions are insufficient and health care workers should be provided and trained on the use of personal protection measures. This should be coordinated with the local hospital protocol for managing patients with COVID 19 infection.

Echocardiogram Laboratory: Specific recommendations for Echocardiograms would include

- Echocardiograms may be performed on patients with suspected COVID-19 infection at initial presentation at the outpatient or fever clinic. The personnel handling the Echocardiogram machine should be well protected and the probe disinfected prior to subsequent use.
- It would be preferable to locate a mobile or dedicated Echo machine within the isolation ward where suspected or confirmed COVID 19 patients are being treated since frequent limited scans may be performed in these patients to periodically assess LV function and volume status.

## CCU/CATH LABORATORY:

Specific recommendations for Cath lab include

- Elective procedures to be postponed especially in patients with significant comorbidities. However the decision making has to be individualised, considering the risk to the treating medical team versus the risk of delay in diagnosis or treatment.
- All catheterization laboratory personnel should use N95 masks and be trained in the proper techniques for donning and doffing of Personal protection equipment (PPE) including eye protection.
- Patients with known COVID-19 or suspected COVID-19 who are required to come to the catheterization laboratory, should wear an appropriate surgical mask. All members of the catheterization laboratory team should wear PPE.
- Intubation, suction, and active CPR can result in aerosolisation of respiratory secretions, thus increasing the exposure to medical personnel. The threshold to consider intubation in a patient with borderline respiratory status may need to be lowered and should preferably be done prior to transfer, in order to avoid emergency intubation in the catheterisation laboratory

## CONCLUSION

- COVID 19 infection is an evolving global pandemic with significant cardiovascular complications that require aggressive management and is prognostically important.
- Guideline directed management to be continued for pre-existing co-morbid conditions including CAD, hypertension, diabetes and heart failure.
- Acute complications include myocarditis, ACS, shock, heart failure and venous thromboembolic disease.
- Long-term cardiovascular effects are yet to be elucidated
- Dedicated Echocardiogram machine within the isolation ward, where COVID 19 patients are being treated, would be preferable
- Cardiac catheterisation procedures to be restricted to only emergency and life-saving situations.
- Sensitisation of the cardiac staff regarding the precautions in handling infected patients, adequate training and utilisation of PPE to be implemented for all medical personnel involved in the management of suspected or confirmed cases of COVID 19 infection.

## ADDITIONAL READINGS

1. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Disease (COVID-19). China CDC Weekly 2020. 2(8): 1
2. ACC CLINICAL BULLETIN COVID-19 Clinical Guidance For the CV Care Team. Brendan Mullen, EVP, Science & Quality, American College of Cardiology. bmullen@acc.org
3. Gabriela M Kuster, Otmar Pfister, Thilo Burkard, Qian Zhou, Raphael Twerenbold, Philip Haaf, Andreas F Widmer, Stefan Oswald, SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19?, *European Heart Journal*, ehaa235, https://doi.org/10.1093/eurheartj/ehaa235
4. Tian-Yuan Xiong, Simon Redwood, Bernard Prendergast, Mao Chen, Coronaviruses and the cardiovascular system: acute and long-term implications, *European Heart Journal*, ehaa231, https://doi.org/10.1093/eurheartj/ehaa231
5. Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic: From ACC's Interventional Council and SCAI  
Forderick G.P. Welt, Pinak B. Shah, Herbert B. Aronow, Michael E. Borntrick, Timothy D. Henry, Matthew W. Sherwood, Anna N. Young, Laura J. Davidson, Sabeeda Kadavath, Ehtisham Mahmud, Ajay J. Kirtane and American College of Cardiology's (ACC) Interventional Council and the Society of Cardiovascular Angiography and Intervention (SCAI)

## CONTRIBUTORS

Thomas Alexander, Koval Medical Center, Coimbatore

Harikrishnan S, SCTIMST, Trivandrum

Shashank Joshi, Lllawati Hospital, Mumbai

## CORRESPONDING AUTHOR

Dr. Thomas Alexander M.D., D.M.: F.A.C.C.; F.I.C.C.; F.C.S.I. Senior Consultant and Interventional Cardiologist, Koval Medical Centre and Hospital, P.B.3209, Avanashi Road, Coimbatore 641014

Viji Samuel Thomson, CMC, Vellore

Sandeep Seth, AIIMS, New Delhi

Mangesh Tiwaskar, Asian Heart Institute, Mumbai

Phone: (0) 91 422 4323123 (R) 0422 2627685 (Mob) 09791907685 Fax: 91 422 2627782

Amit Malviya, NEIGRHMS, Shillong

Sreenivas Reddy, GMCH, Chandigarh

Milind Nadkar, KEM Hospital, Mumbai

E-Mail: tomalex41@gmail.com

Bishav Mohan, DMC Ludhiana

S Arulraj, Sundaram Arulraj Hospitals, Tuturain

Kamlesh Tewary, Mazuffarpur

Gurpreet Singh Wander, DMC Ludhiana

Siddharth Shah, Bhatia Hospital, Mumbai