

Review Article

Practical considerations for cardiovascular care during COVID-19 pandemic

Dnyanoba Kishanrao Bhaskar^{1*}, Vishal Madanlal Chaudhari², Medha Ajit Oak³

¹Department of Medicine, Lifeline Hospital, Pune, Maharashtra, India

²Department of Medicine, Sai Jyot Multispecialty Hospital, Thane, Maharashtra, India

³Department of Medicine, Oak Hospital and Icon Multispecialty Hospital, Thane, Maharashtra, India

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*Correspondence:

Dnyanoba Kishanrao Bhaskar,

E-mail: drbhaskar_dk@yahoo.in

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by a strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered a global pandemic affecting billions of lives and posing a stiff challenge to the delivery of routine healthcare across the world. The new second wave of COVID-19 in India presents with higher rate of infection and percentage of asymptomatic and mildly symptomatic cases is much higher than before, which means more people are spreading the disease. People with co-morbidities such as pre-existing cardiovascular conditions are at risk of suffering from severe complications of COVID-19 including acute respiratory distress and multi-organ failure. The pandemic has also resulted in people deferring routine care for conditions such as hypertension, diabetes and other cardiometabolic diseases. Initial reports also linked major CV drug classes such as the angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to adverse outcomes in COVID-19 patients. While subsequent reports have disproved these earlier findings, the science is rapidly evolving and the information overload has served to confuse general practitioners and consultant physicians alike. This review examined the practical considerations in terms of cardiocascular complications, effect of drugs, older adults and tele-consultation for CV care during COVID-19 pandemic.

Keywords: Cardiovascular complications, CV drugs and COVID-19, Older adults, Teleconsultation

INTRODUCTION

The COVID-19 pandemic has evolved into the worst-recorded public health crisis across the world. COVID-19 is a viral respiratory disease caused by the 2019 novel coronavirus (2019-nCoV), first reported in Wuhan city of China in December 2019. Data from the WHO indicates that India's COVID-19 cases crosses 13.52 million with 168,912 fresh infection and active cases go up by 92,922 as on 11 April 2021.¹

COVID-19 is caused by the novel SARS-CoV-2. Following activation of the viral spike protein, the virus binds itself to the human angiotensin-converting enzyme 2

(ACE-2) receptors which is usually expressed in the lungs, heart, intestinal epithelium, vascular endothelium and kidneys.²

Currently available evidence indicates that the interaction between the viral spike (S) protein and ACE-2, which triggers entry of the virus into host cells, is likely to be involved in the cardiocascular manifestations of COVID-19.³

The data from the pandemic is still evolving, but all evidence suggests that people with co-morbidities such as diabetes, cardiocascular disease, hypertension face an increased risk of experiencing adverse outcomes due to

COVID-19.⁴ One study that examined the prevalence of co-morbidities in patients with COVID-19 who developed the acute respiratory distress syndrome found hypertension (27%), diabetes (19%) and cardiovascular disease (6%) to be the most common pre-existing conditions.⁵

In such a scenario, it becomes imperative that people with these conditions exercise extra precautions and do not stop seeking routine care from their physicians. However, the on-ground situation has radically changed in the pandemic. Restricted movement and access to resources have meant that people have deferred seeking routine care for their conditions.

India is among the worst affected Asian nations and overall has the third-highest number of COVID-19 confirmed cases in the world with more than 6.5 million cases.⁷ The nationwide lockdown initiated in March 2020 ensured that hospitals focused on COVID-19 and postponed non-emergency care, which included the management of ACS (acute coronary syndrome) and STEMI (ST-elevation myocardial infarction) and high-risk NSTEMI (non ST-elevation myocardial infarction).⁷ Further, the initial reports out of China indicated that continued use of angiotensin-converting enzyme inhibitors (ACEIs) may result in adverse outcomes in patients with COVID-19.⁸

While subsequent reports have debunked these earlier findings, the science is rapidly evolving and the information overload has served to confuse physicians and cardiologists alike. This review examines the impact of COVID-19 on routine cardiovascular care including the use of multiple drugs in CARDIOVASCULAR conditions. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the author.

CARDIOVASCULAR SYSTEM AND COVID-19

Some of the evident cardiovascular system damage in COVID-19 patients includes direct myocardial injury, systemic inflammation resulting from high circulatory levels of proinflammatory cytokines, increased myocardial demand-supply ratio, rupture of plaque and consequent resultant coronary thrombosis and electrolyte imbalances.⁴

There are several hypotheses to the cardiovascular manifestations observed in COVID-19. Studies have indicated that the protective effects of ACE-2 receptors are compromised in COVID-19 as they are binding sites for coronavirus spike protein. ACE-2 belongs to the membrane-bound carboxy-dipeptidase family and is active in most tissues and is widely distributed in the heart, kidney, lung and testis. The severely compromised ACE-2 expression leads to hyperinflammation, cellular damage and subsequently respiratory failure. The binding of SARS-CoV-2 spike protein to ACE-2 activates disintegrin and metalloprotease-17 (ADAM17) and induces ACE-2 shedding via a process tightly coupled with TNF-alpha production. ADAM17 cleaves and thereby activates a

variety of cytokines and their receptors leading to the classic cytokine storm that has been identified as a hallmark of COVID-19 in hitherto published research.⁹

Because of these pathogenetic mechanisms and the resulting cascade of inflammatory actions, pre-existing cardiovascular disease leads to an increased vulnerability to COVID-19 and adverse clinical outcomes in affected patients. In summary, COVID-19 has been linked with a high inflammatory burden leading to vascular inflammation, myocarditis and cardiac arrhythmias.¹⁰

IMPACT OF COVID-19 ON CARDIOVASCULAR CARE

The worldwide lockdown measures have affected routine cardiovascular care for patients. Patients with myocardial infarction (MI) worldwide avoid hospitals or present too late to benefit from life-saving treatment globally. A survey conducted by the ESC of 3,101 healthcare professionals in 141 countries in mid-April found that there is a huge collateral damage caused by the ongoing pandemic and most patients have postponed routine care for their cardiovascular conditions.¹¹ There was a 50% decrease in admissions for MI, while most respondents said that of those patients who did go to hospital, 48% arrived later than usual and beyond the optimal window for urgent treatment.¹¹

In India, the CSI has initiated a study to understand the impact of the pandemic on MI admissions and treatment in the country. The results of this study are expected shortly and should provide a direction to cardiologists on how they can optimize care in these times.

CONSIDERATIONS ON CARDIOVASCULAR COMPLICATIONS DURING COVID-19

Early identification and isolation of cardiovascular patients with COVID-19 symptoms from other patients is essential during the pandemic. It must be pointed out that acute viral infections have multiple short-term effects on the cardiovascular system. COVID-19 patients with underlying cardiovascular, diabetic, renal, respiratory or other co-morbid conditions need to be examined and monitored closely to prioritize intervention when needed. Some cardiovascular considerations in this regard are outlined in Table 1.¹²

LINK BETWEEN HYPERTENSION AND COVID-19

Hypertension is a common comorbidity in patients with COVID-19. Many hospitalized COVID-19 patients are older with multiple co-morbidities. Research has found that hypertension is likely to co-exist with diabetes and obesity in this condition and leads to a high morbidity and mortality rates in these patient cohorts.¹³⁻¹⁶ Hypertension remains the greatest modifiable risk factor for atherosclerotic cardiovascular disease.

Table 2 lists the commonly identified co-morbidities in COVID-19 patients with corresponding prevalence rates.¹⁷

An observational study from a combined COHORT of Germany and Netherlands examined the association between antihypertensive agents used in people hospitalized with COVID-19 infection and outcomes. It demonstrated that no evidence of adverse outcomes with

ACEI/ARB. Interestingly, beta blockers provided beneficial role in terms of milder course after admission to hospital. Whereas there was a significant association with poor outcomes in patient treated with calcium channel blockers (CCB).¹⁸ Health care professionals should continue to follow blood pressure management guidelines and protocol to keep the persons with hypertension on goal in times of COVID-19 pandemic to reduce long-term cardiovascular risk associated with hypertension.

Table 1: Considerations for CV complications during COVID-19.

Conditions	General considerations	Treatment considerations
Myocarditis	Acute cardiac injury is present in about 7% of patients with COVID-19 and may represent either as type 2 MI or myocarditis; standard troponin T levels and electrocardiograms should be used to diagnose myocarditis	Standard heart failure medications; ventilatory support where indicated; ECMO
Acute coronary syndrome	Clinicians should not rely only on troponin T levels to diagnose this condition; history and serial troponin T levels should be considered along with angiogram if required	Regular medications like aspirin, statins, beta-blockers and ACEI should be continued or optimized as indicated; patients with COVID-19 can have significant thrombocytopenia; revascularization strategy should be individualized after taking this into consideration
Shock	Consider cardiogenic or mixed etiology in respiratory manifestations of COVID-19; echocardiography and serum brain natriuretic peptide (BNP) can help differentiate between ARDS and cardiogenic shock	Fluid resuscitation should be started after assessing volume status; norepinephrine is the first-line vasoactive agent in COVID-19 and shock, followed by vasopressin or epinephrine; steroids and ECMO may be considered in refractory shock
Thromboembolic disease	D-dimer levels or venous doppler studies should be used to evaluate presence of thromboembolic disease in COVID-19 patients	Unfractionated or LMW heparin and modification of dual anti-platelet therapies form the current management strategies in these patients
Heart failure	Close monitoring of COVID-19 patients for heart failure is very important	Medical management should be based on existing guidelines and includes continuation of ACE inhibitors and ARBs; cardioversion may be required in hemodynamically unstable atrial fibrillation

Table 2: Commonly identified co-morbidities in COVID-19.

Country	Number of patients	Prevalence of comorbidity among all patients (among patients who were ventilated or in ICU)				References
		Cardiovascular disease (%)	Hypertension (%)	Diabetes (%)	Obesity (%)	
China	1,099	2.5 ^a (5.8) ^a	15.0 (23.7)	7.4 (16.2)	NR	11
China	44,672	4.2 (22.7)	12.8 (39.7)	5.3 (19.7)	NR	12
Italy	1,591	NR (21)	NR (49)	NR (17)	NR	13
USA	393	13.7 ^a (19.2) ^a	50.1 (53.8)	25.2 (27.7)	35.8 (43.4)	14
USA	5,700	11.1 ^a (NR)	56.6 (NR)	33.8 (NR)	41.7 (NR)	15

Prevalence of comorbidity among critically ill patients is shown in parentheses; ^aprevalence of coronary artery disease specifically; ^bprevalence of co-morbidity among patients who died; COVID-19=coronavirus disease 2019; ICU=intensive care unit; NR=not reported.

THE ACE INHIBITORS AND ARB CONUNDRUM IN COVID-19

The potential drug-disease interactions in patients with COVID-19 have become a focus area for most research efforts over the last 8 months. The burning question as to whether antihypertensive agents such as ACE inhibitors and ARBs are involved in the progression or prevention of COVID-19 continues to be fiercely debated among clinicians.¹⁸

Early studies in the pandemic have reported the role of ACEIs in upregulating ACE-2 expression.^{19,20} Considering the role of ACE-2 expression in COVID-19 infections, initially there were controversies by recommending discontinuing ACEI therapy to reduce the risk of infection.^{20,21} Interestingly, the preclinical study by Kuba et al demonstrated the downregulation of ACE-2 expression and activation of the renin-angiotensin system (RAS) in the pathogenesis of lung injury in SARS infection.²² The RAS plays an important role in maintaining blood pressure, along with fluid electrolyte homeostasis. In normal physiologic conditions, ACE generates angiotensin II, while ACE-2 decreases angiotensin II, thus maintaining a balance in the RAS system. The binding of the SARS-CoV-2 virus to ACE-2 decreases the level of ACE-2 and increases angiotensin II. The study by Liu et al has demonstrated significantly higher levels of angiotensin II in the plasma of infected persons compared to healthy individuals.²³ Even though the role of RAS dysfunction has been demonstrated in COVID-19 cases, the role of ACEI or ARBs in clinical outcomes is largely unknown. The study by Meng et al demonstrated that persons receiving ACEIs or ARB therapy had lower interleukin-6 (IL-6) levels in peripheral blood, along with a lower rate of severe diseases. Further, there was also an increase in CD3 and CD8 T-cell counts in peripheral blood, along with reduced peak viral load. Based on the results of this study, it was evident that ACEIs or ARBs potentially contribute to improvement in clinical outcomes in COVID-19 persons with hypertension.²⁴

Both ACEIs and ARBs are commonly used worldwide for the treatment of hypertension and other CVDs. Therefore, the debate has questioned if they should be discontinued during the COVID-19 pandemic. Studies out of Spain, Italy and the USA have supported the use of RAAS inhibitors indicating that the continued usage was not associated with a positive COVID-19 test.²⁵⁻²⁷

Further support for continuing the usage of these drugs has been provided by leading medical societies and cardiovascular associations including the American college of cardiology, the American heart association, European society of cardiology and the Chinese society of cardiology.²⁸⁻³¹

The Cardiological society of India (CSI) has also issued a position statement in this regard, stating that guideline directed drug therapy including ACEI/ARB/ARNI is to be

continued in patients with pre-existing HF.³² CSI also says that cardiologists should continue using these drugs to prevent mortality due to heart failure and myocardial infarction, until further research on SARS-Cov-2 interaction with ACEi/ARB's shows a strong reason to stop these drugs.³³ The CSI statement is based on a thorough review of literature on use of ACE inhibitors and COVID-19.

In our clinical experience, the use of ACEIs and ARBs should be continued during and after the pandemic given the fact that these drugs offer a better risk:benefit profile to patients with hypertension and related cardiovascular conditions.

CARDIOVASCULAR EFFECTS OF DRUGS USED IN COVID-19

Drug repurposing has been the main approach in the search for new drugs for COVID-19 so far. In this context, the age old anti-malarial drug hydroxychloroquine (HCQ) has assumed a lot of importance. Chloroquine and HCQ can potentially block virus entry into cells by inhibiting the glycosylation of host receptors, proteolytic processing and endosomal acidification.³⁴

Initial clinical studies conducted in China reported the apparent efficacy and acceptable safety of chloroquine against COVID-19.³⁵ A large observational study involving 1,376 patients receiving HCQ treatment showed that it did not alter the risk of the composite end point of intubation or death. These conflicting data demonstrate that the efficacy of HCQ is still controversial and needs further validation.³⁶

The Indian council of medical research continues to advocate the use of HCQ for frontline workers in India. ICMR has recommended the prophylactic use of HCQ in the following categories. All asymptomatic healthcare workers involved in containment and treatment of COVID19 and asymptomatic healthcare workers working in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks; asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19 related activities; asymptomatic household contacts of laboratory confirmed cases.

A systematic review of the arrhythmogenic effect of short courses of chloroquine or HCQ revealed that approximately 10% of COVID-19 patients treated with these drugs developed QT prolongation and found evidence of ventricular arrhythmia in 2 COVID-19 patients from a group of 28 treated with high-dose chloroquine. These results show a compelling evidence that chloroquine and HCQ induce significant QT-interval prolongation and potentially increase the risk of arrhythmia. Daily electrocardiographic monitoring and other risk mitigation strategies should be considered in order to prevent possible harms from what is currently an unproven therapy.³⁷

Table 3: CV effects of potential co-prescriptions with HCQ.³⁸

Drugs	Interactions and effects	Actions to be considered
Antibiotics macrolides (azithromycin)	QT prolongation and arrhythmias	Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor
Quinolones (ciprofloxacin)	QT prolongation and arrhythmias	Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor
Anti-arrhythmic drugs (amiodarone, disopyramide procainamide, quinidine amiodarone, sotalol)	QT prolongation and arrhythmias	Avoid co-prescription, always weigh the risks and benefit and seek expert option if needed
Anti-diabetic drugs including insulin	HCQ lowers blood sugar levels	May need to monitor blood sugar levels and may need to reduce dose of antidiabetic drugs
Betablockers (metoprolol, carvedilol, bisoprolol)	HCQ increases drug levels of BB interfering with its metabolism at higher doses	Can be continued, but this monitoring may be needed
Digoxin	HCQ increases digoxin levels at high doses	Can be continued, but monitoring may be needed

Some of the routinely used drugs interact with HCQ and may result in QT prolongation. Table 3 lists these therapies and current recommendations for monitoring CV effects.³⁸

Remdesivir is a novel investigational nucleotide analogue for the treatment of COVID-19 that has broad-spectrum antiviral activity and has shown potential to reduce the viral load in COVID-19. The US FDA granted emergency use of remdesivir for COVID-19 in May 2020 to meet the urgent demand for treatment of hospitalized patients, further in October 2020 US FDA approved remdesivir for use in adult and pediatric patients (≥ 12 years and over 40 kgs) for treatment of COVID-19 requiring hospitalization.^{39,40} The impact of this investigational treatment on the CV system is yet to be elucidated in large trials.

CONSIDERATIONS STATIN THERAPY IN TIMES OF COVID-19

Statin therapy are widely prescribed in prevention and treatment for cardiovascular ailments. We have extensive experience with this agent and the likelihood of harm is to be very low. There is no proven clinical evidence till date that statins are beneficial for patients with COVID-19. However, there are reasons to consider statin therapy for the people with cardiovascular ailments in time of COVID-19. Many published data have showed that underlying cardiovascular disease and diabetes are the most important risk factors for severe COVID-19 infection.⁵ Hence statin therapy is most likely are in primary indications in the patient group. Cardiovascular complications of COVID-19 infection are discussed earlier and statin therapy might be beneficial in preventing and managing these complications.¹² There is the theoretical role that statins may play in protecting innate immune responses to viral respiratory infections through inhibiting the MYD88

pathway. The ability of statins to maintain MYD88 levels at normal levels may be protective for patients with COVID-19.⁴¹ There is some epidemiological evidence that statins may lead to fewer severe viral pneumonias.⁴²

ROLE OF ANTICOAGULATION IN COVID-19

The frequent hypercoagulability and increased thrombotic risk observed in COVID-19 critically ill patients has stimulated debate on role of anticoagulants in these patients. It must be noted that thrombocytopenia and elevation of plasma D-dimer levels has been frequently identified in patients with the most severe forms of COVID-19. Acetylsalicylic acid (ASA) or aspirin documented to have anti-inflammatory, antithrombotic and a significant antiviral activity against viruses, including human coronaviruses.⁴³

In this context a recent retrospective analysis of hospitalized patients suggests that ASA or aspirin use may have beneficial effects in patients with COVID-19, but this data needs to be confirmed via randomized controlled trials before any recommendation can be made.⁴⁴

The European society of cardiology has published an anticoagulation algorithm that describes anticoagulation strategies in COVID-19 patients. These strategies need to be considered for high thrombotic risk patients, which is defined as those with dyspnea, respiratory rate >24 , oxygen saturation $<90\%$, elevated C-reactive protein, rising D-dimer levels and elevated fibrinogen levels.⁴⁵

Parenteral heparin drip protocol with close follow up and an active prothromboplastin time (aPTT) goal of 60-85 secs is recommended for ICU patients, while subcutaneous enoxaparin 1 mg/kg twice a day or consideration of the

same heparin protocol used for ICU patients should be considered for non-ICU patients.⁴⁵

CONSIDERATIONS ON OLDER ADULTS WITH CARDIOVASCULAR DISEASE DURING COVID-19

Older adults with cardiovascular disease are potentially at high risk for both severe presentation of COVID-19 and lack of adequate monitoring during the pandemic. Continued focused care and management of cardiac ailments during the COVID-19 pandemic is most essential in this population. This approach may decrease the risk of a cardiac admissions and decrease the vulnerability of exposure to COVID-19. Encourage teleconsultation and advice the care givers of the older adults to get familiarize themselves with a video platform to which they have access and feel comfortable using. It is advised to identify a healthy, low risk, trusted care giver (family/friend/neighbor) with whom healthcare professional can maintain communication.⁴⁶

The importance of maintaining good medical nutrition therapy, hydration and daily exercise despite social isolation measures should be explained in detail. All relevant medications should be continued as earlier in the absence of contraindications.

ROLE OF REMOTE CONSULTATION AND TELEMEDICINE IN CONTINUED CARE AND PREVENTION OF CARDIOVASCULAR AILMENTS

Telemedicine has proved to be useful in providing consultation and education to patients in times of restricted social mobility and continues to be utilized in view of the need to minimize direct contact of patients with hospital/healthcare facility.⁴⁷ However, there are challenges and limitations of telemedicine especially in developing countries. These include poor internet connectivity, poor digital literacy, visual and hearing problems, among others.

Use of telemedicine for delivering routine care is now recommended by the government of India. The ministry of health and family welfare, government of India issued the telemedicine guidelines on 25 March 2020. Formulated by NITI Aayog, which is a digital health policy that advocates use of digital tools for improving the efficiency and outcome of the healthcare system. These guidelines have been notified under the Indian medical council (professional conduct, etiquette and ethics regulation, 2002).⁴⁸

Communication skills and patient empathy is key for healthcare professional in this COVID-19 times, Ghosh et al reviewed existing literature and have emphasized that physicians need to improve communication skills in these times. The authors state that healthcare professions must seek learning opportunities within their hospitals, state, national or international medical community to continue learning and practicing new communication skills.⁴⁹

In time of the pandemic, it is very important to keep an open channel of communication between patients and physicians. Reducing the risk for infection transmission and prevention should be considered at every step while planning, preparing and fighting the COVID-19 pandemic.

RECOMMENDED ROUTINE CARDIOVASCULAR CARE DURING COVID-19 PANDEMIC

The routine cardiovascular care during COVID-19 pandemic are strictly maintaining social distancing and proper hand and respiratory hygiene practices; use teleconsultation or telemedicine for routine care; do not defer regular check-ups especially in patient's high-risk cardiovascular disease; persons with hypertension should monitor their blood pressure at home regularly, routine management of hypertension should be continued via remote consultations unless hospital visits are indicated; stabilizing the cardiac, renal and metabolic status of peoples with underlying conditions is necessary to avoid serious complications. Older adults with cardiovascular ailments are potentially at high risk and need special care; ACE inhibitors and ARBs to be continued in appropriate patients during COVID-19; personalized therapeutic strategies should be initiated for all patients based on age, disease severity and presence of diabetes or CV-related complications. It is advisable to stick to ongoing therapies. However, consult the health care professional for monitoring and dosage adjustment in serious symptomatic cases. Serious symptomatic cases will need to be hospitalized for appropriate care.

CONCLUSION

The evolving evidence indicates that COVID-19 is associated with adverse clinical outcomes for patients with existing CV conditions. In such a scenario, it becomes imperative that practitioners must be cognizant of the cardiovascular complications of COVID-19. Cardiac clinic and hospital staff should be sensitized regarding the precautions in handling infected patients. Administrators should ensure adequate training and utilization of PPE to be implemented for personnel involved in the management of suspected or confirmed cases of COVID 19. Individualized care decisions and a high level of vigilance could help mitigate the adverse effects and improve outcomes in this patient cohort.

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