COVID 19 and Cardiovascular Disease : A Review

Avinash Arke[1]

ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected billions of individuals. Evidence indicate a close association between COVID-19 and cardiovascular diseases (CVDs). Although SARS-CoV-2 principally affects the lungs, many patients develop new-onset cardiac dysfunction during the course of the illness. Pre-existing CVDs make people more vulnerable to SARS-CoV-2 infection and increase risk of death. COVID-19 patients may present with myocarditis, acute myocardial infarction, stroke, cardiomyopathy, heart failure, arrhythmias, acute pericarditis, and venous thromboembolism. Potential drug disease interactions affecting patients with COVID-19 and comorbid cardiovascular diseases are also a serious concern. In this Review, we summarize the current understanding of interaction between COVID-19 and the cardiovascular system.

Background :

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan of Hubei province, China, in late December 2019. Since then, COVID-19 is spreading rapidly worldwide, affecting > 200 countries and territories. It has been declared as pandemic by World Health Organization (WHO) on March 11th 2020. As of 27th November there have been over 60 million cases and 1.4 million deaths reported globally since the start of the pandemic, while in India 9.3 million confirmed cases and 1.36 Lakh deaths have been reported[1]. This pandemic has caused unprecedented effect on public health and health care deliveries and badly affected the global economy.

SARS-CoV-2 has been shown to enter host cell by interaction of viral spike glycoprotein with human membrane bound angiotensin-converting enzyme 2 (ACE2) after spike protein being activated by trans-membrane protease serine 2[2,3]. It is expressed predominantly in heart, intestine, kidney, and pulmonary alveolar (type II) cells[4]. Probably, that is responsible for the multi-organ involvement seen in COVID-19. COVID-19 interacts with the cardiovascular system on multiple levels. In this review, we summarize bidirectional interaction between COVID-19 and cardiovascular conditions.

[1]Specialist Cardiologist under National Health Mission,
Daga Memorial Govt. Women's Hospital, Gandhibag, Nagpur

Address for Correspondence -
Dr. Avinash Arke
E-mail : avinasharke1@gmail.com

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1. COVID 19 in patients with underlying cardiovascular disease

CVD is a common comorbidity observed in patients infected with COVID-19 and tend to have more severe disease with worse clinical outcomes[5,6]. CVD and its risk factors, such as hypertension and diabetes mellitus, were common pre- existing conditions in patients with COVID-19, but the definition of CVD used in each study was vague[5,7]. A meta-analysis of six published studies from China including 1527 patients with COVID-19 reported 9.7%, 16.4% and 17.1% prevalence of diabetes, cardio-cerebrovascular disease and hypertension respectively[6]. Although the prevalence of diabetes and hypertension in this cohort was same as in the Chinese general population, the prevalence of cardio-cerebrovascular disease was considerably higher. Importantly, the prevalence of diabetes, cardio-cerebrovascular disease and hypertension was higher in critically ill patients and in those who died and was associated with a 2-fold, 3-fold and 2-fold greater risk of severe disease or requiring intensive care unit (ICU) admission, suggesting prognostic impact of these comorbidities. According to the report of Chinese Centre for Disease Control and Prevention, clinical outcomes in 44672

confirmed cases of COVID-19, the overall case fatality rate (CFR) was 2.3% in the entire cohort but significantly higher (6%, 7.3% and 10.5% respectively) in patients with hypertension, diabetes and CVD[5]. A similar trend in the prevalence of comorbidities has been reported by researchers in other countries. In a report of 1,591 patients admitted to the ICU in Italy with COVID-19, the prevalence of prior hypertension, diabetes and CVD was 49%, 17% and 21% respectively[8]. Similarly, according to Goyal, P. et al, among 393 consecutive patients hospitalized with COVID-19 in New York, USA, prevalence of pre-existing hypertension, obesity, diabetes, and coronary artery disease was 50%, 36%, 25% and 14% patients respectively[9].

2. COVID 19 and cardiovascular involvement

Direct myocardial injury and myocarditis :

Acute myocardial injury was observed in > 20% of patients with COVID-19 in early studies in China[5,6,7,10]. The definition of acute myocardial injury varied with different studies, like elevated cardiac enzymes and/or electrocardiographic abnormalities. An elevated level of high sensitivity cardiac troponin I (cTnI) above 99th percentile upper reference limit is the most commonly used definition. There is report of COVID-19- induced fulminant myocarditis in a 37 years man, who presented with chest pain and ST segment elevation 2D. Echocardiography revealed an LV dilation (LV diastolic dimension = 58 mm) and LV dysfunction (LVEF = 27%). After treatment with methylprednisolone cardiac size and function recovered to normal after 1 week (LV diastolic dimension = 42 mm, LVEF = 66%). Another report described an endomyocardial biopsy showing low-grade myocardial inflammation and myocardial localization of coronavirus particles (outside of cardiomyocytes), suggesting that SARS-CoV-2 might infect the myocardium directly[12]. Autopsy reports have also revealed the presence of mild inflammation and viral RNA in the hearts of patients with COVID-19[13]. Cardiac Magnetic Resonance Imaging (CMR) in a 53 years old woman who had an elevated levels of cardiac biomarkers and diffuse ST segment elevation on the electrocardiogram showed diffuse biventricular hypokinesis, with severe LV dysfunction (LVEF = 35%)[14]. CMR data also revealed marked biventricular interstitial oedema, diffuse late gadolinium enhancement and circumferential pericardial effusion, features that are consistent with acute myocarditis. The possible mechanisms of acute myocardial injury could be direct (i.e. non-coronary) myocardial injury due to viral myocarditis or the effect of systemic inflammation ***(Figure 1)***[15]. Acute cardiac injury, as evidenced by elevated biomarkers or ECG abnormalities, was associated with poor prognosis and predictive of the risk of in- hospital mortality in patients with severe COVID-19[16]. It has been reported that the rate of death in patients with elevated levels of cardiac troponin T was 37.5%, whereas, in patients with underlying cardiovascular comorbidities plus elevated levels of cardiac troponin T, it was almost double (69.4%)[17]. Those patients who needed admission to intensive care unit or had severe / fatal illness had more likelihood of troponin elevation as compared to those with mild illness[10,18].

Acute coronary syndrome :

Cases of acute myocardial infarction, including ST elevation myocardial infarction have been reported in COVID-19 from New York and Italy requiring percutaneous coronary intervention[19]. However, the incidence of ACS in patients with COVID-19 is still unknown. The possible mechanisms for acute coronary syndrome are Plaque rupture, Microthrombi, endothelial dysfunction, microvascular dysfunction ***(Figure 2)***[20,21].

Heart failure :

Heart failure has been documented as a most common complications of COVID-19, with a reported incidence of 23-24% in all patients and 49-52% in patients who died[18].

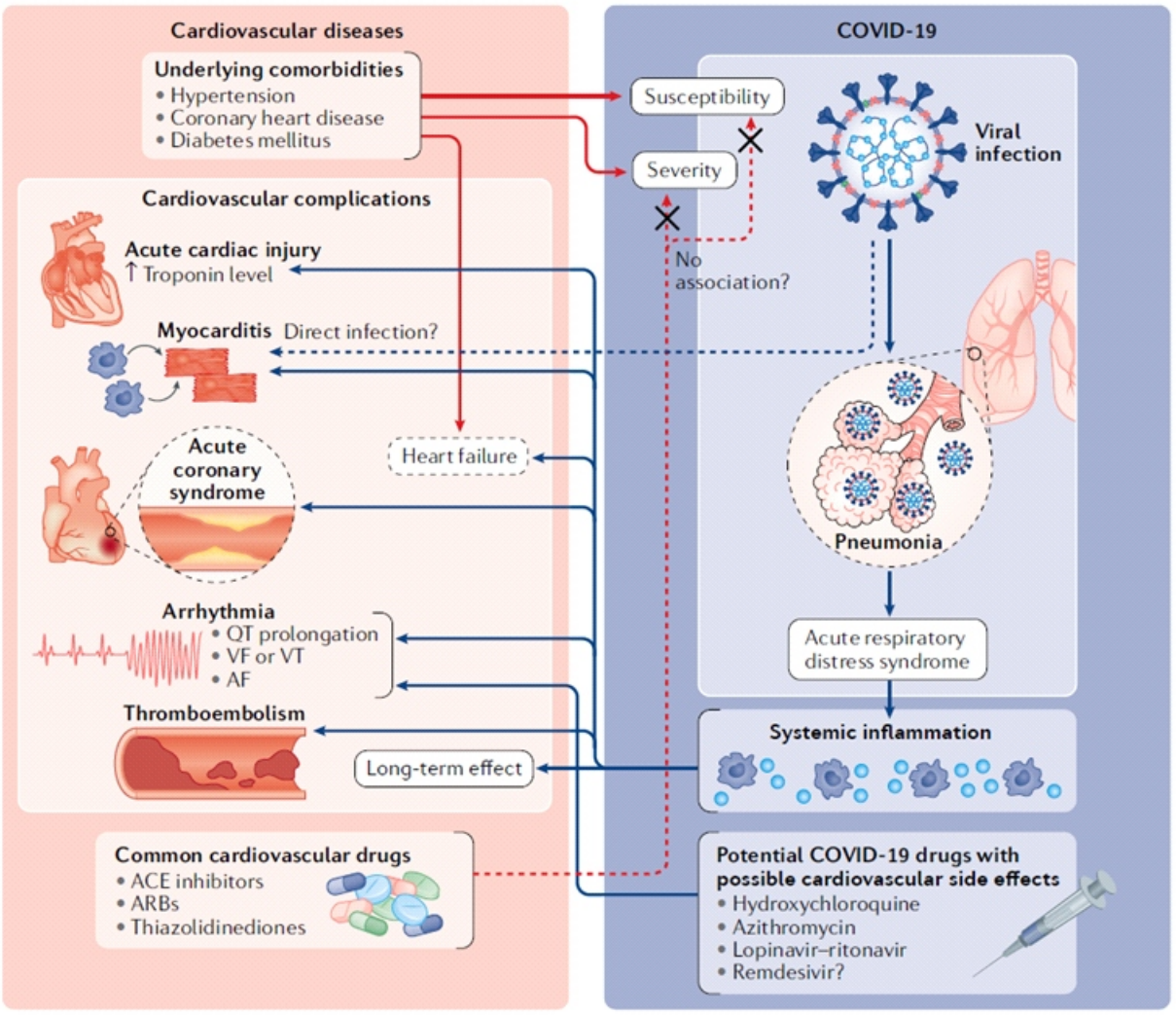

Figure 1. : **Bidirectional interaction between cardiovascular diseases and COVID-19**
Ref : Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease : from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020 Sep;17(9):543-558

Acute decompensated heart failure might be the result of :

1. Exacerbation of pre-existing heart failure, whether already known or unknown, aggravated by fever, tachycardia, renal dysfunction.
2. New onset LV dysfunction related to
   a. Acute myocarditis
   b. Acute coronary syndrome
   c. Stress- induced cardiomyopathy
   d. Cytokine-related myocardial dysfunction.

Since pneumonia with bilateral, peripheral and lower lung involvement with or without acute respiratory distress syndrome (ARDS) is a common presentation of COVID-19, diagnosis of acute left ventricular (LV) failure with pulmonary oedema needs high index of suspicion. Elevated Brain Natriuretic Peptide (BNP) or N-terminal Pro Brain Natriuretic Peptide (NT-Pro BNP) may point towards heart failure. Caution is warranted while interpreting BNP / NT-Pro BNP in these patients, since these values can also be elevated in elderly (age specific upper limit of normal should be

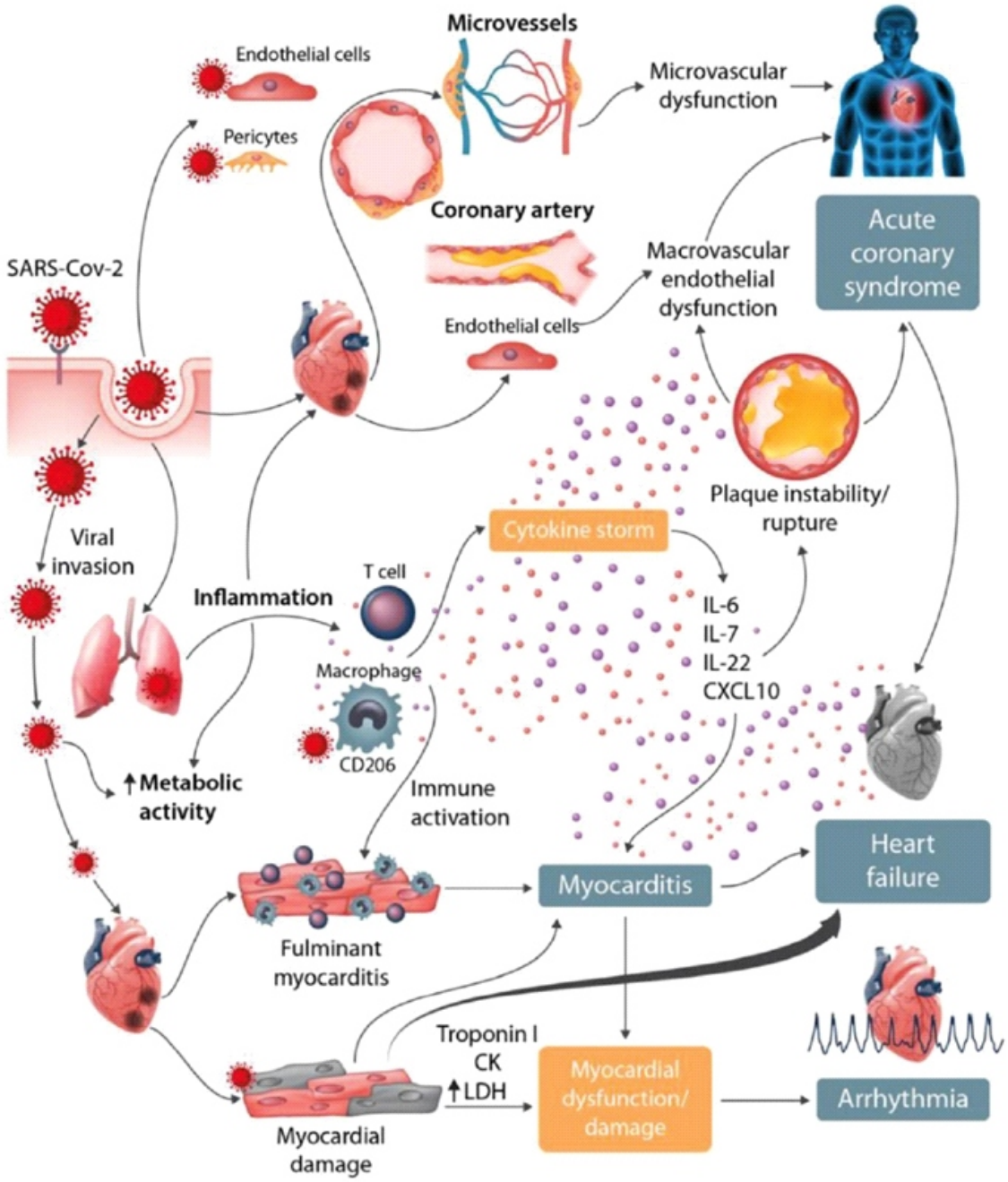

Figure 2. : **Bardiovascular involvement in COVID-19 - key manifestation and hypothetical mechanism**
Ref. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic.

considered), sepsis, renal dysfunction[22]. Moreover, patients with raised BNP / NT-Pro BNP had higher mortality than with normal levels.

Coagulopathy

Coagulopathy is one of the most important complication of COVID-19. Increased thromboembolic events in patients with COVID-

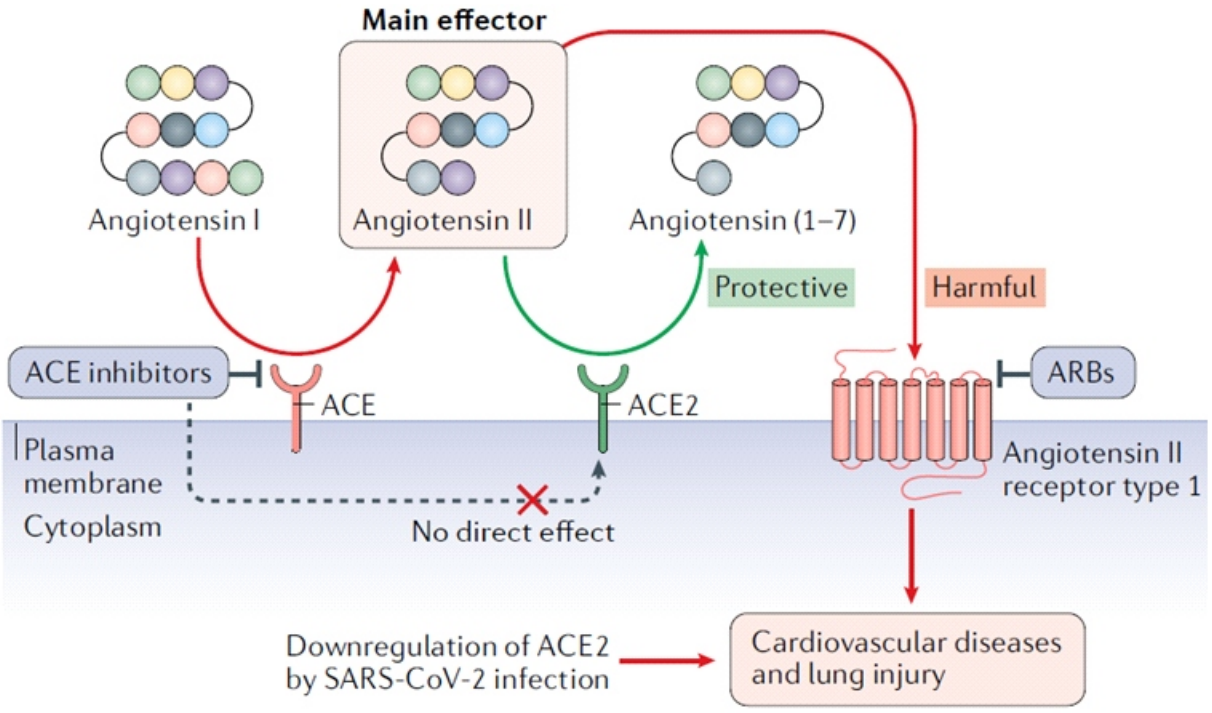

Figure 3. : **Protective effect of ACE2, ACE inhibitor and ARB against cardiovasculardisease and lung injury in COVID-19.**
Ref : Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease : from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020 Sep;17(9):543-558.

19 and raised d-Dimer, fibrinogen and factor VIII levels suggest the presence of a hyper-coagulable state. Severe systemic inflammatory response with activation of macrophages and endothelial damage induced by COVID-19 might be a possible mechanism for a hypercoagulable state.

Venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, is a common complication responsible for COVID-19 mortality. 7 of 12 patients and 4 of 12 patients were found to have deep vein thrombosis and pulmonary embolism respectively in an autopsy study[13]. Arterial thrombosis has also been reported in patients with COVID-19 manifesting as large- vessel ischaemic stroke and acute limb ischemia[23,24].

Arrhythmia :

Arrhythmias are common in COVID-19, with an incidence of 17% as reported in a study from Wuhan, China[11]. Patients who required ICU admission had higher incidence (44%) of arrhythmia than those not requiring ICU admission (9%). Similarly, those with elevated Troponin T level were more likely to have ventricular arrhythmia (ventricular tachycardia and fibrillation) than with normal troponin T level (12% versus 5%)[17]. Exact mechanism of arrhythmias is unknown. Myocardial injury, fever, sepsis, hypoxia or electrolyte abnormalities, use of some antiviral medications and antibiotics may trigger atrial and ventricular tachycardia and fibrillation.

Multisystem Inflammatory Syndrome in Children

Children are thought to be less affected with COVID-19 and most of them are asymptomatic or have mild symptoms. However, COVID-19 has been reported to cause severe inflammatory symptoms in a small proportion of paediatric patients[25]. These patients were older and had a

higher rate of cardiac involvement than patients diagnosed with Kawasaki disease before the pandemic. A review of 39 observational studies (n = 662 patients) reported that fever (100%, n = 662), abdominal pain or diarrhea (73.7%, n = 488), and vomiting (68.3%, n = 452) were the most common clinical presentation, 71% of children (n = 470) needed intensive care unit admission, average length of hospital stay was 7.9 ± 0.6 days, mechanical ventilation and extracorporeal membrane oxygenation were necessary in 22.2% (n = 147) and 4.4% (n = 29) of patients, respectively and the mortality was 1.7% (n = 11)[26]. The most common echocardiographic abnormality was depressed ejection fraction (45.1%, n = 262 of 581), pericardial effusion and coronary artery aneurysm was reported in few patients. A case series from Mumbai, India has reported 23 patients, aged of 0.8-14 year, of whom COVID19 RT PCR or antibody was positive in 39.1% and 30.4%, respectively; 34.8% had a positive contact. 65% patients presented in shock, many of them had myocarditis with elevated Troponin, NT pro BNP and LV dysfunction and 26% patients had coronary artery dilation[25].

3. Antiviral drugs and cardiovascular effects

It has been a great challenge to develop drugs for prevention and treatment of COVID-19. Some of the drugs being used for other indications have been tried for the treatment of COVID-19 at the cost of their known or unknown cardiovascular adverse effects. There is limited clinical data available about cardiovascular effects / adverse effects of Remdesivir, Favipiravir.

Chloroquine and Hydroxychloroquine :

Chloroquine and hydroxychloroquine are used in the treatment of malaria and chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis. These drugs were thought to be useful for the treatment and prevention of COVID-19 as they can block virus entry into cells (via the endosomal pathway, by inhibiting the glycosylation of host receptors, proteolytic processing, endosomal acidification) and mediate immunomodulatory effects (attenuation of cytokine production, inhibition of autophagy and lysosomal activity)[27,28].

Though the initial reports from France and China described improved virus clearance and symptoms remission with hydroxycholroquine, in observational study from New York City involving 1376 patients, hydroxychloroquine treatment did not alter the risk of the composite end point of intubation or death[29,230,31].

Chloroquine and Hydroxychloroquine are known to prolong QT interval and can induce ventricular arrhythmias (Torsade De Pointes, ventricular tachycardia, ventricular fibrillation) and sudden cardiac death[27].

Frequent electrocardiographic evaluation should be strongly considered in patients treated with hydroxychloroquine and/or azithromycin.

Azithromycin :

Azithromycin also appears to block the virus entry into cells[32]. It also up-regulates type I and type III interferon production (especially interferon- and interferon-), and MDA5 and RIG-I gene that is involved in virus recognition[33]. In addition, it regulates and/or decreases the production of IL-1 , IL-6, IL-8, IL-10, IL-12, and IFN- which are involved in COVID-19 severe respiratory syndrome.[34,35]. These mechanisms are universally involved in the innate response against infectious agents, and potentially against SARS-CoV-2.

Azithromycin is also known to prolong the QT interval[36]. There is a greater QT prolongation when it used in combination with hydroxychloroquine[37].

A retrospective cohort study of 1,438 patients hospitalized with COVID-19 in New York reported no increases in in-hospital mortality in a group of patients who were treated with either hydroxychloroquine or azithromycin or both or neither treatment[38]. But the secondary outcome of cardiac arrest was more likely in patients receiving both hydroxychloroquine and

azithromycin than in patients receiving neither drug.

Ray et al had described taking azithromycin for 5 days, as compared to no antibiotics, increases risk of cardiovascular death (hazard ratio, 2.88; 95% confidence interval [CI], 1.79 to 4.63; P<0.001) and death from any cause (hazard ratio, 1.85; 95% CI, 1.25 to 2.75; P=0.002)[39].

4. Effect of RAAS inhibitors on COVID-19

ACE2 is a homolog of angiotensin-converting enzyme that converts angiotensin II to angiotensin 1 to 7, thereby diminishing vasoconstriction mediated by the renin angiotensin system. As ACE2 is a receptor for SARS-CoV-2, it was thought initially that ACE inhibitors and ARBs which upregulate the cell surface expression of ACE2 might be harmful. SARS-CoV-2 entry into cells is ACE2 dependent. However, ACE2 appears to be protective against acute lung injury. Binding of the SARS-CoV spike protein to ACE2 causes ACE2 downregulation, leading to an increase in angiotensin II and ultimately increased pulmonary vascular permeability, inducing pulmonary edema and reduced lung function ***(Figure 3).*** Importantly, indiscriminate withdrawal of these drugs could harm high- risk patients having cardiovascular disease (hypertension, coronary artery disease, congestive heart failure, and DM). Several medical societies including the ACC, AHA, Chinese Society of Cardiology, ESC and the Heart Failure Society of America have issued statements recommending continuation of RAAS antagonists for those who are currently prescribed these agents[40,41,42]. It has been found that the use of RAAS inhibitors was not associated with a positive COVID-19 test, suggesting that these agents do not affect susceptibility to SARS- CoV-2 infection and the use of these agents was not associated with a substantial increase in the risk of severe or fatal illness among patients with COVID-19[43,44].

Conclusion :

Patients with COVID-19 commonly present with respiratory illness. Large number of patients with COVID-19 present with worsening of pre-existing CVD or develop new-onset cardiac dysfunction during course of the illness. Current knowledge of interplay between COVID-19 and CVD is inadequate. Future studies are warranted describing incidence, mechanisms, clinical presentation and outcomes of various CV manifestations in these patients. The COVID-19 pandemic has changed the world in unprecedented ways. In the absence of safe and effective treatment or vaccines for COVID-19, social distancing, wearing a face mask and frequent hand wash are the main strategy to combat the pandemic.

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