HEALTHY HEART

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Patients with COVID 19 infection and with cardiovascular disease are at increased risk of poor prognosis. This topic will address the potential impact of the COVID 19 virus on the Cardio vascular system. Cardiac injury, defined as elevated troponin, significantly relates to inflammation biomarkers (IL-6 and C-reactive protein (CRP), hyperferritinemia, and leukocytosis), portraying an important correlation between myo-cardial injury and inflammatory hype-ractivity triggered by viral infection. Increased risk for myocardial infarction, fulminant myocarditis rapidly evolving with depressed systolic left ventricle function, arrhythmias, venous thrombo-embolism, and cardiomyopathy mimicking STEMI presentations are the most prevalent cardiovascular compli-cations described in patients with COVID-19.

COVID-19 AND CARDIOVASCULAR DISEASE: FROM BASIC MECHANISMS TO CLINICAL PERSPECTIVES

IMPACT ON THE CARDIOVASCULAR SYSTEM

It is likely that COVID-19 directly and indirectly affects the cardiovascular system and the heart in particular. Potential mechanisms of cardiovascular injury have been identified and include direct myocardial injury from hemo-dynamic derangement or hypoxemia, inflammatory myocarditis, stress cardiomyopathy, micro vascular dysfunction or thrombosis due to hypercoagulability, or systemic inflammation (cytokine storm), which may also destabilize coronary artery plaques. Pneumonia and influenza infections have been associated with six fold increased risk of acute MI. Patients with severe COVID-19, such as those with high fever or hypoxia due to lung disease may need a significant increase in cardiac output. Type II myocardial ischemia; therefore, may result in patients with obstructive CAD.

ACUTE CORONARY SYNDROME

The term acute coronary syndrome (ACS) is applied to patients in whom there is a suspicion or confirmation of myocardial injury. ACS patients may have either STEMI or non-ST-elevation ACS, which includes NSTEMI or unstable angina.

The Fourth Universal Definition of MI includes a clinical classification according to the assumed proximate cause of the myocardial ischemia:

Type 1:

MI caused by acute atherothrombotic CAD and usually precipitated by athero-sclerotic plaque disruption (rupture or erosion).

Type 2:

MI consequent to a mismatch between oxygen supply and demand.

With COVID-19 infection, the majority of MIs are type 2 and related to the primary infection, hemodynamic, and respiratory derangement. As such, the primary

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disorders should be treated, and in most cases the patient can be treated conservatively with regard to coronary disease. If a type 1 infarction is thought to be the primary etiology of the MI, standard therapies of reperfusion can be considered.

Physicians report that there are fewer ACS patients presenting to the hospital during the pandemic. In addition, there is concern that patients with ACS are presenting later to emergency departments or not coming at all due to fear of exposure to patients with COVID-19. These patients will suffer unnecessary morbidity and mortality without proper ACS management.

ECG criteria are not specific for coronary artery thrombosis, particularly in COVID-19 patients in whom ST elevation may occur with stress cardio-myopathy or possibly myocarditis. Thus, non-coronary artery COVID-19 associated myocardial injury needs to be carefully considered as a diagnostic possibility before reperfusion therapy is considered.

FOR COVID-19 PATIENTS OR THOSE UNDER INVESTIGATION:

- In patients who are critically ill due to COVID-19 infection (like, acute respiratory distress syndrome or multiorgan failure), the decision of reperfusion therapy (with either primary PCI or fibrinolysis) should be considered on a case-by-case basis
- If the patient is not critically ill, attempt should be made for earliest reperfusion – either thrombolysis or Primary PCI as per the availability and feasibility

When deciding between primary PCI and fibrinolytic therapy, factors such as significant associated co morbidities and hospital resource limitations should be taken into account. For example, a patient with COVID-19 pneumonia with respiratory failure may not be an optimal candidate to reap the benefit of myocardial reperfusion, while a patient with suspected COVID-19 and mild or moderate infection is likely to benefit from myocardial salvage, and if the resources are available, then reperfusion should be performed despite the risk to providers and the resources required.

Irrespective of the initial reperfusion strategy, all STEMI patients should be treated with early aspirin, P2Y12 inhibitor, and anticoagulation. High-dose statin is started as soon as possible after the diagnosis.

ECHOCARDIOGRAPHY:

Findings on an echocardiogram that favor a condition other than ACS (like, stress cardiomyopathy, myocarditis, pericarditis or non-cardiac cause of chest pain) include:

- No wall motion abnormalities during chest pain
- Wall motion abnormalities not supportive of regional injury suggested by the ECG
- Wall motion abnormalities in a non-coronary distribution
- Less specific findings, such as small pericardial effusion

TROPONIN:

Cardiac troponin elevation is seen in about 10 to 30 percent of hospitalized COVID-19 patients and is associated with a higher mortality. Most patients with troponin elevation and COVID-19 do not have a clinical presentation suggestive of an ACS.

COVID-19 & HYPERCOAGULABILITY

There have been reports of increased incidence of thrombotic MI, thrombotic strokes, and arterial thrombosis during the pandemic. Alterations in the coagulation system, abnormal platelet function, or abnormal endothelial function all have been postulated in COVID 19 infection.

VIRCHOW'S TRIAD:

Hypercoagulability can be thought of in terms of Virchow's triad. All three of the major contributions to clot formation apply to severe COVID-19 infection:

- Endothelial injury – There is evidence of direct invasion of endothelial cells by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), potentially leading to cell injury
- Stasis – Immobilization can cause stasis of blood flow in all hospitalized and critically ill patients, regardless of whether they have COVID-19
- Hypercoagulable state – A number of changes in circulating prothrombotic factors have been reported or proposed in patients with severe COVID-19

How coagulation abnormality in COVID 19 is different from Disseminated Intravascular Coagulation (DIC)? - In COVID 19, there is no thrombocytopenia, Fibrinogen level and PT/INR remains normal and there is elevated D-dimer.

What is the recommendation of VTE prophylaxis in patients with COVID-19?

In the absence of data from randomized controlled clinical trials, a number of

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consensus guidelines and recommendations have been published to facilitate clinical decision-making on this issue. A common theme in all of the recommendations is to take an individualized approach to patient management.

Should COVID-19 patients receive post-discharge VTE prophylaxis?

Any decision to use post-discharge thromboprophylaxis should consider the individual patient's VTE risk factors at the time of discharge, including reduced mobility and bleeding risk.

CDC and societal recommendations regarding anticoagulation on discharge:

Recommendations regarding anticoagulation on discharge

CDC and societal recommendations regarding thrombotic prophylaxis and treatment in COVID-19:

VTE prophylaxis regimen and preferred medications		Therapeutic Anticoagulation Regimens and Preferred Medications
CDC	LMWH or UFH (Standard dosing) Insufficient data to recommend for or against the increase of anticoagulation intensity outside of a clinical trial.	Standard regimens for Non-COVID 19 patients.
ISTH-IG	LMWH (standard dosing)	Not Mentioned
ACF	Suggests an increased intensity of venous thromboprophylaxis be considered for critically ill patient (ie. LMWH 40 mg SC twice daily, LMWH 0.5 mg/kg subcutaneous twice daily, heparin 7500 SC three times daily, or low-intensity heparin infusion) that they state is based largely on expert opinion.	LMWH over UFH whenever possible to avoid additional laboratory monitoring, exposure and personal protective equipment. In patients with AKI or creatinine clearance < 15-30 mL/min, UFH is recommended over LMWH.
ASH	LMWH over UFH (standard dosing) to reduce exposure unless risk of bleeding outweighs risk of thrombosis.	LMWH or UFH over direct oral anticoagulants due to reduced drug- drug interactions and shorter hald-life.
ACCP	LMWH (standard dosing)	LMWH or fondaparinux over UFH. UFH preferred in patients at high bleeding risk and in renal failure or needing imminent procedures. Recommend increasing dose of LMWH by 25-30% in patient with recurrent VTE despite therapeutic LMWH anticoagulation.
SCC-ISTH	LMWH or UFH, Intermediate intensity LMWH can be considered in high risk critically ill patient (50% of responders) and may be considered in non-critically ill hospitalized patient (30% of respondents). Mentions that there are several advantages of LMWH over UFH including once vs twice or more injections and less heparin-induced thrombocytopenia. Regimens may be modified base on extremes of body weight (50% increase in dose if obese). severe thrombocytopenia, or worsening renal function.	Not mentioned

CDC and societal recommendations regarding thrombotic prophylaxis and treatment in COVID-19:

VTE prophylaxis regimen and preferred medications		Therapeutic Anticoagulation Regimens and Preferred Medications
ACC	Enoxaparin 40 mg daily or similar LMWH regimen (i.e. dalteparin 5000 u daily) can be administered with consideration of SC heparin (5000 u twice to three times per day) in patient with renal dysfunction (i.e, creatinine clearance <30 mL/min). Once daily regimens of LMWH may be advantageous over UFH to reduce missed doses associated with worse outcomes, reduce healthcare worker exposure, and conserve personal protective equipment. There is insufficient data to consider routine therapeutic or intermediate dose parenteral anticoagulation with UFH or LMWH. Only a minority of the panel considered intermediate intensity (31.6% i.e. enoxaparin 1 mg/kg/day, enoxaparin 40 mg BID, UFH with target PTT 50-70) to therapeutic anticoagulation (5.2%) reasonable.	Medication regimen likely to change depending on co-morbidities (i.e. renal or hepatic dysfunction, gastrointestinal function, thrombocytopenia). Parenteral anticoagulation (i.e. UFH) may be preferred in many ill patients given it may be withheld temporarilly and has no know drug-drug interactions with COVID-19 therapies. LMWH may be preferred in patients who are unlikely to need procedure as there are concerns with UFH regarding the time to achieve therapeutic PTT and increased exposure to healthcare workers. DOACs have advantages including lack of monitoring that is ideal for outpatient management but may have risk in settings of organ dysfunction related to clinical deterioration and lack of timely reversal at some centers.

Recommendations Regarding Anticoagulation on Discharge

CDC : Routine venous thromboprophylaxis post-discharge is not recommended. FDA-approved prophylactic anticoagulation regimen (rivaroxaban and betrixaban) can be considered if high risk for VTE and low risk for bleeding using criteria from clinical trials.

ISTH-IG : No specific recommendations

ACF : No evidence for anticoagulation beyond hospitalization, but reasonable to consider if low risk for bleeding and high risk for VTE including intubated, sedated, and paralyzed for multiple days.

ASH : Reasonable to consider FDA-approved post discharge prophylactic anticoagulation regimen (rivaroxaban and betrixaban) or aspirin if criteria from trials for post-discharge thrombo-prophylaxis s are met.

ACCP : Can be considered in patients who are at low risk of bleeding if emerging data suggests a clinical benefit.

SCC-ISTH : Either LMWH or FDA-approved post discharge prophylactic anti-coagulation regimen (rivaroxaban and betrixaban) should be considered in patient with high VTE risk criteria. Duration is 14 days at least and up to 30 days. recommended aspirin for post-discharge thromboprophylaxis.

ACC : Reasonable to consider extended prophylaxis with LMWH or DOACs for up to 45 days in patients at high risk for VTE (i.e., D-dimer > 2 times the upper limit, reduced mobility active cancer) and low risk of bleeding.

STATIN IN COVID-19

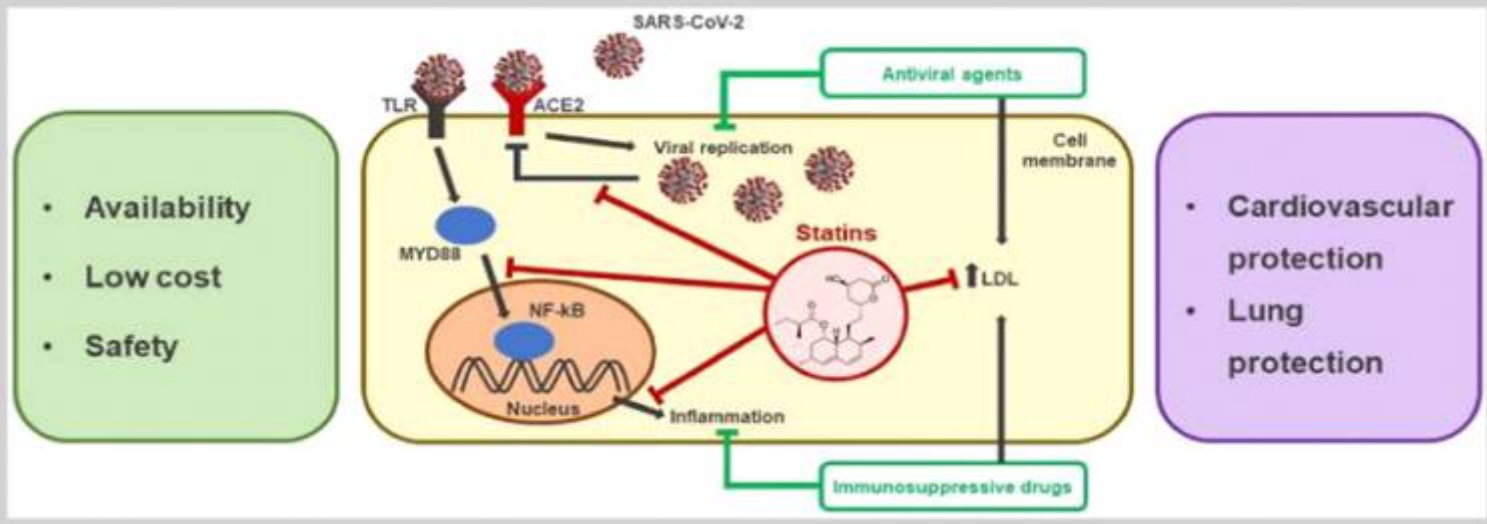
Besides their lipid-lowering activity, statins exert pleiotropic effects on inflammation and oxidative stress, contributing to their beneficial impact on cardiovascular diseases. Statins modulate the immune response at different levels, including immune cell adhesion and migration, antigen presentation, and cytokine production. Moreover, they restore the vascular redox balance by reducing reactive oxygen species and increasing antioxidants, and ameliorate nitric oxide bioavailability, endothelial function, and integrity. Most of these effects depend on statin-mediated inhibition of the production of isoprenoids, which are fundamental constituents of small GTPases (such as Ras, Rho, and Rac), and on consequential

down-regulation of redox-sensitive proinflammatory transcriptional factors such as NF-κB.

Statins also interfere with ACE2 signaling. After initial entry through ACE2, SARS-CoV-2 down-regulates ACE2 expression, possibly facilitating the initial infiltration by innate immunity cells and causing an unopposed angiotensin II accumulation, leading to organ injury.

In conclusion, statins are low-cost, extensively tested, well-tolerated drugs that are less likely to be affected by a shortage in a health crisis such as the current COVID-19 pandemic.

Molecular mechanism of actions and proposed advantages of statin in COVID-19



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CASE PRESENTATION
Successful COVID-19 Care Outcomes in a 90 Year Old Male Patient at CIMS

Background:

Severe acute respiratory syndrome (SARS)-CoV-2, is responsible for the COVID 19 pandemic that is affecting human health and economy across the world[1,2]. Older adults more so males with co-morbidities and individuals with complex underlying health conditions suffer the severest COVID-19 outcomes in terms of complications and higher mortality rates. Evidence suggests that advanced age is the most important predictor for fatal outcome.

We detail here clinical course of a male aged, 90 years with co morbidities who was well treated and recovered from COVID–19 at CIMS.

Case Presentation:

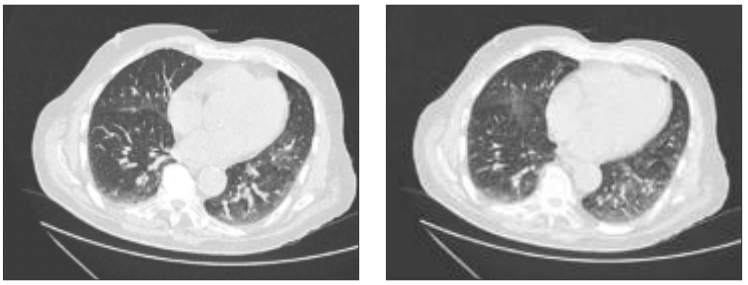
A 90-year-old (corrected age: 90 years and 9 months) gentleman (nonagenarian), known case of hypertension (on regular medications) and peripheral neuropathy, had complaints of cough, weakness, low grade fever and headache since last 4-5 days. Report of RT- PCR for COVID-19 was positive. The gentleman had no history of travel or close contact with a patient suspected of or diagnosed with severe acute respiratory syndrome (SARS).The patient was hospitalized at Care Institute of Medical Sciences (CIMS hospital), Ahmedabad, Gujarat, India under CIMS COVID Care Group.

On admission, the patient was awake and alert with a temperature of 99.8° Fahrenheit, blood pressure of 138/86 mmHg, pulse rate of 64 beats per minute, respiratory rate of 21 cycles per minute, and pulse oxygen saturation of 97% on room air.

A multi-slice high resolution computed tomography (HRCT) scan showed few patchy areas of ground glass densities with interstitial septal thickening seen through it (s/o crazy paving pattern) in bilateral lungs with peripheral predominance and CT severity score was 3 out of 40 (Figure 1). Findings were suggestive of typical Covid-19 pneumonia; CORAD: 6 - PCR positive. Blood investigations including inflammatory markers for Covid -19 were also performed.

The patient was isolated and treatment was started as per Indian council of medical research (ICMR) guidelines for COVID 19.

Figure 1:
Images of High Resolution Computed Tomography (HRCT)



Initial testing revealed D-Dimer -737.40 ng/ml, along with slight elevated levels of Troponin – T (0.022 ng/ml).Aspartate aminotransferase and alanine aminotransferase, C - reactive protein (CRP) 2.24 mg/dl, Ferritin 257 ng/ml, Lactate Dehydrogenase (LDH) 159 u/l, Bilirubin and Urea 31.0 mg/dl were within normal range (Table 1).

Table 1: Laboratory Investigations

Lab Parameters	Day-1	Day-4	Normal Range
Hemoglobin	13.7	14.6	13.5 - 18.0 g/dl
Total count	3990	3710	400 - 10500 /Cmm
Polymorphs	54	46	22-45 %
Lymphocytes	33	46	01-04 %
Eosinophil's	02	01	01-04%
Monocytes	01	07	01-06%
Platelet count	109000	114000	150000-450000/Cmm
C - reactive protein (CRP)	2.24	2.34	0-5 mg/L
D-Dimer	737.40	431.70	0-500 ng/ml
Ferritin	257	598.4	30-400 ng/ml
Sodium (Na+)	124	136	136-145 mmol/L
Potassium (K+)	3.68	3.87	3.50-5.10 mmol/L
Creatinine	1.12	0.95	0.7-1.2 mg/dL
SGPT	8.7	9.7	0-41 U/L
SGOT	12.4	--	0-41 U/L
Alk. Phosphatase	42.7	--	40-129 U/L
T. Protein	6.56	--	6.4-8.3 gm/dl
Albumin	3.67	--	3.97-4.95 gm/dl
Globulin	2.91	--	2.2-3.5 gm/dl

Treatment :

Inj. Remdisivir 200 mg for 1 day and subsequently 100 mg for 4 days, Inj Clexane 60mcg SC Od for 5 days, Tab Zincovit, Tab Vit -C and other supportive medications for treatment of pneumonia were started. SpO2 was maintained between 96% - 99%

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