NOMENCLATURE OF THE NOVEL CORONAVIRUS

- Since early December 2019, a novel coronavirus has caused an outbreak of pneumonia in China, killing over 2000 people and infecting over 77000 people by February 23, 2020[1].
- The World Health Organization (WHO) recently dubbed the disease caused by this new coronavirus as "CoronaVirus Disease 2019" (covid-19).
- The new virus has been given the name "Severe Acute Respiratory Syndrome Coronavirus 2" by the International Committee on Virus Taxonomy (ICTV) (SARS COV-2).
- However, various academic and professional sources have raised concerns about whether the nomenclature is acceptable because of the lack of agreement for a Chinese Medical Journal Invented by Chinese scientists, Epidemiologists, and virologists to participate.

The president of Asian-pacific biosafety Association, Chief Bio safety specialists of the Chinese center for disease control and prevention and director of the National Institute for Viral Disease Control and Preventions Biosafety Research Centre was Gui-Zhen WU

COMMENTS:

According to Scientific Inventions any new Virus or associated diseases can be named by expert consensus while considering existing public knowledge about the disease.

- However, naming the new coronavirus scope is difficult. For starters, it may be misleading, particularly to people who are unfamiliar with virology.
- Alternatively, the current coronavirus may be given a name that corresponds to the original name (covid-19).
- For example, human coronavirus 1, which is identical to the naming of the Influenza Virus Subtype A/H1N1/2009, pdm, can be distinguished based on the year of discovery.

The professor at Institutes of Biomedical Sciences and Shanghai Public Health Clinical Center, Fundan University. Director of Shanghai Institute of Emerging and Re-Emerging Infectious Disease and Director of school of translational Medicines at Shanghai Public Health Clinical centre, Fundan University was Jian-Qing XU.

COMMENTS:

- The genomic sequence of the two corona viruses are similar, the ICTV has recently proposed that the current coronavirus will be SARS-COV-2 (approximately 80% homogeneity).
- Furthermore, both this latest coronavirus and the Sa score of 2003 have a pathogenesis that affects the respiratory system.

- The new coronavirus should be given its own name instead of SARS-COV-2, we propose that the virus be dubbed human coronavirus 2019 (HCOV-19). The name HCOV-19 distinguishes the new virus from SARS-COV and corresponds to the disease's name, COVID-19.

The professor and vice President of Chinese academy of medical sciences and pecking medical college was Jain-Wei Wang. He is also the director of the Christophe Merieux laboratory.

COMMENTS:

- When it comes to pathogenicity and natural host, the latest coronavirus falls somewhere in the middle, but shares more similarities with the latter, so we propose calling it 2019 acute respiratory syndrome coronavirus (SARS-COV).
- SARS-COV is a new coronavirus that can be identified by its SARS- COV and it is distinct from human coronavirus[1].

MECHANISM OF ACTION FOR COVID-19:

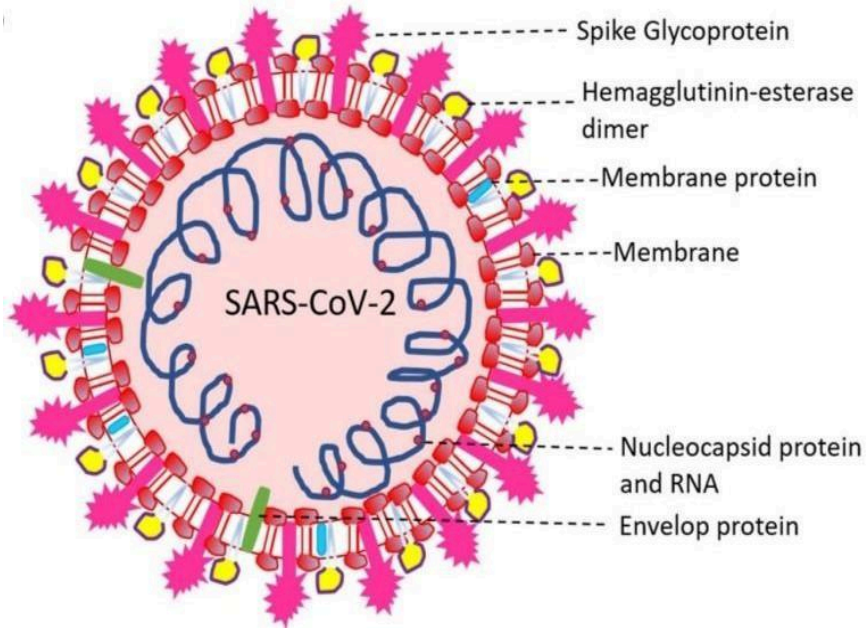


Figure. 1 (Structure of covid 19)

- The genome of the corona virus is ~30,000 nucleotides long. It encodes four structural proteins- Nucleocapsid (N), Membrane (M), Spike (S) and Envelope (E), as well as a number of non-structural proteins (nsp) [2].
- The nuclear capsid or N-protein is attached to the virus' single positive strand RNA that enables the virus to hijack human cells and convert them into virus factories.

- The N-protein coats the viral RNA genome and plays a vital role in its replication and transcription.
- The N-terminal of the N-protein, as well as single positive RNA strand, can prevent viral replication and transcription.
- The M-protein is most abundant on the viral surface and is thought to be the corona virus's central organizer.
- The S-protein is integrated onto the surface of the virus, allowing the virus to bind to the host cell surface receptors and fuse with them.
- The E-protein is a small membrane protein with 76 to 109 amino acids that is a minor component of virus particles. It is involved in virus assembly, host cell membrane permeability, virus host cell interaction.
- A lipid envelope encases the genetic material, and the HE found on the viral surface.
- Although the HQ protein is not necessary for viral replication, it appears to be essential for infection of the natural host cell[2].

PATHOPHYSIOLOGY:

THE VIRAL LIFE CYCLE AND HOST CELL INVASION

Virus transmission is by respiratory droplets and aerosols from person to person.

⇩

Inside the body, the virus binds to the host receptors and enters the host cells through endocytosis membrane fusion.

⇩

The corona virus is made up of four structural proteins, namely, the spike (S), membrane (M), envelop (E) and nucleocapsid (N) protein

⇩

S protein protruding from the viral surface one for host attachment & penetration.

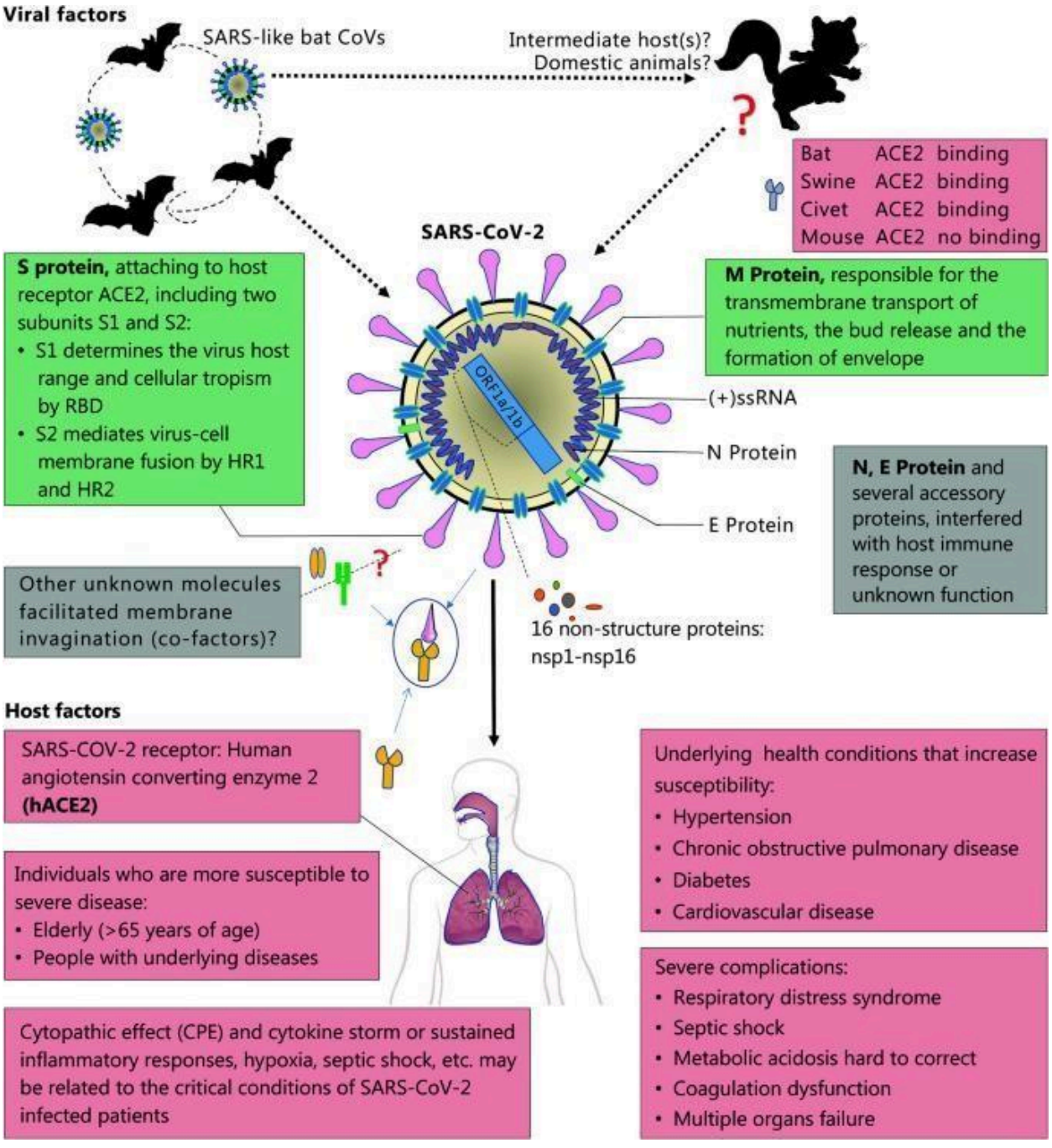


Figure. 2 (Life cycle of SARS -2)

- The Spike protein is made up of three similar chains of 1273 amino acids each as well as t wo well defined protein domain regions, the S1 and S2 subunits, which are involved in cell

recognition and membrane fusion, respectively. The latter occurs as a result of various protein conformational modifications that are still unknown.

- The coronavirus spike protein binds to Angiotensin Converting Enzyme 2(ACE 2) receptors on the surface of many human cells, including those in the lungs, allowing virus entry. The coronavirus spike protein is then cleaved by host proteases. (Trypsin and Furin) in 2 sites (S1/S2 site) at the boundary between S1 and S2 sub-units.

- At a later point, the S2 Domain area cleaved in order to release the fusion, this event would cause the activation of the membrane fusion mechanism, searching for antibodies will find help on molecular targeting, which can use the structural information of the binding site region contained in the ACE 2 receptor to devise a treatment to block viral entry. In this way, this procedure could devise a treatment to block viral entry.

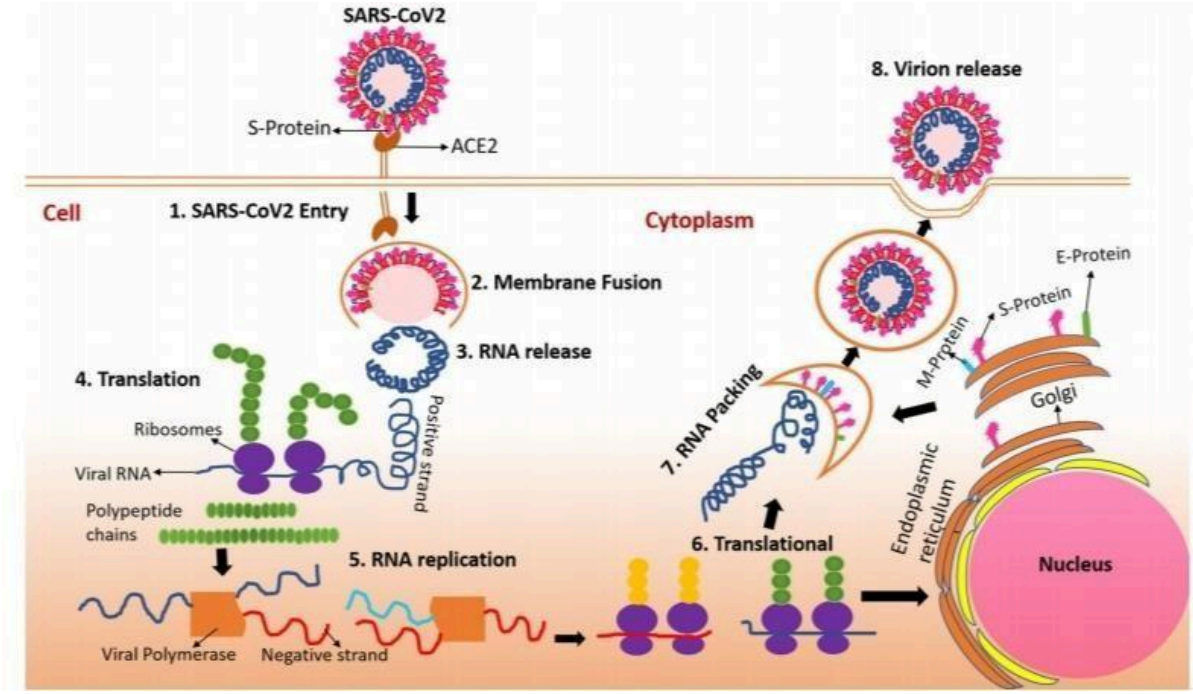


Figure. 3 (Pathophysiology of SARS -2)

- Covid-19 uses a 3-step process for membrane fusion that involves receptor binding and induced conformational changes in spike glycoprotein, followed by cathepsin L proteolysis by intracellular proteases and activation of membrane fusion mechanism within the endosome.

- The Endosome then opens releasing the virus into cytoplasm and the viral nucleocapsid is uncoated by proteasomes but can also degrade exogenous proteins like SARS nucleocapsid protein[2].

EPIDEMIOLOGY:

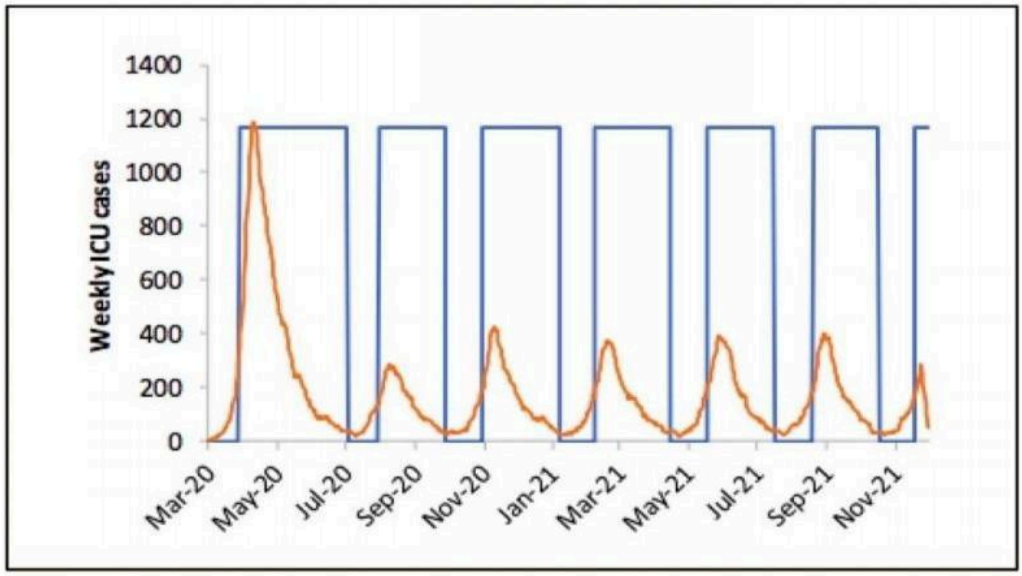


Figure. 4 (Epidemiology of SARS-2)

- A novel coronavirus (SARA-COV-2) has been linked to a human outbreak of serious respiratory infections. That began on December 31, 2009[3].
- As of July 18, 2020, there had been 13,87642 confirmed cases in 216 countries, with 5,93,087 deaths.
- Community transmission has been registered in 92 countries worldwide. There had been clusters of cases in 75 countries including India.
- The majority of them are initially recorded and had a travel history of Wuhan, China. Later countries such as Thailand, Singapore, South Korea, Japan, the US and France, reported covid-19 cases. The majority of the cases in the initial phases are between the ages of 30 and 60 years old (78%) and male (58%) [3].

COURSE OF DISEASE:

- According to the WHO, the average time from infection to symptom presentation is 2 to 5 days, with a range of 1-14 days[4].
- Additionally, the average time from symptom presentation to seeking medical advice is 5- 8 days, and the average time from symptom presentation to hospital admission is 12-15 days.
- The phases of the disease have been identified based on CT scan results after onset of symptoms.
- Early (0-4 days), Progressive (5-8 days), Peak (9-13 days) and absorption stages >14 days.

- Subpleural ground glass opacities (GGO) in the lower lung lobes.

CLINICAL PRESENTATION (SIGNS AND SYMPTOMS):

- The severity of clinical symptoms will differ between individuals, according to the Chinese center per disease control and prevention. 81% cases were classified as moderate (Non-pneumonia) or Mild (Pneumonia). 14% were serious, resulting in dyspnea, blood O2 saturation <93%.

- Partial pressure of arterial O2 to fraction of Inspired O2 ratio with respiratory frequency >30 minutes. Others like fever (92.8% n=258) dyspnea (34.5% n=96), Myalgia (27.7% n=77), Cough (69.8% n=194), Headache (72% n=20), Rhinorrhea (4.0%), a sore throat (5.1%), Pharyngalgia (17.4%), Diarrhea (6.1% n=17).

MANAGEMENT:

PREVENTION:

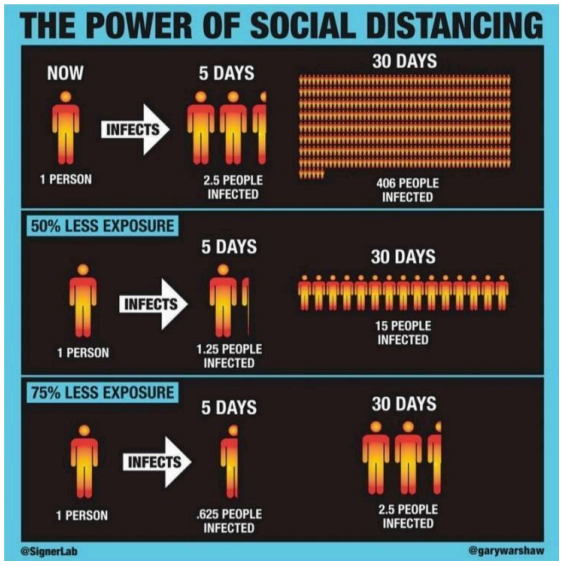
- Transmission amplification incidence should be avoided by limiting human-human transmission. As the resources are currently in short supplies.

- Personal protective equipment use should be carefully considered. Surgical mask is used widely in particular the general population.

- If an infected person has been detected prompt isolation and provision of optimal treatment should be offered. Suspicious patients should also give a medical mask and put in an isolation room if one is available.

NPI provide straight isolation and distancing steps such as:

Figure. 5 (Power of social distancing)



- Case isolation at home, Voluntary home quarantine.
- Physical distance for those who are at the age of 70.
- Physical distance for the whole community, Schools and University closures.

SUPPORTIVE MANAGEMENT:

- HR, RR and SPO2 are important measurements to keep track of.
- If the mother is COVID-19 Positive, Neonatal feeding should be considered, Medical Management and care are needed for symptomatic neonates and for adults with moderate infection, which is usually characterized by an uncomplicated illness in the absence of SARI.

INTRAVENOUS (IV) FLUID ADMINISTRATION:

- In patients with SARI who do not appear to be in shock, use conservative fluid control.
- When it comes to IV fluids, read the labels carefully because vigorous recitation can have a n effect on oxygenation when mechanical ventilation is minimal.

OXYGEN THERAPY:

- If the person has SARI, Hypoxemia or Shock should start supplemental oxygen therapy right away.
- In non-pregnant adults, administer O2 therapy at a rate of 5L/minute to achieve a minimum SPO2 of at least 90% (over 92% in pregnant patients).

INVASIVE MECHANICAL VENTILATION:

According to a review by king's college hospital, NHS trust as well as guidelines issued by the WHO conclude that severe cases require mechanical ventilation and may benefit from the following principles:

- Usage of low tidal volume [(4-8 ml/kg predicted body weight (PBW)] and target plateau pressure <30cm. H20 (28 cmH20 in children).
    1) Adults: Initial Tidal Volume 6 ml/kg PBW, (may be increased to 8 ml/kg PBW if initial tidal volume is not tolerated).
    2) Children: Target tidal volume 3-6 ml/kg PBW (may be increased to 5-8 ml/kg PBW in cases with well-preserved respiratory compliance)

- The titration of positive end-expiratory pressure (PWP) should be guided by the fraction of inspired oxygen (FiO2) to achieve desired arterial oxygen saturation (SPO2).
- Early airway pressure release ventilation should be considered in some patients.
- Consideration of early prone ventilation where there is no instrument observed after 12 hours of ventilator optimization. Prone ventilation should last 12 to 16 hours a day.
- **FLUID RESUSCITATION AND VASOPRESSORS:**

ADULTS- Fluid resuscitation should be administered as 250-500ml crystalloid fluid boluses over 15-30 minutes followed by assessment for fluid overload after each bolus.

- Vasopressors can be used if septic shock persists despite fluid resuscitation to maintain a mean arterial pressure > 65mmHg.
- Norepinephrine is a drug of choice which can be supplemented by epinephrine or vasopressin to maintain MAP targets.

CHILDREN- Fluid resuscitation should be administered as 10-20 ml/kg crystalloid fluid boluses over 30-60 minutes followed by assessment for fluid overload after each bolus.

- Epinephrine is a drug of choice with nor-epinephrine supplementation if septic shock persists.

MANAGEMENT OF CRITICAL COVID-19:

- Admission to ICU: With 5% of all COVID-19 cases becoming seriously or critically unwell and 20-30% of hospitalized patients requiring intensive care support.
- Subjects with failing standard oxygen therapy are required to get advanced oxygen therapy or ventilator support.
- Hospital admissions are immense with healthcare systems worldwide, NICE has published an algorithm to ensure appropriate ICU admissions.
- Decisions must be communicated with the patient when possible and their family, careers and independent mental capacity advocate, if appropriate.

NON-INVASIVE VENTILATION (NIV):

- Initial reports did not favor the use of NIV in COVID-19, over fears of large tidal volumes and high transpulmonary pressure which causes lung damage.
- NIV methods – continuous positive airway Pressure (CPAP) or Bi-level Positive Airway Pressure (BiPAP) were also not recommended as they are aerosol- generating medical procedures and therefore increase the risk of spread of COVID-19.

- National Health Service (NHS) England has specified that CPAP Should be used for hypoxemic respiratory failure and BiPAP for hypercapnic states in cases of acute or chronic respiratory failure.

Endotracheal intubation:

If endotracheal intubation is deemed appropriate, the WHO recommends endotracheal intubation to be performed by experienced clinician using protective equipment[4].

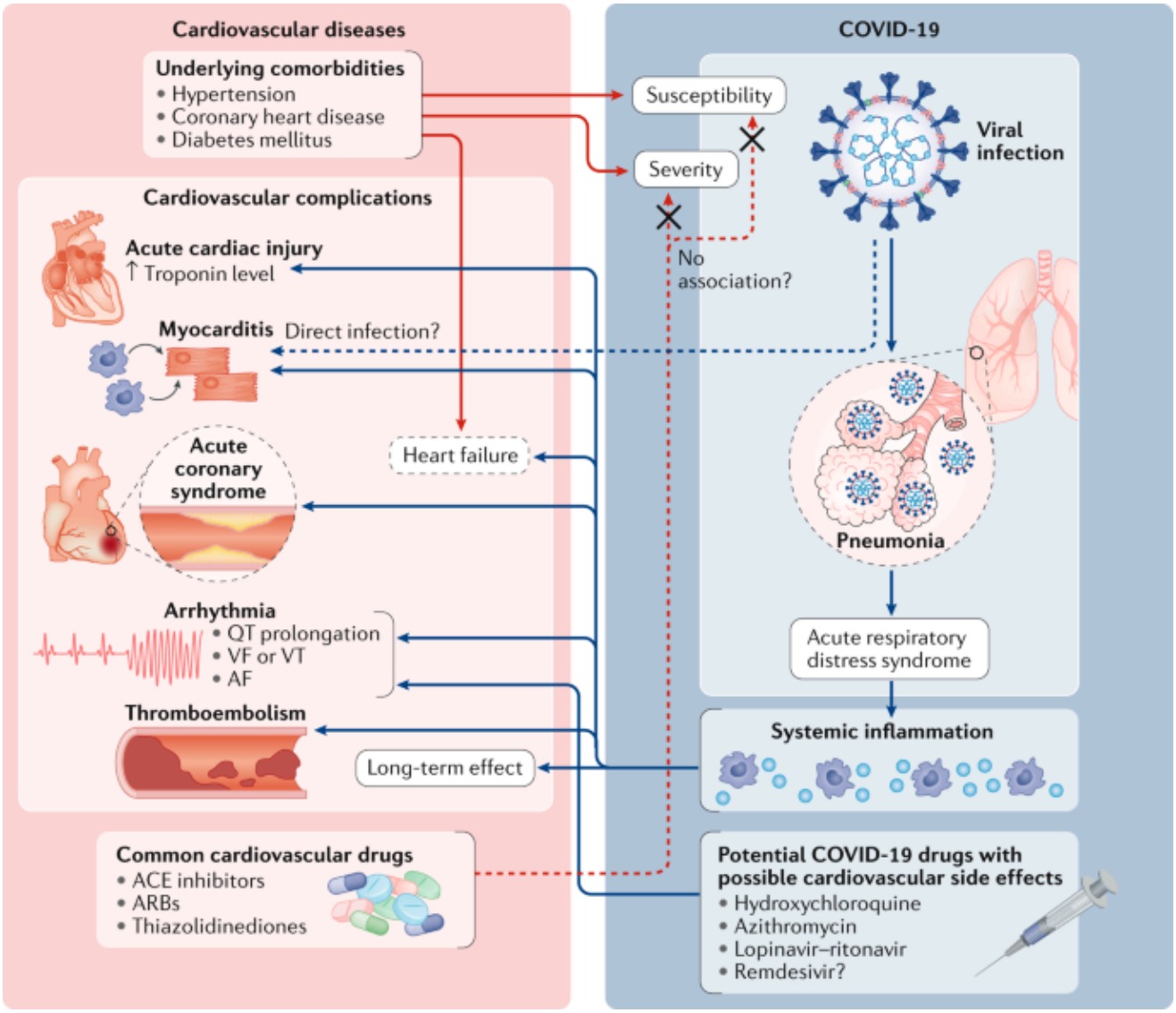


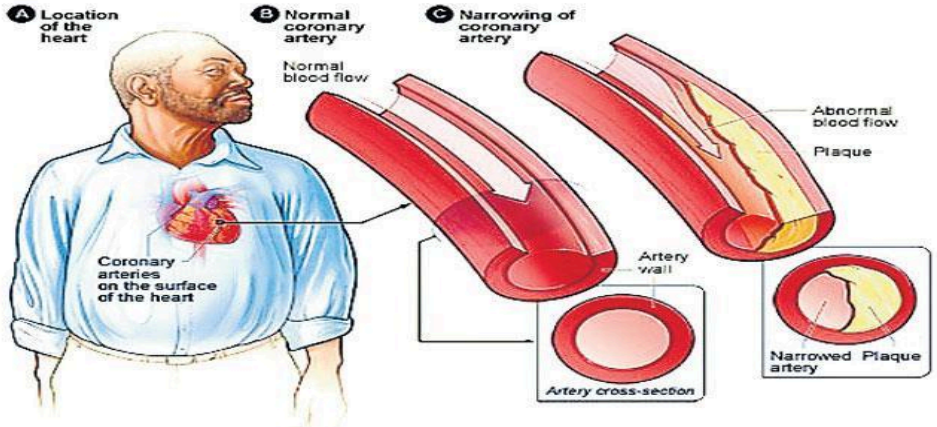
Figure. 6

CORONARY ARTERY DISEASE

Coronary Artery Disease (CAD) also described as Coronary Heart disease (CHD) or Ischemic Heart Disease (IHD), is a condition in which the vascular supply to the heart is impeded by atheroma, thrombosis or spasm of coronary arteries. This may impair the supply of oxygenated blood to cardiac tissue sufficiently to cause myocardial ischemia which, if severe or prolonged, may cause the death of cardiac muscle cells.Similarities in the development of atheromatous plaques in other vasculature, in particular the carotid arteries, with the resultant cerebral ischemia has resulted in the term CVD being adopted to incorporate CHD, cerebrovascular disease, and peripheral vascular disease.

Myocardial ischemia occurs when the oxygen demand exceeds myocardial oxygen supply. The resultant ischemic myocardium releases adenosine, the main mediator of chest pain, by stimulating the A1 receptors located on the cardiac nerve endings. Myocardial ischemia may be 'silent' if the duration is of insufficient length, the afferent cardiac nerves are damaged (as with diabetics) or there is inhibition of the pain at the spinal or supraspinal level. It may occur in patients with thyrotoxicosis or severe ventricular hypertrophy due to hypertension. Myocardial oxygen supply is dependent on the luminal cross-sectional area of the coronary artery and coronary arteriolar tone. Atheromatous plaques decrease the lumen diameter and, when extensive, reduce the ability of the coronary artery to dilate in response to increased myocardial oxygen demand.

Ischemia may also occur when the oxygen-carrying capacity of blood is impaired, as in iron deficiency anemia, or when the circulatory volume is depleted. CHD kills over 6.5 million people worldwide each year.



A diagram showing how high cholesterol could lead to coronary heart disease where plaque builds up in your arteries reducing blood flow.

Figure. 7

EPIDEMIOLOGY:

Almost 200,000 people die from CVD in the UK each year with CHD accounting for almost a half of these. About 30% of premature deaths (below 75 years old) in men and 22% of premature deaths in women result from CVD.

PREVALENCE:

Women appear less susceptible to CHD than men, although they seem to lose this protection after menopause, presumably because of hormonal changes. Race has not proved to be a clear risk factor since the prevalence of CHD seems to depend much more strongly on location and lifestyle than on ethnic origin or place of birth. It has been shown that lower social or economic class is associated with:

- Increased obesity
- Poor cholesterol indicators
- Higher blood pressure
- Higher C-reactive protein (CRP) measures an indicator of inflammatory activity.

RISK FACTORS:

Modifiable Risk Factors:

- Hypertension
- Cigarette smoking
- Raised serum cholesterol
- Diabetes
- Psychological Stress
- Abdominal Obesity

Patients with a combination of all these risk factors are at risk of suffering a myocardial infarction some 500 times greater than individuals without any of the risk factors. Stopping smoking, moderating alcohol intake, regular exercise and consumption of fresh fruit and vegetables were associated independently and additively with reduction in the risk of having a myocardial infarction.

Non-Modifiable Risk Factors:

- Age
- Gender
- Race
- Family history

A family history of CHD is a positive risk factor, independent of diet and other risk factors. Hostility, anxiety, or depression are associated with increased CHD and death, especially after myocardial

infarction when mortality is doubled by anxiety and quadrupled by depression.

Box 20.1 Factors that increase or decrease the risk of developing CHD

Factors that increase the risk of CHD
Cigarette smoking
Raised serum cholesterol
Hypertension
Diabetes
Abdominal obesity
Increased personal stress

Factors that decrease the risk of CHD
Regular consumption of fresh fruit and vegetables
Regular exercise
Moderate alcohol consumption
Modification of factors that increase the risk of CHD

Figure. 8

AETIOLOGY:

- Plaque a combination of cholesterol, fat and other substances starts to stick to the walls lining your blood vessels. It builds up over time, which makes arteries become harder and narrower called Atherosclerosis.
- In some cases, plaque can break or rupture. Without enough oxygen, the heart can become weaker. This can lead to an irregular heartbeat (arrhythmia).
- It can also cause heart failure, which means the heart can't pump enough blood throughout the body to meet the body's needs. If a plaque grows so large that it stops blood flow to the heart muscle, you could have a heart attack.

Table 20.1 Effect of interventions on risk of myocardial infarction

Intervention	Control	Benefit of intervention
Stopping smoking for ≥5 years	Current smokers	50–70% lower risk
Reducing serum cholesterol		2% lower risk for each 1% reduction in cholesterol
Treatment of hypertension		2–3% lower risk for each 1 mmHg decrease in diastolic pressure
Active lifestyle	Sedentary lifestyle	45% lower risk
Mild to moderate alcohol consumption (approx. 1 unit/day)	Total abstainers	25–45% lower risk
Low-dose aspirin	Non-users	33% lower risk in men
Postmenopausal oestrogen replacement	Non-users	44% lower risk

The quality of data associated with these interventions varies greatly and figures may not apply to all patient groups.

Figure. 9(Effect of interventions on risk of MI)

PATHOPHYSIOLOGY:

The hallmark of the pathophysiology of CAD is the development of atherosclerotic plaque. Plaque is a build-up of fatty material that narrows the vessel lumen and impedes the blood flow. The first step in the process is the formation of a "fatty streak."

Fatty streak is formed by subendothelial deposition of lipid-laden macrophages, also called foam cells.

When a vascular insult occurs, the intima layer breaks, and monocytes migrate into the subendothelial space where they become macrophages. These macrophages take up oxidized low-density lipoprotein (LDL) particles, and foam cells are formed.

T cells get activated, which releases cytokines only to aid in the pathologic process. Growth factors released activate smooth muscles, which also take up oxidized LDL particles and collagen and deposit along with activated macrophages and increase the population of foam cells. This process leads to the formation of subendothelial plaque.

Over time, this plaque could grow in size or become stable if no further insult occurs to the endothelium. If it becomes stable, a fibrous cap will form, and the lesion will become calcified over time.

As time passes, the lesion can become hemodynamically significant enough that not enough blood would reach the myocardial tissue at the time of increased demands, and angina symptoms would occur. However, symptoms would abate at rest as the oxygen requirement comes down. For a lesion to cause angina at rest, it must be at least 90% stenosed.

Some plaques can rupture and lead to exposure of tissue factor, which culminates in thrombosis. This thrombosis could cause subtotal or total occlusion of the lumen and could result in the development

of acute coronary syndrome (ACS) in the form of unstable angina, NSTEMI, or STEMI, depending on the level of insult.

Classification of coronary artery disease is typically done as under:

1. Stable ischemic heart disease (SIHD)
2. Acute coronary syndrome (ACS):
3. ST-elevation MI (STEMI)
4. Non-ST elevation MI (NSTEMI)
5. Unstable angina

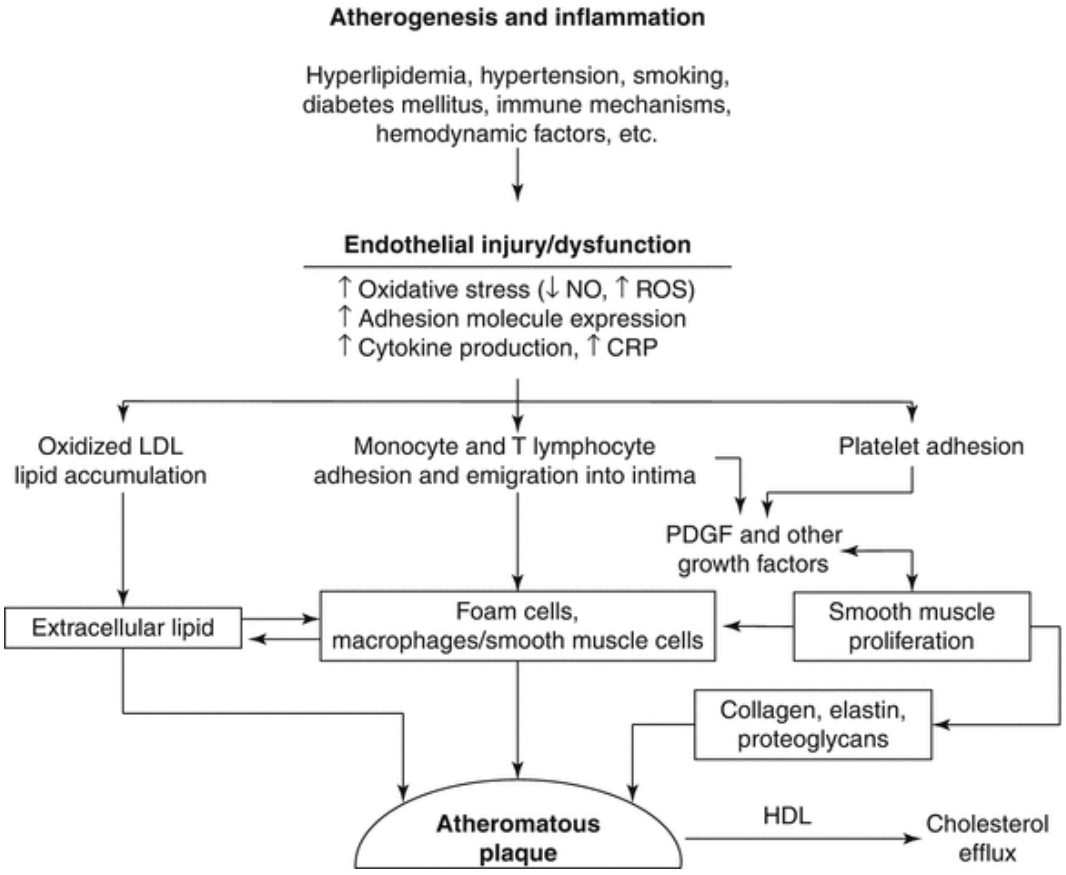


Figure. 10(Atherogenesis and inflammation)

CLINICAL SYNDROMES:

The primary clinical manifestation of CHD is chest pain.

Chest pain arising from stable coronary atheromatous disease leads to stable angina and normally arises when narrowing of the coronary artery lumen exceeds 50% of the original luminal diameter.

Stable angina is characterised by chest pain and breathlessness on exertion; symptoms are relieved promptly by rest. These patients are at high risk of myocardial infarction and death and require prompt hospitalisation.

A stable coronary atheromatous plaque may become unstable as a result of either plaque erosion or rupture. Exposure of the subendothelial lipid and collagen stimulates the formation of thrombus which causes sudden narrowing of the vessel.

Many aspects of the treatment of stable angina and ACS are similar but there is a much greater urgency and intensity in the management of ACS.

STABLE ANGINA:

Stable angina is a clinical syndrome characterised by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitro-glycerine.

The discomfort occurs after a predictable level of exertion, classically when climbing hills or stairs, and resolves within a few minutes of resting.

Many patients mistake the discomfort for indigestion. Some patients, particularly diabetics and the elderly, may not experience pain at all but present with breathlessness or fatigue; this is termed silent ischaemia.

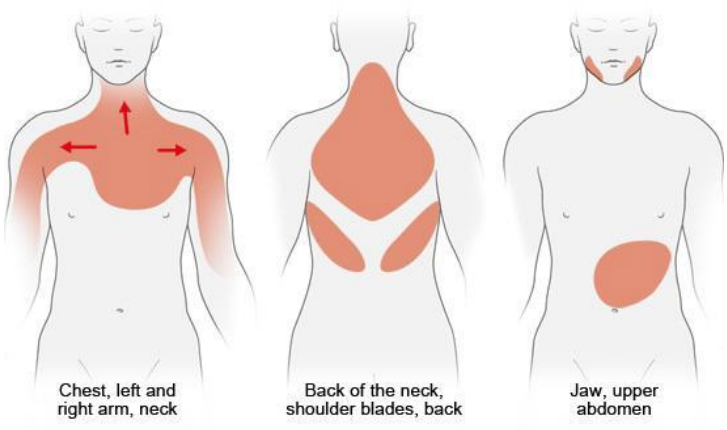


Figure. 11(Angina)

CAD is a chronic disease. Someone may first notice that they have it after experiencing angina symptoms, but CAD can also cause a heart attack without any previous symptoms. Sometimes a heart attack might even go unnoticed. This is known as a silent heart attack. People who have nerve damage due to diabetes, for example, might not feel the typical symptoms of a heart attack.

There are four grades of severity:

Grade	Severity of symptoms
Grade 1	Chest pain only in response to sudden physical or emotional strain, but not during basic everyday activities like walking or climbing stairs.
Grade 2	Chest pain during more intense activities like walking quickly, walking uphill and climbing stairs after eating, when it is cold or when also emotionally stressed.
Grade 3	Chest pain even during low-intensity physical exertion like walking or getting dressed.
Grade 4	Chest pain when at rest or during slightest physical exertion.

Table. 1(Severity of symptoms)

DIAGNOSIS:

Coronary angiography is regarded as the gold standard for the assessment of CAD and involves the passage of a catheter through the arterial circulation and the injection of radio-opaque contrast media into the coronary arteries.

The X-ray images obtained permit confirmation of the diagnosis, aid assessment of prognosis and guide therapy like angioplasty or coronary artery bypass grafting.

- **Electrocardiogram (ECG or EKG):** This quick and painless test measures the electrical activity of the heart. It can show how fast or slow the heart is beating.
- **Echocardiogram:** This test uses sound waves to create pictures of the beating heart. An echocardiogram can show how blood moves through the heart and heart valves. This may be a sign of coronary artery disease or other conditions.
- **Exercise stress test:** If signs and symptoms occur most often during exercise, your provider may ask you to walk on a treadmill or ride a stationary bike during an ECG. If an echocardiogram is done while you do these exercises, the test is called a stress echo.
- **Nuclear stress test:** This test is similar to an exercise stress test but adds images to the ECG recordings. A nuclear stress test shows how blood moves to the heart muscle at rest and during stress. A radioactive tracer is given by IV.
- **Heart (cardiac) CT scan:** A CT scan of the heart can show calcium deposits and blockages in the heart arteries. Calcium deposits can narrow the arteries. Sometimes dye is given by IV during this test. The dye helps create detailed pictures of the heart arteries. If dye is used, the test is called a CT coronary angiogram.
- **Cardiac catheterization and angiogram:** During cardiac catheterization, a heart doctor (cardiologist) gently inserts a flexible tube (catheter) into a blood vessel, usually in the wrist or groin. The catheter is gently guided to the heart. X-rays help guide it. Dye flows through the catheter. The dye helps blood vessels show up better on the images and outlines any blockages.
- Non-invasive techniques: Magnetic resonance imaging (MRI) and Multi-slice CT scanning, are being developed and tested as alternatives to angiography.

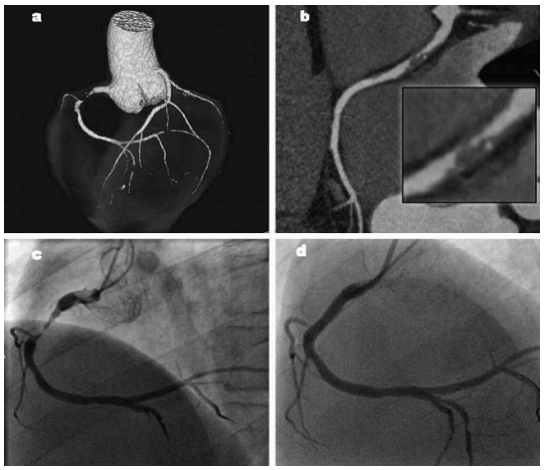


Figure. 12(Cardiac CT)

TREATMENT:

ANTITHROMBOTIC DRUGS:

One of the major complications arising from atheromatous plaque is thrombus formation. This causes an increase in plaque size and may result in myocardial infarction.

Antiplatelet agents, in particular aspirin, are effective in preventing platelet activation and thus thrombus formation.

Aspirin:

This antiplatelet action is apparent within an hour of taking a dose of 300mg.

MOA: Aspirin acts via irreversible inhibition of platelet COX-1 and thus thromboxane production, which is normally complete with chronic dosing of 75mg/day.

The optimal maintenance dose seems to be **75–150 mg/day** with lower doses having limited cardiac risk protection and higher doses increasing the risk of gastro-intestinal side effects.

Dyspepsia is relatively common in patients taking aspirin and patients should be advised to take the medicine with or immediately after food.

Adverse reactions: Allergy, Bronchospasm.

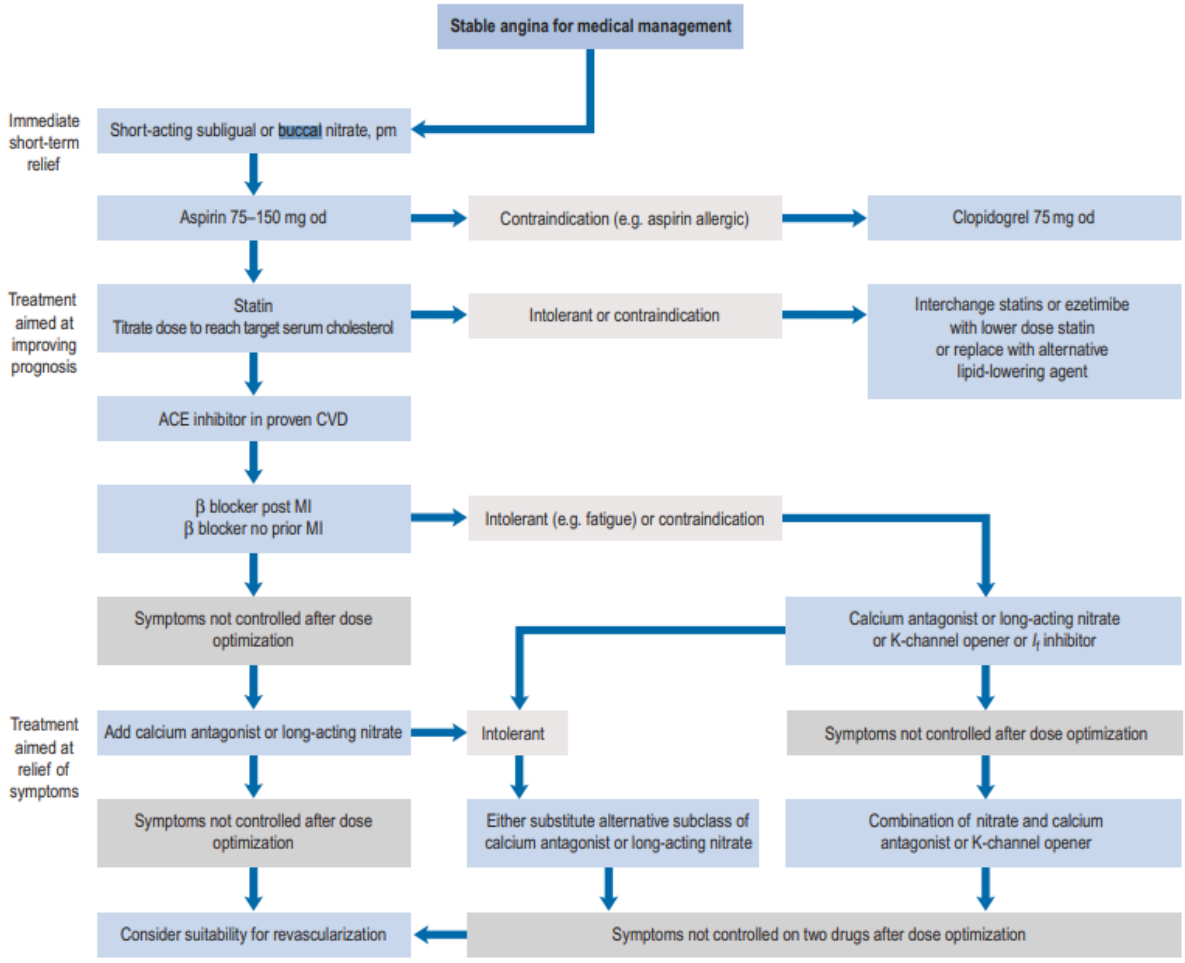


Figure. 13(Algorithm for medical management of stable angina)

Clopidogrel:

MOA: Clopidogrel inhibits ADP activation of platelets.

Useful as an alternative to aspirin in patients who are allergic or cannot tolerate aspirin

Dose: 300mg once, then 75 mg daily

Likely to cause gastric erosion and ulceration, gastro-intestinal bleeding is still a major complication of clopidogrel therapy.

There is evidence that the combination of a proton pump inhibitor and aspirin is as effective as using clopidogrel alone in patients with a history of upper gastro-intestinal bleeding.

COX-2 inhibitors:

MOA: The analgesic and anti-inflammatory action of non-steroidal anti-inflammatory drugs (NSAIDs) is believed to depend mainly on their inhibition of COX-2, and the unwanted gastro-intestinal effects of NSAIDs on their inhibition of COX-1.

COX-2 inhibition reduces the production of prostacyclin, which has vasodilatory and platelet-inhibiting effects.

NSAIDs with high COX-2 specificity increase the risk of myocardial infarction and should be avoided where possible in patients with stable angina.

ACE Inhibitors:

NSAIDs with high COX-2 specificity increase the risk of myocardial infarction and should be avoided where possible in patients with stable angina.

In addition to the vasodilation caused by inhibiting the production of angiotensin II, ACE inhibitors have anti-inflammatory, antithrombotic and antiproliferative properties.

Some of these effects are mediated by actions on vascular endothelium and might be expected to be of benefit in all patients with CAD. ACE inhibitors also reduce the production of ROS.

Statins:

Levels of LDL-C of <2 mmol/L and total Cholesterol <4 mmol/L are recommended for patients with established CVD.

In addition to cholesterol-lowering properties, statins also have antithrombotic, anti-inflammatory and antiproliferative properties.

Most patients with stable angina will be on statins for their cholesterol-lowering effects.

β Blockers:

β-Blockers are particularly useful in exertional angina.

Patients treated optimally should have a resting heart rate of around 60 beats/min.

β-Blockers should be used with caution in patients with diabetes as the production of insulin is under adrenergic system control and thus their concomitant use may worsen glucose control.

While β-blockers are widely used, their tendency to cause bronchospasm and peripheral vascular spasm means that they are contraindicated in patients with asthma and used with caution in chronic obstructive airways diseases and peripheral vascular disease as well as in acute heart failure and bradycardia.

β-Blockers should not be stopped abruptly for fear of precipitating angina through rebound receptor hypersensitivity.

They are contraindicated in the rare Prinz metal's angina were coronary spasm is a major factor.

Calcium Channel Blockers:

Short-acting dihydropyridine CCBs have been implicated in the exacerbation of angina due to the phenomenon of 'coronary steal', longer acting dihydropyridines, for example: amlodipine and felodipine or longer acting formulations, example: nifedipine LA, have demonstrated symptom relieving potential similar to β-blockers.

Verapamil and diltiazem should be used with caution in patients already receiving β-blockers, as bradycardia and heart block have been reported with this combination.

CCBs have a particular role in the management of Prinz metal's (variant) angina which is thought to be due to coronary artery spasm.

Nitrates:

Organic nitrates are valuable in angina because they dilate veins and thereby decrease preload, dilate arteries to a lesser extent thereby decreasing afterload, and promote flow in collateral coronary vessels, diverting blood from the epicardium to the endocardium.

Antioxidants such as vitamin C have also been used.

Tolerance is one of the main limitations to the use of nitrates. This develops rapidly, and a 'nitrate-free' period of a few hours in each 24-h period is beneficial in maintaining the effectiveness of treatment.

The nitrate-free period should coincide with the period of lowest risk, and this is usually night time, but not early morning, which is a high-risk period for infarction.

Table 20.3 Properties of commonly used nitrates

Drug	Speed of onset	Duration of action	Notes
Glyceryl trinitrate (GTN)			
Intravenous	Immediate	Duration of infusion	
Transdermal	30 min	Designed to release drug steadily for 24 h	Tolerance develops if applied continuously
SR tablets and capsules	Slow	8–12 h	
Sublingual tablets	Rapid (1–4 min)	<30 min	Inactivated if swallowed Less effective if dry mouth
Spray	Rapid (1–4 min)	<30 min	
Buccal tablets	Rapid (1–4 min)	4–8 h	Nearly as rapid in onset as sublingual tablets
Isosorbide dinitrate			
SR tablets	Similar to GTN		
Intravenous	Similar to GTN		
Sublingual	Slightly slower than GTN	As for GTN	
Chewable tablets	2–5 min	2–4 h	Less prone to cause headaches than sublingual tablets
Oral tablets	30–40 min	4–8 h	
Isosorbide mononitrate			
Oral tablets	30–40 min	6–12 h	
SR tablets or capsules	Slow	12–24 h	Some brands claim a nitrate-free period if given once daily

SR, sustained-release.

Figure. 14 (Commonly used Nitrates)

ACUTE CORONARY SYNDROME:

Acute coronary syndrome is a term used to describe a range of conditions associated with sudden, reduced blood flow to the heart.

These conditions include acute myocardial infarction (AMI), UA and non-ST-elevation myocardial infarction (NSTEMI).

AMI with persistent ST segment elevation on the ECG usually develops Q waves, indicating transmural infarction. UA and NSTEMI present without persistent ST segment elevation.

Patients with an occluded coronary artery suffer myocardial damage, the extent of which is determined by the duration and site of the occlusion.

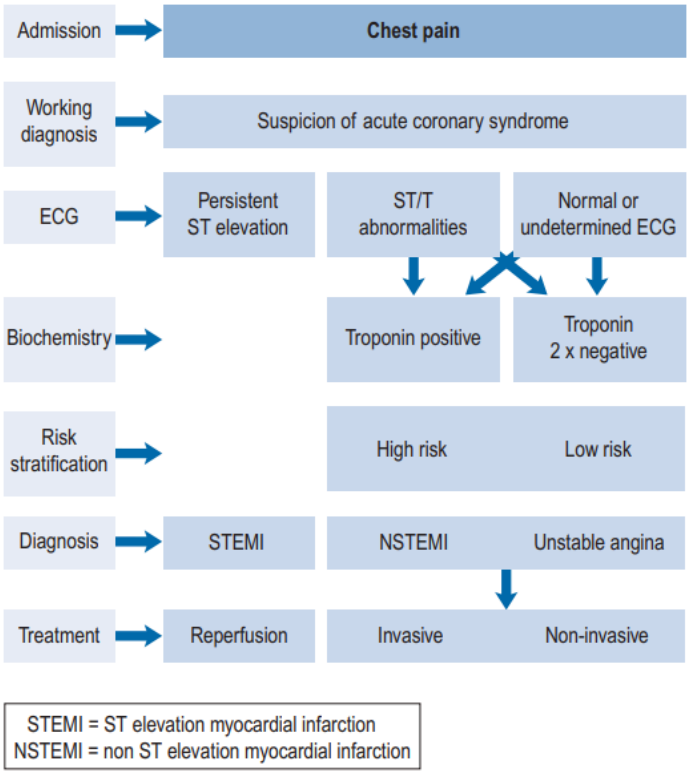


Figure. 15

Troponins (troponin I or troponin T) are cardiac muscle proteins which are released following myocardial cell damage and are highly sensitive and specific for myocardial infarction.

They are useful in diagnosing patients with ACS and for predicting response to drug therapy, they are now key to the management of these patients and have replaced cardiac enzymes such as CK, AST and LDH.

According to European Society of Cardiology:

- ECG changes indicative of new ischemia- New ST changes (STEMI or LBBB).
- Development of pathological Q waves in the ECG.
- Image evidence of new loss of viable myocardium or new regional wall motion abnormality.
- The most dangerous time after a myocardial infarction is the first few hours when VF is most likely to occur.
- Patients without persistent ST elevation on the ECG may still have experienced myocardial damage due to temporary occlusion of the vessel or emboli from the plaque-related thrombus blocking smaller distal vessels and will have raised levels of troponin. These patients have had a NSTEMI.

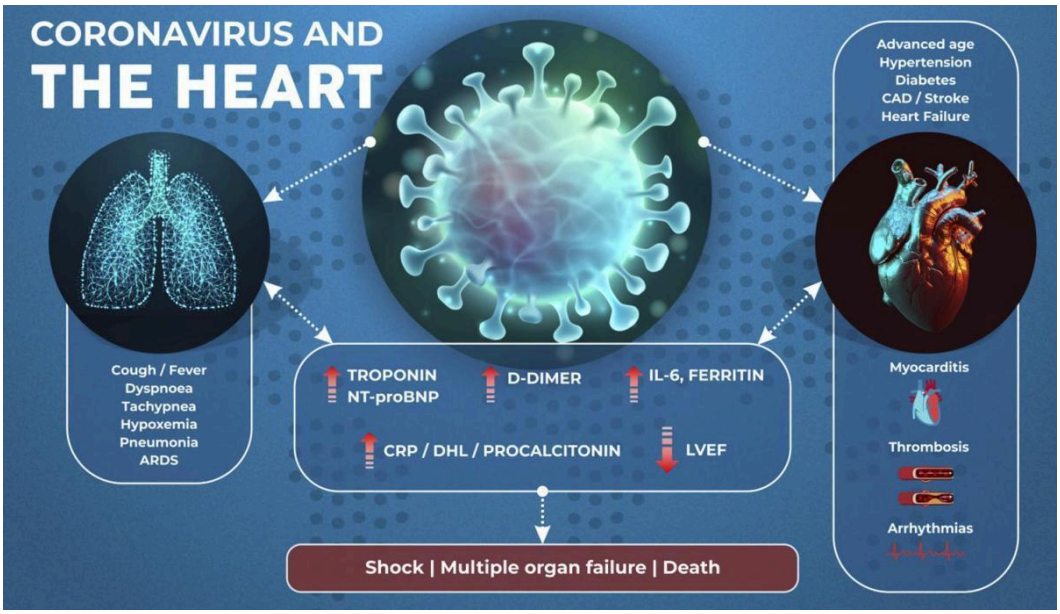


Figure. 16

- Patients without ST elevation and without a rise in troponin or cardiac enzymes are defined as having UA.

TREATMENT OF ST ELEVATION MYOCARDIAL INFARCTION:

Treatment of STEMI may be divided into three categories:

- Provide immediate care to alleviate pain, prevent deterioration and improve cardiac function.

- Manage complications, notably heart failure and arrhythmias.
- Prevent further infarction or death (secondary prophylaxis).

Immediate care to alleviate pain, prevent deterioration and improve cardiac function:

Pain relief:

Patients with suspected STEMI should receive sublingual GTN under the tongue, oxygen administered, and intravenous access established immediately. If sublingual GTN fails to relieve the chest pain, intravenous morphine may be administered together with an antiemetic such as prochlorperazine or metoclopramide.

Pain is associated with sympathetic activation, which causes vasoconstriction, increases the workload of the heart and can exacerbate the underlying condition.

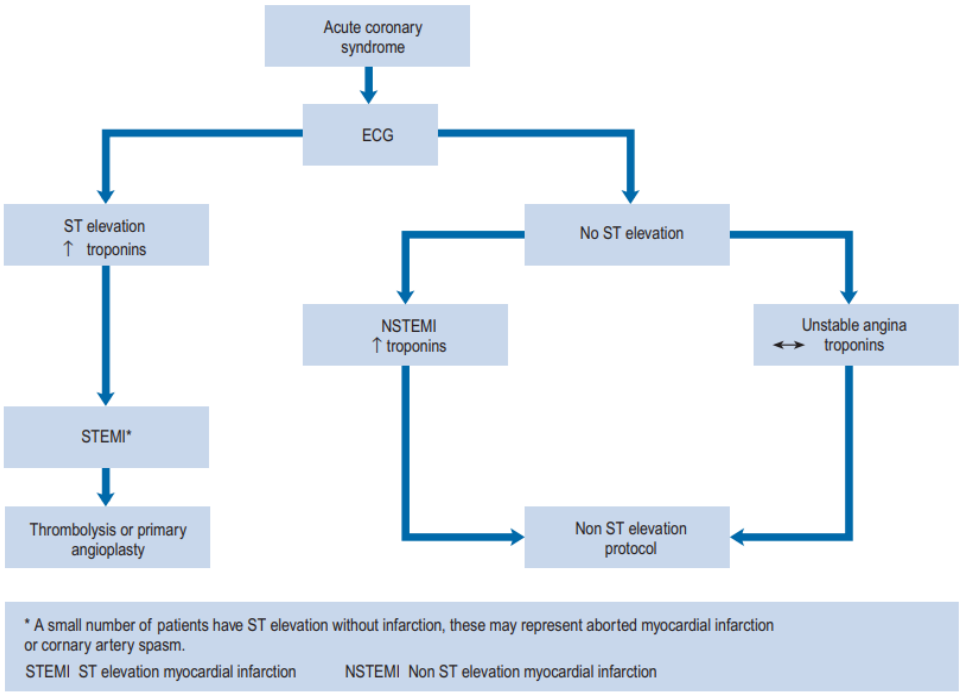


Figure. 17

Antiplatelet Therapy: Aspirin

Fibrinolytics:

Fibrinolytic agents have transformed the management of patients by substantially improving coronary artery patency rates which has translated into a 25% relative reduction in mortality.

Percutaneous coronary intervention:

The introduction of primary PCI (angioplasty or stent insertion without prior or concomitant fibrinolytic therapy) has demonstrated superiority to fibrinolysis when it can be performed expeditiously by an experienced team in a hospital with an established 24h a day interventional programme.

Antiplatelet and Anticoagulant therapy:

The combination of clopidogrel (600mg initiated pre-procedure and 75mg daily thereafter) and aspirin has been shown to reduce the risk of myocardial infarction and need for reperfusion therapy and decrease the length of hospital stay.

Patients undergoing primary PCI should receive aspirin and clopidogrel as early as possible.

Antiplatelet naive patients should receive 300mg of aspirin and 600 mg of clopidogrel.

In combination with aspirin, it is recommended for preventing atherothrombotic events in individuals undergoing PCI only when:

- Immediate primary PCI for STEMI is necessary
- Stent thrombosis has occurred during clopidogrel treatment
- The individual has diabetes mellitus

Heparin is routinely administered during the PCI procedure and is titrated to maintain an activated clotting time (ACT) of 250–350s.

MANAGEMENT OF COMPLICATIONS:

Heart Failure:

Heart failure during the acute phase of STEMI is associated with a poor short- and long-term prognosis.

It should be managed with oxygen, intravenous furosemide and nitrates. More severe failure or cardiogenic shock (tissue hypoperfusion resulting from cardiac failure with symptoms of hypotension, peripheral vasoconstriction and diminished pulses, decreased urine output and decreased mental status) should be treated with inotropes and/or intra-aortic balloon pumps to maintain the systolic blood pressure above 90mmHg. Invasive monitoring may be required.

Arrhythmia:

Life-threatening arrhythmias such as ventricular tachycardia, sustained VF or atrio-ventricular block

occur in about one fifth of patients presenting with a STEMI, although this is decreasing due to early reperfusion therapy. The early administration of an intravenous β-blocker was shown to limit infarct size.

Diltiazem is less effective but may be used as an alternative. Nifedipine increases mortality in patients following a myocardial infarction. Sinus bradycardia and heart block may also occur after a myocardial infarction and patients may require temporary or permanent pacemaker insertion.

Blood Glucose: Patients with a myocardial infarction are often found to have high serum and urinary glucose levels, usually described as a stress response. Up to 20% of patients who have a MI have DM.

TREATMENT OF NON-ST ELEVATION ACUTE CORONARY SYNDROME:

ACS without ST elevation is classified as either UA or NSTEMI. UA is defined as angina that occurs at rest or with minimal exertion, or new onset of severe angina or worsening of previously stable angina. NSTEMI is the more severe manifestation of ACS.

Patients presenting with UA/NSTEMI can be classified into three categories depending on their risk of death or likelihood of developing an AMI.

High-risk patients (those with ST segment changes during chest pain, chest pain within 48h, troponin T-positive patients and those presenting already on intensive anti-anginal therapy) can be effectively managed with aggressive medical and interventional therapy.

Various pharmacological agents such as antithrombin and antiplatelet drugs, and coronary revascularization have been shown to improve the outcome of patients with UA or NSTEMI. Measures of risk can be derived from the clinical assessment of a patient and the use of a formal risk scoring system, such as the GRACE, PURSUIT, PREDICT or TIMI scores.

In patients with NSTEMI, the immediate administration of 300mg aspirin can reduce mortality or subsequent myocardial infarction by 50%[5].

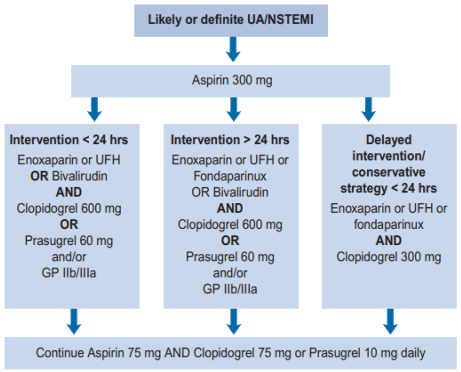


Figure. 18

LEFT VENTRICULAR DYSFUNCTION:

Left ventricular dysfunction refers to the condition characterized by dilation of the left ventricle of the heart. It is also associated with the narrowing of blood vessels.

The main function of the left ventricle is to pump the oxygen-rich blood to all body parts.

Normal LV function can be disturbed due to several causes. Certain cardiac defects like valvular malformations or diseases block the passage of blood into the body.

Hence, any medical problem that interferes with the pumping of blood by heart poses the risk of developing left ventricular dysfunction. Some of these are aortic stenosis, presence of blood clot in lungs, congenital heart disease, diabetes, etc.

This compels the left ventricle to work harder and pump blood faster to compensate for the lack of oxygen-rich blood in the body tissues. Over time, the heart muscles become thicker, weaker and the walls stretch to accommodate more blood. This eventually leads to ventricular dysfunction, especially left ventricular dysfunction.
Males in the age group of 50-70 years are more likely to develop left ventricular dysfunction. Males are more prone to the condition than females.

Mostly, left ventricular dysfunction does not have any symptoms. Sometimes, affected individuals exhibit symptoms of heart failure.

LV systolic dysfunction was graded as:

- Mild (LVEF 41–45%)
- Moderate (LVEF 36–40%) or
- Severe (LVEF ⩽35%).

LV end diastolic diameter was measured perpendicularly from the interventricular septum to the lateral wall through the plane of the tip of the mitral valve leaflets[6].

IMPACT OF COVID-19 ON THE CLINICAL AND ANGIOGRAPHIC PROFILE IN PATIENTS WITH CAD

The cause of COVID-19 is characterized by acute clinical pathologies, including various coagulopathies that may be accompanied by hypercoagulation and platelet hyperactivation.

Long COVID/PASC Lingering symptoms persist for as much as 6 months (or longer) after acute infection, where COVID-19 survivors complain of recurring fatigue or muscle weakness, being out of breath, sleep difficulties, and anxiety or depression.

Predisposing risk factors or comorbidities that may also lead to a poor prognosis of acute COVID-19, are cardiovascular disease, diabetes, arterial hypertension, obesity, as well as cancer. Complications like liver injury, ARDS, sepsis, MI, renal insufficiency, and MODS are common in cancer patients with COVID‑19.

Recently, a new COVID-19 phenotype has been noted in patients after they have ostensibly recovered from acute COVID-19 symptoms. This new syndrome is commonly termed PASC. We use the terminology Long COVID. Long COVID/PASC can involve sequelae and other medical complications that last for weeks to months after initial recovery and may include more than 50 long-term effects.

COVID-19 has been found to interact with and affect the cardiovascular system leading to myocardial damage, cardiac and endothelial dysfunction mainly via the Angiotensin-Converting Enzyme 2 (ACE-2) Receptor.

In fact, cardiac damage has been noted even without clinical features of respiratory disease. On the one hand, respiratory symptoms are worse in COVID-19 affected patients with pre-existing cardiac ailments. New-onset cardiac dysfunction is common in this subset. In fact, cardiac damage has been noted even without clinical features of respiratory disease [7].

PATHOPHYSIOLOGY:

ACE2 RECEPTOR:

SARS-CoV-2 uses its S-spike to bind to ACE2 receptors as the point of entry into the cell. These ACE2 receptors are expressed in type 1 and type 2 pneumocytes and other cell types, including endothelial cells. ACE2 is an inverse regulator of the renin-angiotensin-aldosterone system. Like other coronaviruses, SARS-CoV-2 uses these ACE2 receptors to target the respiratory system primarily.

SARS-CoV-2 and the Immune Response

- There are two immune-response phases of COVID-19 disease. Phase 1 occurs during the incubation stage of the disease, during which the adaptive immune system works to eliminate the virus, if any defects occur at this stage, SARS-CoV-2 will disseminate and induce systemic organ

damage, with more significant destruction of organs with higher expression of ACE2 receptors, including lung, endothelial cells, the heart, and the kidneys.

- This massive damage leads to phase-2 is severe inflammation in the affected organs. Diabetes, atherosclerosis, and obesity, which are risk factors for cardiovascular disease, down regulate the immune system. These have been associated with a poor prognosis in COVID-19.
- Multiple mechanisms have been suggested for cardiac damage, based on studies conducted during the previous SARS and MERS epidemics and the ongoing COVID-19 epidemic. Part of the systemic inflammatory response in severe COVID-19 is the release of high levels of cytokines (known as cytokine release syndrome) that can injure multiple tissues, including vascular endothelium and cardiac myocytes.

Cytokine Release Syndrome:

Cytokine release syndrome occurs in patients with severe COVID-19 infection. Many proinflammatory cytokines are significantly elevated in severe cases, including interleukin (IL)-2, IL-10, IL-6, IL-8, and tumour necrosis factor (TNF)-α. Cytokines play an important role during infection with the virus (phase 1) and during ongoing severe inflammation (phase 2), resulting in acute respiratory distress syndrome (ARDS) and other end-organ damage.

Direct Myocardial Cell Injury

The interaction of SARS-CoV-2 with ACE2 can cause changes to the ACE2 pathways, leading to acute injury of the lung, heart, and endothelial cells. A small number of case reports have indicated that SARS-CoV2 might directly infect the myocardium, causing viral myocarditis. However, in most cases myocardial damage appeared to be caused by increased cardio metabolic demand associated with the systemic infection and ongoing hypoxia caused by severe pneumonia or ARDS.

Acute Coronary Syndrome

Plaque rupture leading to ACS can result from the systemic inflammation and catecholamine surge inherent in this disease. Coronary thrombosis also has been identified as a possible cause of ACS in COVID-19 patients.

Other Possible Mechanisms

Certain medications such as corticosteroids, antiviral medications, and immunological agents may have cardiotoxic side effects. Electrolyte disturbances can occur in any critical systemic illness and trigger arrhythmias, for which patients with underlying cardiac disease are at higher risk.

- There is particular concern about hypokalemia in patients with COVID-19, given the interaction of SARS-CoV-2 with the RAAS. Hypokalemia is well known to increase vulnerability to various kinds of arrhythmia[8].
-

- Patients with non-obstructive CAD had more diffuse ST-segment elevation and diffuse left ventricular wall-motion abnormality compared to obstructive CAD. In patients with previous coronary stent, the 76% presented with stent thrombosis.
- It is recognized that COVID-19 is not only responsible for viral pneumonia because it can also cause a wide range of CV (e. g. MI, pericarditis, myocarditis, cardiac arrhythmia, heart failure, and thromboembolism), regardless of pre-existing heart conditions. Thus, adequate recognition and management of acute cardiac events such as STEMI in patients with COVID-19 are necessary.
- Primary PCI was the main reperfusion strategy in COVID-19 patients with ST-segment elevation[9].
- Persistent symptoms in patients who initially presented with asymptomatic, mild, or moderate acute COVID-19 (‘long-hauler’ COVID-19).
- Cardiovascular complications in patients with moderate-to-severe COVID-19 and evidence of cardiac injury (elevated troponin levels and/or reduced left ventricular ejection fraction).
- Reports have documented cases of postural orthostatic tachycardia syndrome as a cause of palpitations after recovery from acute COVID-19, as has been described after other viral illnesses.
- Elevated levels of troponin and C-reactive protein can occur even in patients with mild COVID-19 who did not require hospitalization [10].
- The possible pathophysiology includes dysregulation of the RAAS, destabilization of plaques, cytokine release syndrome, and disorders of coagulation processes.
- The patients underwent laboratory testing, echocardiography, and 24-hour ECG monitoring. We defined severe complications as: myocarditis, pulmonary embolism, angina pectoris requiring myocardial revascularization, a decrease in left ventricular ejection fraction from the pre-disease value greater than 10%, the onset of atrial fibrillation or supraventricular tachycardia, or thrombi within the heart cavities.
- Patients with severe complications had higher C-reactive protein and troponin T. In comparison to those with mild complications, patients with severe complications also had significantly more often a decrease in ejection fraction and higher resting heart rate at admission.
- High CRP and troponin levels were also previously observed as a biomarker of severe complications but mainly in the acute phase of the COVID-19 disease[11].