Myocardial infarction

Introduction:
Myocardial infarction (MI) it is myocardial necrosis due to prolonged imbalance between the myocardial oxygen supply and its demand (Lopez AD, et al., 1998). It is said to be part of a spectrum of diseases known as Acute Coronary Syndromes (ACS). The diseases that make up the spectrum are unstable angina, acute myocardial infarction, and sudden cardiac death (Petrich ER et al., 1996 and Thygesen K, et al., 2007).

Development of myocardial infarction
Myocardial infarction (i.e. irreversible injury) caused by complete coronary artery occlusion (or one of its branches) begins to develop after 15–20 minutes of severe ischaemia (no forward or collateral flow). Within the perfusion area of the occluded artery, flow deprivation and myocardial ischaemia are usually most severe subendocardially and cell death progresses from the sub- endocardium to the subepicardium. Although the susceptibility to ischaemic necrosis differs significantly among patients (related to, for example, variability in preconditioning and oxygen demand/ consumption). There are two well-characterized major determinants of the ultimate extent of infarction:

- Location of the occlusion.
- Severity and duration of myocardial ischaemia (residual flow and rapidity of recanalization) (Thygesen K., et al., 2012).

Pathophysiology:
Among the various proposed mechanisms, the accumulations of free radicals have been implicated in the pathophysiology of acute myocardial infarction (Zhou R. et al., 2008). It is well known that coronary
vascular diseases (CVD) are directly or indirectly related to oxidative damage that shares a common mechanism of molecular and cellular damage. There are two basic types of acute myocardial infarction:

1) Transmural myocardial infarction (involving the full thickness of a wall) is associated with atherosclerotic plaques in the coronary arteries that cause complete occlusion of a coronary artery. These are labeled by the wall(s) involved: anterior, posterior, lateral, inferior, and septum (i.e. anterior wall myocardial infarction). ST-segment elevation (electrical impulse change) is seen on electrocardiogram (ECG), and these are diagnosed as ST-Segment Elevation Myocardial Infarction (STEMI). Over the long term permanent ECG changes develop as Q-waves (small extra wave in each QRS complex in areas corresponding to the muscle section(s) that infarct). As a result, these are also diagnosed as Q-wave MI (a term not used in the German language) (Gabriel Steg., et al., 2012).

2) Non-transmural (subendocardial) myocardial infarction involves a small area in the subendocardial wall (innermost layer of heart wall muscle) of the left ventricle, ventricular septum, or papillary muscles. These are caused by a local decrease in blood supply from narrowing of the coronary arteries. Blood supply to the ventricle runs from the outside to the inside of the muscle. The subendocardium is the farthest from the blood supply and is therefore most susceptible to decreased blood flow. No ST-segment elevation is seen on ECG; most commonly, ST-segment depression or T-wave inversion are seen and these are diagnosed as Non-ST-Segment Elevation Myocardial Infarction.
(NSTEMI). These normally do not lead to later development of Q-waves and are later termed Non-Q-wave MI. Sometimes there are no ECG changes and diagnosis is based on signs, symptoms, and laboratory values (Robbert J. et al., 2012).

**sequence of acute coronary syndrome:**

1) **Thrombotic complications of atherosclerosis:**

If the progression of luminal stenosis to a critical narrowing does not cause many acute coronary syndromes, the question is what mechanism produces these dramatic and sudden manifestations of chronic atherosclerosis? The longstanding focus on stenosis has diverted attention from autopsy studies conducted by generations of pathologists who have ascribed most fatal coronary events to a physical disruption of coronary arterial plaques. Frank rupture of the plaque’s fibrous cap causes the majority of these deaths; superficial erosion of a coronary artery accounts for most of the balance of fatal events. Autopsy studies have shown that erosion through the intima of a calcified nodule and intra plaque hemorrhage each trigger only a small percentage of acute coronary syndromes (Arbab-Zadeh et al., 2012).

Much of the work addressing the mechanisms of coronary thrombosis has focused on plaque rupture, the most common cause of fatal acute coronary syndromes. A fibrous cap typically overlies the lipid-rich center also known as the necrotic core of an atheromatous plaque (Fig. 1).
This fibrous cap stands between the blood compartment, with its latent coagulation factors, and the lipid core, a portion of the plaque filled with thrombogenic material. Quantitative morphometric studies have identified the characteristics of plaques that have ruptured and caused a fatal myocardial infarction. Such plaques often, but not always, have thin fibrous caps (50 to 65 μm thick) (Yonetsu et al., 2011). Ruptured plaques also tend to have large lipid cores and abundant inflammatory cells, as well as punctate or spotty calcification fig.(2) (Maldonado et al., 2012).

2) Inflammation, collagen metabolism, plaque rupture and thrombosis:

Extensive research has focused on the fibrous cap of the plaque because of its importance in the majority of fatal acute myocardial infarctions. This structure,
which protects the plaque from rupture, owes its tensile strength to interstitial forms of collagen synthesized primarily by arterial smooth muscle cells. The association between thinning of the fibrous cap and fatal plaque rupture lead to the hypothesis that a defect in plaque collagen metabolism contributes to the depletion of this extracellular matrix protein, which has a critical role in strengthening the fibrous cap (*Libby, 1995*).

These considerations have engendered much interest in molecular mediators of collagen metabolism that may operate during atherogenesis. Since inflammatory cells accumulate at the site of ruptured plaques, and since biomarkers of inflammation predict acute coronary syndromes, studies have focused on the hypothesis that macrophages and the mediators that they produce and that regulate their function disrupt the collagen in the plaque in a manner that may jeopardize the integrity of the fibrous cap, thus precipitating an acute coronary syndrome. A study of the control of collagen biosynthesis by human vascular smooth-muscle cells in culture revealed that exposure to interferon-γ, a product of activated T cells, strongly inhibited the ability of smooth-muscle cells to make the new collagen required to repair and maintain the integrity of the fibrous cap (*Amento et al., 1991*).

Even in smooth-muscle cells maximally stimulated with transforming growth factor β to produce interstitial collagen, interferon-γ reduced collagen synthesis to baseline levels or lower. Another study showed an inverse correlation between T-cell accumulation in human atherosclerotic plaques and the messenger RNA that encodes the precursor of interstitial collagen, an observation that supports the relevance in vivo of the profound inhibition of new collagen synthesis by a T-cell–derived mediator (*Rekhter et al., 1993*). *Fig(3).*
Figure (3): Inflammatory pathways predisposing coronary arteries to rupture and thrombosis.

3) **Superficial erosion of plaques:**

Superficial erosion of coronary atheromata causes approximately 20 to 25% of cases of fatal acute myocardial infarctions (*Arbab-Zadeh et al., 2012*). Observations made with the use of optical coherence tomography support the relevance of findings in autopsy studies to clinical acute coronary syndromes (*Holmes et al., 2013*).

This anatomical substrate for coronary thrombosis occurs more frequently in women than in men and in persons with certain risk factors, such as hypertriglyceridemia. Many lesions that cause coronary thrombosis because of superficial erosion lack prominent inflammatory infiltrates; such plaques exhibit proteoglycan accumulation (*Fig. 4*).
The mechanisms of superficial erosion have received much less attention than those involved in the rupture of the fibrous cap. The programmed cell death (apoptosis) of endothelial cells could contribute to their desquamation (Libby, 2008).

Oxidative stress can promote endothelial apoptosis. In particular, hypochlorous acid, the product of myeloperoxidase, an enzyme released by activated leukocytes associated with atheromata can initiate apoptosis of endothelial cells (Sugiyama et al., 2004).

As these cells undergo apoptosis, they produce the procoagulant tissue factor. The oxidant hypochlorous acid may thus initiate or propagate endothelial cell loss and local thrombosis in coronary arteries. Endothelial cells can also express proteinases that may sever their tethers to the underlying basement membrane (Libby, 2008).

Modified low-density lipoprotein (LDL), for example, can induce the expression of the enzyme matrix-metalloproteinase (MMP-14) by human endothelial cells. MMP-14 can activate MMP-2, an enzyme that degrades basement membrane forms of non fibrillar collagen (type IV). The mechanisms of superficial erosion merit attention in investigations; they are much less well (Rajavashisth et al., 1999).
Risk factors of myocardial infarction:

A-Non-modifiable risk factors:

In addition to the modifiable risk factors, there are some risk factors that cannot be changed. However, people in these high-risk categories should receive regular check-ups.

1-Age

Age is by far the most important risk factor in developing cardiovascular diseases, with approximately a tripling of risk with each decade of life (Finegold et al, 2012). It is estimated that 82% of people who die of coronary heart disease are 65 years and older (Mackay et al, 2004).

Multiple explanations have been proposed to explain why age increases the risk of cardiovascular diseases. As serum cholesterol level that increases as age increases. In men, this increase levels off around age 45 to 50 years. In women, the increase continues sharply until age 60 to 65 years (Jousilahti et al, 1999).

Also, aging is associated with changes in the mechanical and structural properties of the vascular wall, which leads to the loss of arterial elasticity and reduced arterial compliance and may subsequently lead to coronary artery disease (Jani et al, 2006).

2-Gender

Men are at greater risk of heart disease than pre-menopausal women (Finegold et al, 2012). Once past menopause, it has been argued that a woman's risk is similar to a man's (Hu & Hennekens, 1999). Among middle-aged people, coronary heart disease is 2-5 times more common in men than in women (Finegold et al, 2012). This difference between males and females is due to:
a) **Hormonal difference:** One of the proposed explanations for the gender difference in cardiovascular disease. Among women, estrogen is the predominant sex hormone. It may have protective effects through glucose metabolism and hemostatic system, and it may have a direct effect on improving endothelial cell function. The production of estrogen decreases after menopause. That shift the female lipid metabolism toward a more atherogenic form by decreasing the high density lipoprotein (HDL) cholesterol level and by increasing LDL and total cholesterol levels. Women who have experienced early menopause, either naturally or because they have had a hysterectomy, are twice as likely to develop heart disease as women of the same age group who have not yet gone through menopause (Jousilahti & Tuomilehto, 1999).

b) In the very elderly, age related large artery pulsatility and stiffness is more pronounced in women. This may be caused by the smaller body size and arterial dimensions independent of menopause (Jani & Rajkumar, 2006).

3- **Family history**

A family’s history of CVD indicates a person’s risk. If a first-degree blood relative has had coronary heart disease or stroke before the age of 60 years, the risk increases (Merry et al, 2011).

**B-modifiable risk factors:**

1- **Lipid profile:**

   **A- Cholesterol:** Cholesterol is vital for healthy cells. It is so important that the body does not rely on a dietary source, it makes its own. However, if the body accumulates too much, cholesterol will deposit in the walls of arteries, which
become damaged and may become blocked. If this happens, a heart attack could result. (Finn et al., 2010).

**B- Triglyceride**: triglyceride is often coupled with having too little HDL (high density lipoprotein). This combination is commonly associated with premature coronary heart disease. It may be inherited but also occurs in individuals who are obese. Weight reduction and regular exercise may help to reduce triglyceride levels and increase HDL levels (Sarwar et al., 2007).

**C-High density lipoprotein (HDL)**: A higher level of HDL is useful, as this is the component in the blood which brings excess cholesterol from the tissues to the liver for processing and excretion. Low levels of HDL in the blood appear to be an important predictor for heart disease (Natarajan et al., 2010).

**D- Lipoprotein (a) [Lp (a)]**: Lipoprotein (a) [Lp (a)] has homology to plasminogen. This homology between Lp (a) has raised the possibility that this lipoprotein may inhibit endogenous fibrinolysis by competing with plasminogen binding site on endothelium. Studies have suggested that Lp (a) bind and inactivates tissue factor pathway inhibitor, further linking lipoproteins and thrombosis (Tsimikas et al., 2005).

**3-Blood Pressure (BP)**

High blood pressure, or hypertension, is often referred to as the “silent killer” due to its lack of symptoms and warning signs. When blood pressure is too high, the heart works harder to pump blood, and can lead to serious CVD complications.

Hypertension is quantitatively the most important risk factor for premature cardiovascular disease, being more common than cigarette smoking, dyslipidemia, and diabetes, which are the other major risk factors. Hypertension accounts for an
estimated 54% of all strokes and 47% of all ischemic heart disease events globally (Lawes et al., 2008).

The higher the Blood Pressure the greater the chance of myocardial infarction, heart failure (HF), and stroke. For individuals aged 40 to 70 years, each increment of 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP doubles the risk of CVD across the entire BP range from 115/75 to 185/115 mm Hg (Iqbal R., et al., 2012).

Angiotensin II concentrations are often elevated in patients with hypertension resulting in smooth muscle contraction, increasing protein synthesis and induce smooth muscle hypertrophy (Fuster et al., 2001). Hypertension also increases the formation of hydrogen peroxide and free radicals such as superoxide and hydroxyl radicals in the plasma which have a proinflammatory action as well as they reduce the formation of nitric oxide (NO) by the endothelium, increasing platelet adhesion and peripheral resistance (Vonhoute and Boulanger, 1995).

**4-Diabetes**

Having diabetes puts people with the condition at a much higher risk of CHD. People with diabetes have a 2-5 fold risk of developing heart disease than who doesn’t have diabetes (Norhammar, 2004). This seems to be an effect of several interacting metabolic changes in the pre-diabetic state, such as development of atherogenic dyslipidemia, impaired endothelial function, increased levels of free fatty acids, subclinical inflammation, changes in adipokines, and changes in thrombosis and fibrinolysis. Lipid profiles in people with diabetes tend to be characterised by elevated very-low-density lipoproteins (VLDL), small low-density lipoproteins and low HDLs. This combination is commonly termed diabetic dyslipidaemia and is particularly atherogenic (Evan et al, 2007).
5-Smoking

The risk-increasing effect of tobacco smoking on CHD is well established. There is a clear dose-response relationship with CHD (Teo KK., et al, 2006). The Interheart study identified smoking as the second most important risk factor for acute myocardial infarction (AMI) world-wide and this was consistent with regards to sex, ethnicity, and geographical region (Ambrose JA., et al, 2004). The detrimental effects of smoking on the cardiovascular system seem to act through promotion of vasomotor dysfunction, atherogenesis (e.g. inflammation and dyslipidemia), and thrombosis in multiple vascular beds. Whereas the specific mechanisms behind these effects are yet to be fully understood. Free radical-mediated oxidative stress seems to be a central feature (Huxley RR., et al, 2011).

6-Inactivity and obesity

Physical activity has several beneficial effects on the cardiovascular system. The most important ones are associated with increased myocardial oxygen supply and decreased myocardial work and oxygen demand. Furthermore, Regular moderate-intensity exercise has many benefits for people with CHD: it prevents the blood vessels from narrowing further (anti-atherosclerotic), prevents blood clotting (anti-thrombotic), helps deliver blood to the heart (anti-ischaemic), and helps to maintain a normal heart rhythm (anti-arrhythmic). These changes reduce the load on the heart at rest and during exercise, which helps to lessen some of the symptoms of CHD, as well as decrease the risk of death from CHD. Additional benefits from exercise in those with CHD include: improved physical function and psychological wellbeing, and favourable changes in body weight and composition (Wise FM., 2010).
7-Stress

A certain amount of stress may be desirable, in that it keeps people alert and motivated what is called positive stress. However, as the stress level builds and, especially if prolonged, it can be counter-productive by being injurious to health. (Ornish et al., 1998). There have been numerous studies found CHD/AMI to be associated with anxiety, depression, low social support, different aspects of stress at work and in family life, as well as with different personality traits such as hostility and anger. The stress responses in the body are subordinated under “the stress system”. Its crucial functions are mediated by the hypothalamo-pituitary adrenal axis HPA-axis and the autonomic nervous system. The “end-product” of the HPA-axis is thus cortisol (Kyrou I. et al, 2006). In the acute phase, cortisol has potential effects on the whole body metabolism since the body aims to utilize all energy resources to be able to meet the increased demands that a stressor enforces. Cortisol also has blood pressure increasing effects and suppresses inflammation. This “catabolic shift” of the metabolism is usually reversed when the stressor is removed. However, chronic stress with prolonged activation of the HPA-axis and sustained cortisol secretion is expected to decrease muscle and bone mass and increase visceral obesity and insulin resistance (Kyrou I., et al, 2009).

13- Oxidative stress:

Oxidative stress is the result of an imbalance between increased generation of reactive oxygen species (ROS) and the decreased ability of endogenous antioxidant system to scavenge them. ROS induce cell, tissue, or organ damage and are involved in the pathogenesis of several diseases, including atherosclerosis (Seetharam et al., 2006).
The production of ROS in vascular endothelial cells induces the oxidation of LDL and the expression of ROS-sensitive inflammatory genes. This process is involved in early atherosclerotic processes, such as ROS sensitive expression of vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1). These changes may induce alteration in structure and function of endothelial cells and contribute to initiation of atherosclerosis (Ganji et al., 2009).

➢ Role of Isopreoterenol in inducing myocardial infarction:

Isoprenaline or isoproterenol is a medication used for the treatment of bradycardia, heart block, and rarely for asthma. It is a non-selective beta-adrenergic agonist and structurally similar to adrenaline (Shen and Howard, 2008). It has been reported to exhibit many metabolic and morphological aberration in heart tissue of human and experimental animal (Yan J. et al, 2008). Isoproterenol (ISO) has been found to induce myocardial injury in rat as a result of disturbance in physiological balance between production of free radicals and antioxidative defense system (Zhou R., 2008).

It produces myocardial infarction which causes cardiac dysfunction. Isoprenaline induced myocardial infarction there by serve as a well standardized model to standby the beneficial effects of many drugs and cardiac function (Karthikeyan K., 2007).

Isoprenaline induces myocardial necrosis by a multiple mechanisms:

(1) A relative cardiac hypoxemia due to increased cardiac work and myocardial oxygen demands (Mahammad Rahmathulla S. B et al, 2013).
(2) Coronary arterial vasoconstriction (spasm) causing endocardial ischemia. (Mahammad Rahmathulla S. B et al, 2013).

(3) Alterations in metabolism: isoprenaline has been reported to enhance adenylate cyclase activity resulting in increased C-AMP formation which in turn leads to increased lipid accumulation in the myocardium. It is also well known to generate free radicals and to stimulate lipid per oxidation, which may be a causative factor for irreversible damage to the myocardial membrane (Crlg SA, 2004).

(4) Decreased level of high-energy phosphate stores: as ISO produces uncoupling of oxidation phosphorylation in rat heart mitochondria (Daniel Acosta JR., 2001).

(5) Intracellular Ca²⁺ overload: as ISO result in activation of C-AMP as the second messenger of the β-adrenergic signaling pathway activates protein kinase A, thereby phosphorylating the L-type calcium channel. Thus, ensemble average current increases due to a rise in channel open probability and availability (Gunnar Klein. Et al, 2000).

(6) It also increases the levels of (LDL), and cholesterol in the blood, which in turn leads to the formation of atherosclerosis in the arteries thus favoring coronary heart disease (M. Murugesan, et al, 2012).

(7) ISO down regulates copper-zinc superoxide dismutase enzyme activity, protein and mRNA and reduces glutathione level, leading to the loss of membrane integrity, inducing heart contractile dysfunction and myocyte toxicity finally producing myocardial necrosis (C.P Pullaiah, et al, 2013).

(8) Oxidative stress: oxidative stress is, more probably, one of the main mechanisms through which catecholamines exert their toxic effects. Spontaneous
oxidation of catecholamines results in the formation of catecholamine-o-quinones, which generate aminochromes through cyclization. Adrenochrome (which results from the cyclization of epinephrine-o-quinone) can be oxidized to several other compounds such as adrenolutin, 5, 6-dihydroxy-1-methylindole (DHMI) or adrenochrome-adrenolutin dimmer. All these redox reactions generate free radicals. Consequently, catecholamine-o-quinones, aminochromes and the radical species resulting from the oxidation of catecholamines are thought to be involved in catecholamine-related toxicity. The aminochrome undergo further oxidation similarly to that of adrenochrome which isomerizes to adrenolutin this oxidative reactions produce free radicals (Aman upaganlawar, et al, 2011).

The oxidized products have the ability to interact with sulphhydryl groups of various proteins and also lead to production of superoxide anions and subsequently hydrogen peroxide. This results in changes in microsomal permeability, mitochondrial Ca2+ uptake, decrease in ATP production and the formation of highly reactive hydroxyl radicals which causes protein, lipid and DNA damage (Dhalla et al., 2010).

➢ Diagnosis of myocardial infarction:

The initial diagnosis of acute coronary syndrome is based on history, risk factors, clinical picture, cardiac enzymes, echo., and ECG finding. (Drew et al., 2005).

1) Clinical presentation:

a) Chest pain described as a pressure sensation, fullness, or squeezing in the midportion of the thorax which radiate into the jaw or teeth, shoulder, arm, and/or back.

b) Associated shortness of breath (dyspnea).
c) Associated epigastric discomfort with or without nausea and vomiting.

d) Associated diaphoresis or sweating.

e) Syncope or near syncope without other cause (Thygesen K. et al, 2007).

2) Electrocardiography (ECG):

The ECG is a cornerstone in the diagnosis of acute and chronic ischemic heart disease. The findings depend on several key factors:

A- The nature of the process [reversible (i.e., ischemia) versus irreversible (i.e., infarction)].

B- The duration (acute versus chronic).

C- The extent (transmural versus subendocardial).

D- The localization (anterior versus inferoposterior).

E- The presence of other underlying abnormalities (ventricular hypertrophy, conduction defects) (Ashley EA., et al, 2001).

Changes in ECG with CHD or MI:

a) Changes in S-T segment:

Ischemia exerts complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia lowers the resting membrane potential and shortens the duration of the action potential. Such changes cause a voltage gradient between normal and ischemic zones. As a consequence, current flows between these regions. These currents of injury are represented on the surface ECG by deviation of the ST segment (Fig. 5).
When the acute ischemia is transmural, the ST vector is usually shifted to epicardial layers, producing ST elevations. In the earliest stages of ischemia, tall, positive so-called hyperacute T waves over the ischemic zone. With ischemia confined primarily to the subendocardium, the ST vector typically shifts toward the subendocardium and ventricular cavity, so that overlying leads show ST-segment depression. Multiple factors affect the amplitude of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. From a clinical viewpoint, the division of acute myocardial infarction into ST segment elevation and non-ST elevation types is useful since the efficacy of acute reperfusion therapy is limited to the former group (Mirvis DM., et al, 2008).

**FIG. (6)** Current-of-injury patterns with acute ischemia.
b) **QRS changes with ischemia:**

With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial tissue may lead to decreased R-wave amplitude or abnormal Q waves in the anterior or inferior leads (Fig. 7). Previously, abnormal Q waves were considered to be markers of transmural myocardial infarction, while subendocardial infarcts were thought not to produce Q waves. However, careful ECG-pathology correlative studies have indicated that transmural infarcts may occur without Q waves and that subendocardial (nontransmural) infarcts may sometimes be associated with Q waves. Therefore, infarcts are more appropriately classified as "Q-wave" or "non-Q-wave" (Goldberger AL., 2006).

c) **ECG changes during recovery period:**

In the weeks and months following infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG following Q-wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder (akinetetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm (Surawicz B., et al, 2001).

The ECG has important limitations in both sensitivity and specificity in the diagnosis of ischemic heart disease. Although a single normal ECG does not exclude ischemia or even acute infarction. A normal ECG throughout the course of an acute infarct is distinctly uncommon. Prolonged chest pain without diagnostic ECG changes, therefore, should always prompt a careful search for other noncoronary causes of chest pain (Guglin MF., et al, 2006).
3) Echocardiography:

Echocardiogram may play an important role in the setting of acute coronary syndrome. Regional wall motion abnormalities can be identified (Sekhri et al., 2008).

Echocardiogram can also help in defining the extent of the infarction and assess overall function of the left and right ventricles. In addition, it can help to identify complications such as mitral regurgitation, left ventricular rupture, and pericardial effusion (Goodacre et al., 2009). Absence of segmental wall motion abnormality on echocardiography during active chest discomfort is a highly reliable indicator of a non ischemic origin of symptoms (Chun and McGee, 2004).

4) BioMarkers of Myocardial Damage:

I. **Lactate dehydrogenase (LDH):**
Patients with MI exhibit a characteristic pattern of ‘flipped’ LD, where the normal finding LD2>LD1 is reversed (Chan D et al, 2010).

II. **Creatin Kinase (CK):**
In the normal heart, an average of 15-20% of the CK is CK-MB; its distribution is not uniform, with CK-MB percentage greater in the right heart than in the left heart. A single study, however, suggests that CK-MB is not found in normal myocardium, only appearing when the muscle becomes diseased (Halkin A et al, 2006).

III. **Cardiac Troponin cTn:**
Within the cardiac myocytes, cTnT and cTnI are predominantly bound to muscle fibers, and the bound form is released slowly over the course of 1-2 weeks following myocardial infarction. A small fraction of cTn in the myocardial cell is
free within the cytoplasm; this averages 6% for cTnT and slightly lower (2-5%) for cTnI. The free fraction allows early leakage from injured myocardial cells and detection in a time frame similar to that of CK-MB, with cTn reaching a peak at about 24 h following MI. Due to the slow release of the fiber-bound cTn, the rapid decline in circulating cTn right after its peak is typically followed by a plateau and even a small secondary increase. It is important that such an increase not be interpreted as evidence of reinfarction. Circulating cTn declines to baseline levels in about 5-10 days, depending on infarct size (Sabatine MS., et al., 2009).

IV. Myoglobin
V. Creatine Kinase Isoforms
VI. Glycogen Phosphorylase (GP)
VII. Heart Fatty Acid Binding Protein (HFABP)
VIII. Myosin
IX. Ischemia Modified Albumin (IMA)

Complications:
The most serious complication is cardiogenic shock, occurring in approximately 10% of hospitalized MI patients. Mortality in cardiogenic shock patients with MI is high, approaching 60% (Goldberg et al., 2001). Other complications that may result from MI are heart failure, valvular dysfunction, ventricular and atrial tachyarrhythmias, bradycardia, heart block, pericarditis, stroke secondary to left ventricular (LV) thrombus embolization, venous thromboembolism (Lavie and Gersh, 1990). In fact, more than one-quarter of MI patients die, presumably from ventricular fibrillation, prior to reaching the hospital (Dallas, 2002).
Prognosis:

People with non-ST-segment elevation acute coronary syndrome (ACS) have a high incidence of recurrent myocardial ischaemia, a similar long-term outcome to those with STEMI, and a worse outcome than for people with unstable angina. Factors associated with a poorer prognosis include:

- Advancing age.
- Presence and severity of ECG changes of ischaemia.
- Magnitude of rise in biomarkers of myocardial injury (e.g., serum troponin).
- Left ventricular dysfunction, cardiogenic shock, increased heart rate, arrhythmias (ventricular fibrillation, atrial fibrillation).
- Renal impairment.
- Diabetes mellitus.
- Anaemia.
- Cerebrovascular disease, peripheral vascular disease.

Any delay in arranging angiography for high-risk patients is associated with increased mortality and adverse outcomes (Swanson et al., 2009).

Treatment:

- Medicines

1- Beta blockers: Beta blockers decrease heart's workload. These medicines also are used to relieve chest pain and discomfort and have a role in prevention of repetition of heart attacks. Beta blockers also are used to treat arrhythmias (irregular heartbeats).

2- ACE inhibitors: ACE inhibitors lower blood pressure and reduce strain on heart. They also help slow down further weakening of the heart muscle.
3- **Anticoagulants:** Anticoagulants, or "blood thinners," prevent blood clots from forming in arteries. These medicines also keep existing clots from getting larger.

4- **Anticlotting medicines:** Anticlotting medicines stop platelets from clumping together and forming unwanted blood clots. Examples of anticlotting medicines include aspirin and clopidogrel.

5- Medicines to relieve pain and anxiety, treat arrhythmias (which often occur during a heart attack), or lower your cholesterol (these medicines are called statins) may be given.

(Cabello JB., et al, 2010).

- **Medical Procedures**

  1- percutaneous coronary intervention (PCI).
  2- Coronary bypass surgery.

N-acetylcysteine (NAC)

Introduction:

N-acetylcysteine (NAC) a sulphydryl substance is a derivative of amino acid L-cysteine. It has mucolytic activity (Webb WR, 1962), detoxifying properties (Ziment I, 1986), and antioxidant action (Sadowska AM. Et al., 2006).

Mechanism of action:

a) Antioxidant action:

Antioxidant properties of NAC come from its specific structure. As it contains amino acid L-cysteine plus an acetyl (CO-CH3) group attached to the amino (NH2) group. All amino acids including L-cysteine with sulphur group are characterized by antioxidant properties. Since L-cysteine is a precursor of reduced glutathione (GSH), synthesis of NAC contributes to augmentation of the level of this major intracellular antioxidant (Sadowska AM. Et al., 2006).

Glutathione a sulphur containing amino acid, is primarily synthesized in liver. It is present in fruits, vegetables and meat products. It has many biological action including myocardial antioxidant defense, alternate oxidative change induced by Ischemia/ Reperfusion I/R. This action is performed by important myocardial adaptations at cellular and organ levels like enhanced high energy phosphate reserve, coronary collateral blood flow, Ca 2+ homeostasis, antioxidant defense, peripheral adaptation such as vascular proliferation and hormonal changes (Sudha M. et al., 2013).

Depleted pool of GSH is often caused by oxidative stress and inflammation. N-acetylcysteine can therefore normalize disturbed redox status of
the cells and thus influence redox – sensitive cell signaling and transcription pathways.

Sulfhydryl group (–SH) in the NAC molecule make possible also to directly scavenge reactive oxygen species (ROS) such as superoxide radical (O2), hydrogen peroxide (H2O2), and hydroxyl radical OH (Sadowska AM. Et al., 2006 and Zafarullah M.et al., 2003). These species primarily are produced by the mitochondria in the cells as by-products of cellular metabolic pathways. In physiological level ROS play a significant role in proper functioning of many mechanisms that control cell division. They serve as critical second messengers in a variety of intracellular signaling pathways mediating a lot of important processes e.g. activation of transcriptions factors (NF-κB, AP-1), regulation of protein phosphorylation and regulation of calcium level inside the cells as well as phagocytosis process. However they possess highly reactive and toxic properties (Ścibiór-Bętkowska D.et al., 2009).

Surprisingly, NAC can exert also pro-oxidant capabilities (auto-oxidation process), inducing generation of H2O2 in the presence of O2 and leading to cell damage (Lee YJ.et al., 2011).

b) Anti-inflammatory action:

Antiinflammatory action of NAC manifests by inhibition of many proinflammatory cytokines activity including interleukin 8 (IL-8), IL-6, tumour necrosis factor α (TNF-α) (Maher TM. Et al., 2007 and Radomska-Leśniewska DM. et al.,2010). Fibroblast proliferation and collagen synthesis is also down-regulated by this drug (Ask K, Martin GE. Et al., 2006). These kinds of NAC activities can be a result of modulation of transcriptional activities through several
pathways involving c-Fos/c-Jun, NF-κB, STAT, and cyclin inhibitors (Zafarullah M. et al., 2003).

c) Antiangiogenic action:

Since disturbed angiogenesis is associated with a number of diseases, therapeutic efficiency of NAC may also be correlated with its antiangiogenic activity. N-acetylcysteine was described as inhibitor of vascular endothelial growth factor (VEGF) – induced angiogenesis (Ushio-Fukai M. et al., 2002), endothelial cell invasion as well as angiogenesis in vitro, presumably because of the inhibition of metalloproteinase activities (MMP) (Cai T. et al., 1999). Radomska-Leśniewska DM. et al., 2010 and Radomska-Leśniewska DM. et al., 2006 confirmed MMP9 and proangiogenic intercellular adhesion molecule-1 (ICAM-1) inhibition by this drug. Vascular endothelial growth factor, the most powerful stimulator of angiogenesis, was also downregulated by NAC (Nijmeh J. et al., 2010). This antioxidant drug reduced VEGF expression in ras-transformed tumor cells (Rak J. et al., 2000). Aluigi et al. (Aluigi MG. et al., 2000) demonstrated direct cytoprotective and anti-genotoxic effects mediated by NAC on endothelial cells.

➤ Clinical Benefits:

1. **Cardiovascular System Benefits:**

   NAC has detected to have cardioprotective effect, this effect can be explained by these mechanisms:

   I. Prevent LDL-cholesterol (“bad” cholesterol) from being oxidized and causing inflammatory damage to the blood vessels (Palmer LA., et al. 2007).
II. It lowers the levels of homocysteine, which prevents the buildup of plaque in the arteries. The lower the homocysteine, the less likelihood of arterial blockage (Palmer LA., et al. 2007).

III. NAC is the most effective natural remedy that lowers the blood levels of lipoprotein a (Lp(a)), thought by many scientists to be a more accurate predictor of cardiovascular disease than blood levels of cholesterol. Diet changes and drugs do not lower Lp(a) anywhere as well as NAC (Marsden PA. 2007).

IV. NAC has been shown to increase nitric oxide production that has vasodilating action thus increase blood flow in coronaries (Viora M., et al. 2002 and Anfossi G., et al. 2001).

V. NAC may also be an angiotensin-converting enzyme inhibitor. It significantly reduce angiotensin II level in humans by 50% and ACE activity by 31% in plasma of rats (Jan Šochman., et al., 2009).

VI. NAC also seems to be pleuripotent protector against cell death induced by various stimuli (Jan Šochman., et al. 2009).

VII. NAC act against oxidative stress by:

   a) NAC as a precursor of glutathione may replete dwindling glutathione stores.

   b) By the direct redox mechanisms of the cysteine-cystine system it may directly eliminate free radicals.

   c) Using its sulphydryl group, NAC by binding with the –SH groups of the membrane enzymatic system, may form mixed disulphides and reversible as the binding is. NAC may afford temporary
protection to these structures against oxidation / lipid peroxidation. (Jan Šochman., et al., 2009).

Beside this cardioprotective effect it also can reduce cardiac ischemia as NAC has been suggested to reverse the tolerance of nitrates. It is postulated that nitrates act by providing a precursor for nitric oxide which stimulates soluble guanylate cyclase resulting in vasodilatation. This vasodilatation decreases with time when nitrates are given by prolonged infusion. The administration of NAC would appear to reverse the tolerance and enhance the degree of vasodilation for a given dose of nitrate. N-acetylcysteine has also been used to reduce the cardiotoxicity of doxorubicin (M. C. ATKINSON, 2002).

2-Neurological Benefits:

Since GSH has been documented to help numerous neurological conditions such as Parkinson’s Disease, multiple sclerosis, Alzheimer’s, hearing damage, and ataxia. it stands to reason that NAC would be helpful because supplementation of it raises the blood levels of GSH (Chen G, et al., 2008)

3-Detoxification and Drug Addiction Benefits:

NAC protects the body from many different toxins because of its content of sulfhydryl groups that can bind and inactivate herbicides, mercury, cadmium, lead, other toxic heavy metals, drugs like acetaminophen, environmental pollutants, microbes like E. Coli, carbon tertrachloride and aflatoxin. Although not a drug, NAC has government approval as a drug to prevent liver damage from acetaminophen (Tylenol) poisoning (Marchetti A. et al., 2009).

A very common condition that plagues more than 50 million people in North America is a condition known as non-alcoholic fatty liver disease (NAFLD). In
this condition, the liver stores excessive amounts of fat mostly due to insulin resistance, metabolic syndrome or diabetes. Liver function tests are usually elevated indicating damage to liver cells and the liver appears grossly fatty on an ultrasound. Studies also show a significant improvement in liver function tests with supplementation of NAC. Not only it protect liver cells but it also helps heal a damaged liver (Chun L.J., et al., 2009).

Studies also indicate that NAC also diminishes the craving for highly addictive drugs including cocaine and nicotine. It may be a useful adjunct in any drug detoxification program (Olivia D. et al., 2011).

4- **Respiratory Tract Benefits:**

NAC is mucolytic (dissolves mucous). Just about any lung or bronchial problem can benefit from high NAC supplementation. Whether chronic bronchitis, cystic fibrosis, asthma, sinusitis or pneumonia, NAC helps reduce the viscosity of mucous so that the body can more easily cough it up. A number of studies also conclude that NAC prevents influenza, possible through this mucolytic mechanism (Rogers DF, 2007).

NAC reduces both the frequency and duration of COPD (chronic obstructive pulmonary disease) attacks and may blunt the ravaging clinical course of pulmonary fibrosis, a usually lethal lung disease (Stav D. et al., 2009).

5- **Gynaecological disorders:**

N-acetylcysteine was found to exert a benefit effect in polycystic ovary (PCOS) and endometriosis as have shown last year trials (Masha A. et al., 2009). N-acetylcysteine exerted action seems to be promising in endometriosis treatment.
as it can reduce oxidative stress, chronic inflammation and elevated angiogenesis level (Maria GP., et al. 2013).

6-gastrointestinal Benefits:

The bacteria known as H. Pylori has been known to be the cause of ulcers, gastritis, reflux disorder discomforts and even different types of gastrointestinal cancer. In fact, it’s the second leading known cause of all cancers (Konturek PC. Et al., 2009). NAC supplementation is capable of inactivating H. Pylori and is something worth adding to any resistant to antibiotics H. Pylori infections (Gurbuz AK. Et al., 2005).

7-Renal Benefits:

Kidney disease is greatly helped by NAC supplementation. Even dialysis patients can be helped by as little as 600 mg NAC daily to reduce inflammation occurring in chronic kidney disease (Bagshaw SM., et al, 2006).

8- Immunological Benefits:

Because NAC boosts the body’s levels of GSH, it helps fight most viruses, including the influenza virus and HIV, the AIDS virus. GSH is vital for optimal T and B-lymphocyte function. NAC can block the production of the AIDS virus so is a valuable natural defense against at least this virus if not millions of others (Us D, 2008). Aside from viruses, NAC protects the body from numerous pollutants, drugs, microbes and toxic heavy metals like mercury (Garozzo A. et al. 2007).

One would think it might be a good idea to supplement the body with GSH, but the major problem here is that GSH is not absorbed intact from the gastrointestinal tract. Oral GSH supplementation is destroyed and inactivated by stomach acid. NAC is not. Supplementation of NAC is therefore more desirable.
because the body will make much more GSH than if supplementing GSH orally in any form (Kerksick C, et al., 2005).

Evidence exists that NAC blocks the progression of most cancers and could be taken with chemotherapy to improve treatment outcomes (De Flora., et al, 2001).

9- Athletic Benefits:

NAC improves athletic performance as it reduces muscle fatigue and as proven in double blind studies, enhances athletic endurance Due to its antioxidant effects and benefits to the respiratory system. (Zembron-Lacny A. et al., 2007).

10 - Anti-Aging Benefits:

If you can effectively scavenge harmful free radicals it stands to reason that you can prevent premature aging. This phenomenon has indeed been proven in numerous scientific studies (Peake J. et al., 2004).

11 - Eye disorders:

The role of oxidative mechanisms in diabetes, AMD (age macular degeneration), dry eye syndrome and cataract seems to be essential for development of the pathological changes in ophthalamic tissues. The eye is at high risk to be damaged by oxidative stress. Molecular oxygen is able to directly destruct or lead to the generation of secondary reactions which can initiate oxidative processes .NAC is used in the treatment of a range of ophthalmic disorders. (Augustin AJ. 2010) .
**Recommended dose:**

The recommended dose is 600 mg/day and it’s available in the form of capsules and solution for IV administration. *(Hendler SS., 2001).*

**Side Effects:**

At dosages of 1,200 mg twice daily or lower, N-acetylcysteine is well tolerated. At these dosages, side effects are unusual, but may include nausea, vomiting, diarrhea, transient skin rash, flushing, epigastric pain, and constipation. At the much larger dosages used to treat acetaminophen overdose, N-acetylcysteine is often poorly tolerated, with side effects such as headache, tinnitus, urticaria, rash, chills, fever, and anaphylactoid reactions (pseudoanaphylaxis). N-acetylcysteine strongly potentiates the effect of nitroglycerin and related medications, and caution should be used in patients receiving these agents in whom it may cause hypotension *(Atkuri KR., et al. 2007).*