INTRODUCTION

Cardiovascular diseases are currently the leading cause of death in industrialized countries and are expected to become so in emerging countries by 2020. Non ST elevation acute coronary syndrome (NSTE-ACS) is one of the most frequent manifestations of acute coronary syndrome. Despite advances in medical & interventional treatment, the mortality & morbidity are still high **(Thygesen K et al., 2012)**.

NSTE-ACS is an unstable coronary condition prone to ischemic recurrences and other complications that may lead to death or MI in the short and long term. The management, which includes pharmacological treatment as well as various strategies for coronary revascularization, is directed to prevent or reduce such complications and to improve outcomes. Risk assessment is a continuous process until hospital discharge that may modify the treatment strategy at any time. Even after discharge, the NSTE-ACS patient remains at elevated risk and deserves special attention **(Hasin Y et al., 2005)**.

The high-sensitive C-reactive protein (HS-CRP) assay is being increasingly used as a marker for cardiac risk

assessment and as a prognostic tool in heart disease. There is a relationship between serum level of HS-CRP and extension of myocardial involvement in myocardial infarction. It may be also helpful in assessing risk of other processes involving inflammation **(Rifai N, 2001).**

Because survival in acute myocardial infarction is best predicted by the extent of left ventricular dysfunction, the ability to accurately measure infarct size & assess functional recovery after therapy has become increasingly important. Echocardiography is the most important modality in the acute setting in patients follow up because it is rapidly and widely available. Left ventricular global and regional systolic function is an important prognostic variable in patients with CAD and can be easily and accurately assessed by echocardiography **(Cheitlin MD et al., 2003)**.

The use of two dimensional echocardiography is a reasonable tool in diagnosis, early risk stratification, decision making of management plan and follow up for patients with non ST elevation myocardial infarction **(Romano et al., 2000)**.

AIM OF THE STUDY

The aim of our study was to correlate between HS-CRP level and degree of infarction size in patients with non ST- elevation myocardial infarction.

Chapter (1)

NON-ST ELEVATION MYOCARDIAL INFARCTION

Pathophysiology, Diagnosis and Risk Stratification

Acute coronary syndrome is the clinical manifestation of the critical phase of coronary artery disease. Based on ECG and biochemical markers it is distinguished from ST elevation myocardial infarction, non ST elevation myocardial infarction and unstable angina. The common underlying pathophysiology is related to plaque rupture or erosion with subsequent thrombus formation **(Falk E et al., 2004)**.

Pathophysiology:

Atherosclerosis is by far the most frequent cause of coronary artery disease, carotid artery disease and peripheral artery disease, but atherosclerosis alone is rarely fatal Life threatening. Manifestation of atherosclerosis such as ACS are usually precipitated by acute thrombosis, superimposed on a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow **(Davies MJ, 2000).**

Atherothrombosis:

Atherosclerosis is a chronic and multifocal immune-inflammatory, fibro-proliferative disease of medium sized and large arteries mainly driven by lipid accumulation**.** Atherosclerosis begins to develop early in life and progress with time, but the speed of progression is unpredictable and varies markedly among different subjects. At every level of risk factor exposure, there is substantial variation in the amount of evolved atherosclerosis. Probably because the individual vulnerability to atherosclerosis and its risk factors varies greatly. However even in vulnerable individuals, it usually takes several decades to develop obstructive or thrombosis-prone plaques **(Libby P, 2002).**

Systemic and local inflammation:

Three key pathophysiological mechanisms link vascular inflammation with the early development of ACS. Inflammation within the atherosclerotic plaque is reflected by monocyte recruitment, macrophage activation and the release of free radicals. The consequence is metalloproteinase activation and destabilization of plaques. Paradoxical vasoconstriction is linked with endothelial dysfunction, triggered by platelet aggregation,

the release of thrombin and endothelin-1, and sympathetic stimulation. Thrombogenicity arises from an imbalance between endogenous concentrations of nitric oxide, prostacyclin, protein C/S and tissue plasminogen activator, and the prothrombotic stimulus from plaque components including tissue factor and apoptotic microparticles of endothelial origin **(Mallat Z et al., 2000).**

The endothelium plays a critical role not only in the regulation of vasomotor tone, but is responsible for release of prostacyclin, endothelin-1, hyperpolarizing factor and nitric oxide, all of which influence thrombotic risk and vascular tone. Endothelial dysfunction is associated with enhanced oxidative stress and reduced nitric oxide bioavailability. Nitric oxide is synthesized from L-arginine under the influence of the enzyme nitric oxide synthase and is the key endothelium-derived relaxing factor playing a pivotal role in the maintenance of vascular tone and reactivity **(Moncada S, 1993).**

In addition to being the main determinant of basal vascular smooth muscle tone, nitric oxide opposes the actions of potent endothelium-derived contracting factors such as angiotensin-II and endothelin-1. Furthermore, nitric oxide

inhibits platelet and leucocyte activation and maintains the vascular smooth muscle in a non-proliferative state. Although pathological findings associate ACS with the rupture or erosion of specific plaques, evidence exists for more widespread inflammation both in the systemic circulation and the arterial wall. Neutrophil activation has been demonstrated in both non- culprit and culprit coronary arteries in ACS, as evidence of general inflammatory up-regulation **(Buffon A et al., 2002).**

In contrast, such changes were not present in patients with stable angina, despite a similar extent of coronary artery disease. Furthermore, there is clinical evidence that acute systemic inflammation influences endogenous endothelium-dependent tissue plasminogen activator release in clinical studies. The findings suggest that more extensive inflammation exists in the arterial wall in the context of ACS with increased susceptibility to ACS events in more than one vascular territory **(Vita JA, 2002).**

Although studies often report endothelial dysfunction as a loss of the vasodilatory capacity (in response to a nitric oxide-releasing stimulus such as acetylcholine), the term encompasses a generalized defect in all the homeostatic mechanisms.

Endothelial dysfunction is a broad term that implies diminished production or availability of nitric oxide and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors (such as endothelin-1, angiotensin and oxidants).Endothelial dysfunction has been implicated in the pathogenesis and clinical course of all known cardiovascular diseases and is associated with future risk of adverse cardiovascular events **(Britten MB, 2000).**

Vulnerable plaques:

Coronary atherosclerotic plaques are very heterogenous structurally as well as biologically, and even neighboring plaques in the same artery may differ markedly during a lifetime, none or only few coronary plaques become complicated by clinically significant thrombosis, and these rare but dangerous thrombosis-prone plaques are called vulnerable. Thus, a vulnerable plaque is a plaque assumed to be at high short-term risk of thrombosis, i.e. causing an ACS. Approximately 75% of all coronary thrombi responsible for ACS are precipitated by plaque rupture **(Muller JE et al., 2004)**

In plaque rupture, there is a structural defect (a gap) in the fibrous cap that separates the lipid-rich core of an inflamed

plaque from the lumen of the artery. Lipid accumulation, thining of the plaque's fibrous cap with local loss of smooth muscle cells and inflammation with many macrophages and few mast cells and neutrophils and intraplaque heamorrhage destabilize plaques, making them vulnerable to rupture. In contrast, smooth muscle cell-mediated healing and repair processes stabilize plaques, protecting them against rupture**.** Plaque size or stenosis severity reveals nothing, or only a little about a plaque's vulnerability **(Mills PG, 2002).**

Many rupture-prone plaques are invisible angiographically, because of compensatory vascular remodeling, and they appear to be highly thrombogenic after rupture, probably because of a high content of tissue factor **(Mallat Z, 2001).**

Clinical observations suggest that culprit lesions responsible for ACS generally are less calcified than plaques responsible for stable angina, indicating that calcium confers stability to plaques rather than the opposite **(Ganz P et al., 2001).**

The total amount of calcification (the calcium score) is a marker of plaque burden (and thus a marker of cardiovascular

risk) rather than a marker of risk conferred by the individual calcified plaque **(Severson A et al., 1998).**

Plaque vulnerability and remodelling:

Arterial remodeling is bidirectional. Plaques responsible for ACS are usually relatively large and associated with compensatory enlargement that tends to preserve a normal lumen despite the presence of significant and potentially dangerous vessel wall disease. Such lesions, hidden in the arterial wall, may not be seen by angiography. As many as three-quarters of all infarct-related thrombi appear to evolve over plaques causing only mild to moderate stenosis prior to infarction, partly because their propensity for outward remodeling, partly because of their much greater prevalence compared to stenotic plaques. Thus, the great majority of myocardial infarctions originate from atherosclerotic lesions that prior to acute events were heamodynamically insignificant and probably asymptomatic. In contrast, plaques responsible for stable angina are usually smaller but nevertheless may cause more severe luminal narrowing because of concomitant local shrinkage of the artery (inward remodeling) **(Fuster V, 2004).**

Onset of acute coronary syndrome (vulnerability versus triggers):

Sudden rupture of a thin and inflamed fibrous cap may occur spontaneously but triggering could also play a role and thus help explain the non-random onset of ACS. Potential triggers may include extreme physical activity, especially in someone unaccustomed to regular physical activity, severe emotional trauma, sexual activity, exposure to illicit drugs such as cocaine or amphetamines, cold exposure and acute infections-or simply normal daily activities **(Muller JE, 2002).**

Thrombotic response:

There are three major determinants of the thrombotic response to plaque rupture: the local thrombogenic substrate, the local flow disturbances, and the systemic thrombotic propensity.

Local thrombogenic substrate

Macrophage infiltration and activation, and lipid accumulation destabilize plaques making them vulnerable to rupture. These plaque components appear to be highly thrombogenic when exposed to flowing blood after plaque

rupture. Activated macrophages express tissue factor, and the lipid rich atheromatous core contains high amounts of tissue factor. Oxidized lipids in the lipid rich core may stimulate platelet aggregation **(Falk E et al., 1994).**

Local flow disturbances

A platelet rich thrombus may form and grow within a sever stenosis, where the blood velocity and shear forces are highest **(Ruggeri ZM, 2002).**

Systemic thrombotic propensity

Tissue factor plays an important prothrombotic role both locally and systemically. The initial flow obstruction is usually caused by platelet aggregation, but fibrin is important for stabilization of the early and fragile platelet thrombus **(Ruggeri ZM, 2002)**.

Dynamic thrombosis and microembolization:

The thrombotic response to plaque rupture is dynamic: thrombosis and thrombolysis, often associated with vasospasm, causing intermittent flow obstruction and distal embolization **(Falk E, 2003).**

Diagnosis and risk stratification of NSTEMI

Clinical presentation

The typical clinical presentation of NSTEMI is retrosternal pressure or heaviness (angina) radiating to the left arm, neck or jaw which may be intermittent (usually lasting several minutes) or persistent. There are several atypical symptoms and these include epigastric pain, recent onset indigestion, stabbing chest pain and chest pain with pleuritic symptoms or increasing dyspnea. Atypical complaints are often observed in younger and older patients, in women and in patients with diabetes **(Goldman L, 2000)**.

Detailed history and physical examination:

History of presenting symptoms and standard risk factors (Age, DM, HTN, Smoking, family history, anginal episodes, dyspnea, aspirin intake, past history of similar episodes, CAD, dyslipidemia, etc) has to be taken and evaluated. The clinical examination is frequently normal. The presence of tachycardia, heart failure or heamodynamic instability must prompt the physician to expedite the diagnosis and treatment of patients. It is important to identify clinical circumstances that may precipitate NSTEMI such as anemia, infection, fever and

metabolic or thyroid disorders. An important goal of physical examination is to exclude non-cardiac causes of chest pain and non-ischemic cardiac disorders (e.g. pulmonary embolism, aortic dissection, pericarditis and valvular heart disease) or extra cardiac causes **(Linadhi B et al., 2003**).

Electrocardiogram (ECG):

In NSTEMI, ECG may show ST segment deviation, T wave changes or may remain normal. ST segment shifts and T wave changes are the ECG indicators of unstable CAD. The number of leads showing ST segment depression and the magnitude of ST depression are indicative of the extent and severity of ischemia and correlate with the prognosis**.** ST depression of >2mm carries an increased mortality risk. Inverted T wave, especially if marked (greater than or equal to 2mm) also indicates NSTEMI. Q waves suggesting prior MI indicate a high likelihood of IHD **(Linadhi B et al., 2003)**.

Biochemical Markers:

Cardiac troponin (CTn) is the biomarker of choice because it is the most sensitive and specific marker of myocardial injury/necrosis available. Troponin levels usually increase after 3-4 hours. If the first blood sample for CTn is not

elevated, a second sample should be obtained after 6-9 hours, and sometimes a third sample is required after 12 to 24 hours. Troponin level may remain elevated up to 2 weeks. Elevated CTn values signal a higher acute risk and an adverse long term prognosis. Creatine kinase, creatine kinase MB and LDH are less sensitive and specific for the diagnosis of NSTEMI. However, they remain useful for the diagnosis of early infarct extension (re-infarction) and peri-procedural MI because of their short half-life. NT-pro BNP is helpful in assessing left ventricular failure **(Mair J et al., 2010).**

Echocardiography:

Echocardiography and Doppler examination should be done after hospitalization to assess the global left ventricular function and any regional wall motion abnormality. Echocardiography also helps in excluding other causes of chest pain **(Mair J et al., 2010)**.

Risk stratification at presentation:

NSTEMI includes a heterogeneous group of patients with a highly variable prognosis. The risk stratification is necessary for prognosis assessment and treatment. A simple TIMI risk score can be used **(Cohen M et al., 2000)**.