Introduction

Myocardial Infarction during PCI is recently defined, as an elevation of serum biomarkers (preferably cardiac troponins) above the 99th percentile upper reference limit (URL) after PCI, assuming a normal baseline troponin value. According to these published guidelines, an elevation in serum cardiac enzyme to more than three times the 99th percentile URL has been defined as a Type 4a PCI-related myocardial infarction ***(Thygesen et al., 2007).***

The most common mechanisms of myocardial injury during PCI are distal embolization and side branch occlusion (SBO). Other significant causes include dissection, thrombus, no reflow/slow flow, or coronary perforation ***(Ganesha et al., 2011).***

Moreover, the iatrogenic plaques rupture during PCI, besides the risk of mechanical complications, many vasoactive and bioactive substances are released downstream into the microcirculation, leading to vasoconstriction, endothelial dysfunction, myocardial ischemia, and necrosis. These include cholesterol clefts, thrombus, apoptotic bodies, microparticles derived from platelets and inflammatory cells, oxidized lipids, endothelin, angiotensin II, and other factors ***(Tsimikas, 2009).***

As regard PCI in diabetic patients, it was shown that the adverse macrovascular consequences of DM are well recognized, as the accompanying accelerated rate of atherosclerosis that predisposes patients with DM are prone to occlusive CAD with diffuse and rapidly progressive form of atherosclerosis, which increases their likelihood of requiring revascularization ***(Berry et al., 2007).***

Thus, this unique pathophysiology of atherosclerosis in DM modifies the response to arterial injury, with profound clinical consequences to patients with diabetes undergoing PCI ***(Gerstein et al., 2008).***

Statins act via inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. In doing so, they prevent the formation of the cholesterol precursor mevalonate that limits isoprenoid production that binds to G proteins such as Rho and Ras leading to activation of nuclear transcription factors involved in pro inflammatory actions and in the down-regulation of endothelial nitric oxide synthetase **(*Ellis and Anwaruddin, 2009).***

Thus, it has been shown that statins may provide beneficial effects outside of reductions in LDL and triglycerides by the improvement of endothelial function, stabilization of atherosclerotic plaque, decrease of oxidative stress and inflammation, and inhibition of thrombogenic response: the so-called (pleiotropic effects) ***(Nusca et al., 2010).***

Aim of the Work

To compare between diabetic patients who received high loading dose rosuvastatin (40mg) for at least 3days prior to PCI and those received low dose rosuvastatin(10mg) in the incidence of six weeks major adverse cardiac event and periprocedural myocardial infarction

Acute Coronary Syndrome

Introduction:

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI) ***(Cumar and Canon 2009).***

The term "NSTE ACS" describes populations presenting with acute chest pain lasting more than 20 minutes and either positive cardiac markers or dynamic ST-segment changes on the initial ECG without persistent ST-segment elevation ***(Alexander et al., 2007).***

Unstable angina and NSTEMI are closely related conditions: their pathophysiologic origins& clinical presentations are similar, but they differ in severity. A diagnosis of NSTEMI can be made when the ischemia is sufficiently severe to cause myocardial damage that results in the release of a biomarker of myocardial necrosis into the circulation.

In contrast, UA is diagnosed if such biomarker can not be detected in the bloodstream hours after the initial onset of ischemic chest pain ***(Cumar and Canon 2009).***

The definition of acute MI as: a clinical event consequent to the death of cardiac myocytes (myocardial necrosis) caused by ischemia, resulting from an imbalance between supply and demand; is further clinically classified according to the assumed proximate cause of the myocardial ischemia:

Type 1: MI consequent to a pathologic process in the wall of the coronary artery (e.g. plaque erosion/rupture, fissuring, or dissection).

Type 2: MI consequent to increased oxygen demand or decreased supply (e.g. coronary artery spasm, coronary artery embolus, anemia, arrhythmias, hypertension or hypotension.

Type 3: Sudden unexpected cardiac death before blood samples for biomarkers could be drawn or before their appearance in the blood.

Type 4a: MI associated with PCI

Type 4b: MI associated with stent thrombosis

Type 5: MI associated with coronary artery bypass graft surgery

(Thygesen et al., 2007)

Diagnosis requires an electrocardiogram and a careful review for signs and symptoms of cardiac ischemia. Risk

stratification allows appropriate referral of patients to a chest pain center or emergency department, where cardiac enzyme levels can be assessed. Most high risk patients should be hospitalized. Intermediate-risk patients should undergo a structured evaluation, often in a chest pain unit. Many low-risk patients can be discharged with appropriate follow-up. Troponin T or I generally is the most sensitive determinant of acute coronary syndrome ***(Achar et al., 2005).***

Etiology :

Non-ST-segment elevation ACS is usually caused by incomplete coronary occlusion due to thrombus formation at a point of the atherosclerotic plaque rupture or erosion, or to downstream embolization of coronary artery thrombus into smaller vessels, while the thrombus in (STEMI) causes a complete blockage in a major coronary artery ***(Pollack 2008).***

The duration of ischemia caused by the platelet-fibrin thrombi and severe dynamic vasoconstriction determines the overall clinical picture. If ischemia is neither severe nor prolonged (usually <20 min) and often recurs at rest, patients are given a diagnosis of UA. However, if ischemia lasts longer than 30 minutes (usually 1–2 hr) and is associated with elevated cardiac markers, a diagnosis of MI is made ***(Sami and Willerson 2010).***

Plaque rupture generates large amounts of thrombin, causing substantial platelet aggregation and fibrin formation

that lead to the occluding thrombus. As such, thrombi that result in complete occlusion usually contain plasminogen and fibrin, making them accessible to treatment with fibrinolytics. In contrast, if the rupture is small, the reduced amount of thrombin generated creates a smaller non-occluding thrombus that consists predominantly of platelets with little fibrin ***(Otterstad et al., 2003).***

Pathophysiology of acute coronary syndrome:

The pathogenesis of ACS involves an interplay among the endothelium, the inflammatory cells, and the thrombogenicity of the blood ***(Naghavi et al., 2003).***

1. Initiation of Atherosclerosis: Role of the Endothelium:

Endothelial dysfunction is considered a precursor of atherosclerosis. It is characterized by disruption of vessel-wall homeostasis, which is signified by decreased vasodilation, increased oxidative stress and inflammation, with abnormal smooth-muscle-cell proliferation. Risk factors, such as hypertension, dyslipidemia, diabetes, and smoking, induce the overproduction of reactive oxygen species that accelerate the degradation of NO and up-regulation of redox-sensitive genes, including adhesion molecules, cytokines and chemokines which participate in the recruitment and infiltration of inflammatory cells into the vascular wall ***(Sami and Willerson 2010).***

Moreover, dysfunctional endothelium is characterized by excessive production of endothelin 1, which impairs vascular hemostasis; increased expression of adhesion molecules; and increased thrombogenicity of blood through the secretion of several locally active substances ***(Cumar and Canon 2009).***

2. Progression of Atherosclerotic Plaque: Role of Inflammation:

The damaged endothelium release inflammatory cells, especially monocytes, that migrate inside the vascular wall& differentiate into macrophages, which later change into foam cells. Smooth muscle cells also migrate to the intima. These cells proliferate together and secrete a rich and complex extracellular matrix and matrix metalloproteinase (MMP) ***(Lippy, 2008).***

The strength of the fibrous atherosclerotic cap depends on a dynamic balance of collagen synthesis and degradation. Inflammatory cytokines and inflammatory mediators inhibit de novo synthesis of interstitial collagen and increase the production of MMPs, which degrade the fibrous cap and make the atherosclerotic plaque vulnerable to rupture ***(Sami and Willerson, 2010).***

Vulnerable plaques is characterized by a large lipid core, thin fibrous caps, a high density of macrophages and T lymphocytes, a relative paucity of smooth muscle cells, locally increased expression of matrix metalloproteinases that degrade

collagen, eccentric outward remodeling, and increases in plaque neovascularity and intraplaque hemorrhage ***(Cumar and Canon, 2009).***

Inflammation, a particularly important determinant of the "vulnerability" of plaques, is related to an increase in the activity of macrophages at the site of plaque with characteristics that render the plaque more vulnerable to rupture. Elevated levels of C-reactive protein (CRP) have been found to correlate positively with the number of plaque ruptures and may reflect the activity of these macrophages ***(Tanaka et al., 2005).***

In asymptomatic patients, testing for various markers of inflammation, including high-sensitivity C-reactive protein (hs-CRP), has been shown to improve risk stratification and prognostication ***(Tsimikas et al., 2006).***

Since plaque rupture accounts for approximately 55 to 75 percent of acute thrombi in patients with acute coronary syndromes .early recognition of the thin-cap fibroatheroma might lead to early treatment of potentially fatal lesions ***(Ino et al., 2011).***

Most atherosclerotic plaques responsible for future acute coronary events have angiographically mild stenosis ***(Glaser et al., 2005).***

In acute ST-segment elevation myocardial infarction (STEMI), an autopsy has shown that approximately 75 percent of cases are due to plaque rupture, and remaining 25 percent are

attributed to plaque erosion confirmed by clinical studies utilizing high-resolution (10-15 μm) imaging modality optical coherence tomography (OCT) ***(Kubo et al., 2007).***

While in non-ST-segment elevation acute coronary syndromes using OCT, plaque rupture was in 47 percent of cases ***(Ino et al., 2011).***

That was confirmed by studies using intravascular ultrasound (IVUS) that also report an incidence of plaque rupture more frequently in patients with STEMI than in those with non-ST elevation myocardial infarction (NSTEMI) (46 versus 29 percent) ***(Hong et al., 2010).***

Another OCT study has reported that the incidence of plaque rupture in NSTEMI/unstable angina is 47 percent, whereas in STEMI it is 70 percent ***(Ino et al., 2011).***

Thus, identification of vulnerable plaque by Computed tomography (CT) angiography is considered now as emerging & promising approach for the noninvasive assessment of coronary artery stenosis and plaque characteristics ***(Hoffmann et al., 2006).***

3. *Platelets*: Adhesion, activation, and aggregation of platelets at sites of atherosclerotic plaque disruption are pivotal events leading to arterial thrombus formation ***(Lippy 2005).***

Platelet activation is driven by vascular injury, inflammation, and amplification of the coagulation cascade.

Vascular inflammation and impaired endothelium-dependent vasodilatation are regulated by a variety of cellular adhesion molecules (CAMs) that stimulates NAPDH oxidase which generates reactive oxygen species that alter endothelial cell structure and facilitate leukocyte migration into intracellular spaces mediates monocyte rolling platelet-neutrophil interactions ***(Maksimowicz-McKinnon et al., 2004).***

Monocyte chemoattractant protein-1 (MCP-1) regulates monocyte and macrophage migration and infiltration to sites of active inflammation. MCP-1 further upregulates CAM production and induces proinflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs). MCP-1 induces proinflammatory interleukin-6 (IL-6) and promotes vascular smooth muscle cell proliferation at inflamed plaques ***(Viedt et al., 2002).***

Activated T-cells and prothrombotic, proinflammatory CD40-CD40L interactions trigger Gp IIb/IIIa receptor expression on platelet surfaces. The concentration of MMP-9 becomes elevated, which further destabilizes vulnerable necrotic plaque by stimulating reactive oxygen species, enhancing lipid peroxidation, and destroying cellular membranes ***(Viedt et al., 2002 and Egashira, 2003).***

This progression facilitates atherosclerotic plaque rupture exposing collagen and von Willebrand factor on the damaged endothelium to create an extensive surface for platelet adhesion. Adherent platelets subsequently aggregate, following

a release of a variety of platelet intracellular signaling molecules as thromboxane A2(TxA2), adenosine diphoshphate (ADP), serotonin (5-HT) Additional platelets are recruited to the site of injury and adhesion where conformational changes in platelet cytoskeletal proteins result in upregulation and expression of Gp IIb/IIIa receptors on platelet surfaces. Gp IIb/IIIa receptor to fibrinogen-binding causes extensive cross linking, which facilitates thrombus formation ***(Silva et al., 2006).***

Diagnosis:

- Clinical presentation: several clinical presentations have been distinguished:
- Prolonged (>20 min) anginal pain at rest.
- New onset (de novo) angina (Class II or III of the Classification of the Canadian Cardiovascular Society.
- Recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics crescendo angina);
- Post-MI angina ***(ESC guidelines, 2011)***

Pain may be referred to either arm, the jaw, the neck, the back, or even the abdomen. Pain radiating to the shoulder, left arm, or both arms typical angina is described as pain that is substernal, occurs on exertion, and is relieved with rest ***(Achar et al.,2005).***

Although chest pain remains a common presentation of ACS regardless of age, elderly patients were more likely to present with dyspnea (49%), diaphoresis (26%), nausea and vomiting (24%), and syncope (19%) as a primary complaint; hence, MI may go unrecognized ***(Alexander et al., 2007).***

Risk Stratification to Determine the Likelihood of Acute Coronary syndrome:

The first step in assessing patients with chest discomfort or other symptoms suggestive of ACS is determining the likelihood that the symptoms and signs represent ACS secondary to obstructive CAD ***(ACC/AHA guidelines for managing UA/NSTEMI, 2007).***

Table (1): Likelihood That Signs and Symptoms Indicate an ACS Secondary to CAD:

Feature	High likelihood *Any of the following:*	Intermediate likelihood *Absence of high-likelihood features and presence of any of the following:*	Low likelihood *Absence of high- or intermediate-likelihood features but may have:*
History	Chest or left arm pain or discomfort as chief symptom reproducing previously documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age ≥70 y Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥1 mm) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression of 0.5-1.0 mm or T-wave inversion >1.0 mm	T-wave flattening or inversion <1 mm in leads with dominant R waves Normal ECG tracing
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB levels	Normal	Normal

. ACS = acute coronary syndrome; CAD = coronary artery disease; CK-MB = muscle and brain fraction of creatine kinase; ECG = electrocardiography; MI =myocardial infarction; MR = mitral regurgitation; TnI = troponin I; TnT = troponin T

Diagnostic Tools:

1-Resting electrocardiography:

It is recommended that a 12-lead ECG be obtained immediately (within 10 minutes) in patients with chest discomfort or other symptoms consistent with ACS. In fact, the average time between presentation and first ECG was 40 minutes; it was 7 minutes longer in the group >85 than in those <65 years of age, this delay refers to lack of chest pain on presentation with subsequent lower use of early antithrombotic therapy for ACS in elderly patients***(Alexander et al., 2007).***

ECG changes in acute ischemia are best visualized in limb leads I, II and precordial leads V4–6, which represent the most myocardial mass of the anterior and apical area of the left ventricle. The course of the ST depression is horizontal or descending and can be accompanied by a T-wave flattening or a preterminal negative T-wave. Less common manifestations of acute coronary insufficiency are temporary banking of the T wave or U wave inversion ***(Huebner et al., 2010).***

It is found that diagnosis of NSTEMI is greater than three times more likely in patients with chest pain whose ECG showed ST-segment depression in three or more leads or ST-segment depressions that were greater than or equal to 0.2 mV ***(Achar et al., 2005).***

However, diagnosis of NSTE-acute coronary syndrome can be presumed in Patients with acute chest pain lasting longer that 20 min and a normal resting ECG without ST-elevation. ECG's sensitivity for detecting true NST-ASC is very low (~20%) ***(Drew et al., 2005).***

2- Diagnosis of STEMI:

Epicardial injury is diagnosed when the J point (origin of the ST segment at its junction with the QRS complex) is (1) elevated by 1 mm or more in two or more limb leads or precordial leads V4 to V6 or by 2 mm or more in two or more precordial leads V1 to V3; or is (2) depressed by 1 mm or more in two or more precordial leads V1 to V3, in the limb leads. Significant Q waves (greater than 0.04 seconds in duration and at least one quarter of the height of the corresponding R wave) suggest myocardial infarction ***(Wagner and Marriot, 2001).***

Classic ECG changes occur in STEMI Within minutes, there is J-point elevation, and tall, peaked, "hyperacute" T waves develop; ST-segment elevation and reciprocal-lead ST-segment depression also occur. Abnormal Q waves usually develop within the first day, and T-wave inversion and normalization of ST segments occur within hours to days ***(Achar et al., 2005).***

2-The physical examination:

In patients with acute coronary syndrome frequently is normal. Chest-wall tenderness reduces the likelihood of acute coronary syndrome ***(Achar et al., 2005).***