NON-ST Segment Elevation Acute Coronary Syndrome In Patients With Renal Dysfunction: Benefit Of Low Molecular Weight Heparin With Glycoprotein IIb/IIIa Inhibitors on Outcome Compared To Unfractionated Heparin With Glycoprotein IIb/IIIa Inhibitors

Thesis

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INTRODUCTION:

Ischemic heart disease is one of the leading causes of death in the united states; it accounted for more than 20% of a total mortality of 2,443,387 in 2002 (**Kochanek KD, et al., 2006)**

Acute coronary syndrome (ACS) represents a significant public health burden. According to the American Heart Association, preliminary estimates indicate that for 2003, approximately 106 million patients were hospitalized for ACS, including 946,000 patients diagnosed with Myocardial Infarction (MI) and 650,000 with UA. UA/NSTEMI is the more common diagnosis, with only 30% to 40% of MI patients diagnosed with acute STEMI. **(Wiviott SD, et al., 2004)**

Strong evidence exists to show that enaxoparin is superior to unfractionated heparin (UFH) in patients with unstable angina or non ST-segment elevation myocardial infarction. **(Petersen IL, et al., 2004)**

However, the use of low molecular-weight heparin (LMWH) remains disproportionately low, probably because these data were obtained from selected population. At least 40% of patients with unstable angina (UA) or non ST segment elevation myocardial infarction (NSTEMI) seen in routine clinical practice would have been excluded from randomized pivotal trials performed with LMWH. Severe renal dysfunction is one of the most critical exclusion criteria and is found in 40% of excluded patients**. (Collet JP, et al., 2003)**

Acute coronary syndrome are condition characterized by the sudden onset of coronary insufficiency as a result of thrombotic occlusion of one or more coronary arteries..**(Antman EM,, et al., 2004)**

The seminal event in all these conditions is coronary thrombosis. The nidus for thrombus formation is rupture of an atherosclerotic plaque which exposes the blood to thrombogenic lipids and leads to activation of platelets and clotting factors **(Davies Mj, et al., 1985)**

Aim of the work:

Aims to determine whether low molecular weight heparin (LMWH) + glycoprotein (GP) IIb /IIIa inhibitors provide greater benefit than unfractionated heparin (UFH) + GP IIb/IIIa inhibitors, irrespective of renal status.

PATIENTS AND METHODS

This study will include 50 patients admitted to CCU with NSTEMI which is defined as the presence of at least one positive cardiac biochemical marker of necrosis without new ST segment elevation for all patients the following will be carried out after hospitalization:

- History taking with special emphasis on cardiovascular risk factors and other co morbidities
- Thorough clinical examination
- Complete blood picture
- Surface 12 leads ECG on the day of admission
- Kidney function test including: urea – creatinine
- Cardiac enzymes

  CKMB isoenzyme – total CK – cardiac Troponin

Patients will be divided into two groups

1 – group one : will receive low molecular heparin with glycoprotein IIb /IIIa inhibitors
2 – second group: will receive unfractionated heparin with glycoprotein IIb /IIIa inhibitors

Then patients will be divided again according to renal status into subgroups: patients with normal renal function (creatinine< 2) and patients with renal impairment (creatinine > 2).

CLINICAL END POINTS:

1- mortality and MACE (Major Adverse Cardiac Events) at 30 days
2- major bleeding during hospital stay

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Acute Coronary Syndrome

Acute coronary syndrome (ACS) is a term used to describe a group of conditions ranging from unstable angina to acute myocardial infarction, in patients with ischemic heart disease **(Thom et al., 2006)**.

Decisions regarding medical and interventional treatment s are based on the presence or absence of ST segment elevation on the presenting electrocardiogram and abnormal elevation of myocardial enzymes.

Based on these diagnostic criteria, a patients is clinically classified into 3 categories:

- ST segment elevation myocardial infarction (STEMI) (defined as typical chest pain and persistent (>20 min) ST-segment elevation)
- non ST segment elevation myocardial infarction (NSTEMI) (defined as the presence of at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation)
- Unstable angina (UA) (defined as the absence of both ST-segment elevation on the ECG and serum biochemical markers of myocardial necrosis) **(Thom et al., 2006)**.

- The syndrome is the consequence of disruption of a vulnerable coronary artery plaque, complicated by intraluminal thrombosis, embolization, and varying degrees of obstruction to perfusion the severity of coronary arterial obstruction and the volume of affected myocardium determine the characteristics of clinical presentation **(Werf et al., 2003).**

Patients with complete occlusion may manifest ST segment elevation infarction if the lesion occludes an artery supplying a substantial volume of myocardium, but the same occlusion in presence of extensive collateralization may manifest as infarction without ST segment elevation (non- ST segment elevation ACS) **(Bertrand et al., 2002)**.

Similarly, incomplete occlusion at the site of a disrupted arterial plaque may produce ischemia or micro infarction, depending on the volume of myocardium affected and the extent of distal embolization. Sensitive and specific markers of myocytes injury (Troponin) allow the detection of more sutble volume of infarction than possible using conventional cardiac enzymes **(Bertrand et al., 2002).**

The consequence of ACS are not benign among these who survive to reach hospital a live, approximately 12% of patients with ST segment elevation MI will be die in the succeeding six months, 13% of these with non- ST segment

elevation ACS and 8% with unstable angina (GRACE registry). The frequency of new stork is between 1.3 – 3% and rehospitalization for a further ACS, between 17 – 20 % in the same time interval **(Morrow et al., 2000)**.

Incidence of Acute coronary syndrome

Acute coronary syndrome remains an enduring and daunting healthcare problem. Despite vigorous attempts at population risk factor modification and primary prevention of athrosclerosis, the incidence of hospitalization for myocardial infarction (MI) remains stable or increasing slightly.

Annually, there are 17 million patients with Acute coronary syndrome are admitted each year to hospitals in united state of these only one quarter present with Acute myocardial infarction associated with ST segment elevation, three quarters or approximately 1.4 million patients have unstable angina or non ST segment elevation myocardial infarction (US/NSTEMI) **(A(Drew and Fenton, 2005)**.

Mortality/morbidity: when the only treatment for angina was nitroglycerin and limitation of activity, studies of patient with newly diagnosed angina indicated 40% incidence of MI and 17% mortality within 3 months of onset. More recent studies show that prognosis of patients with stable angina pectoris is significantly better due to improvements in

identification, risk stratification, and intervention. Clinically characteristic associated with a poor prognosis include advanced age, male sex, prior MI, diabetes, hypertension, and multiple vessel or left main stem disease **(Drew and Fenton, 2005)**.

Pathophysiology of Acute coronary syndrome:

All Acute coronary events share a common pathologic back ground, consisting of a thrombus growing on plaques undergoing important inflammation and remodeling phenomena **(Yong et al., 2005)**.

The former can be detected by presence T cell, macrophage, foam cells and smooth muscle cells with synthetic phenotype expressing pro inflammatory cytokines, and the latter by erosion or fissuration of plaque and expression of proteoses and their inhibitor **(Virmani et al., 2006)**.

Probability of restenosis and recurrent angina are related to density of T cells and macrophage within plaque that in turn act through expression of cytokine and remodeling agents **(Gorcia – Touchard et al., 2005)**.

Plaque rupture and erosion

The plaque rupture occurred in 46% of patients with unstable angina and 33% of patients with MI but also observed

in 11% of patients with stable angina. The atherosclerotic plaques consist of a soft central core that has a variable lipid-laden content, covered by a fibrous cap that varies in thickness, smoothness, and fragility surface of some plaque is smooth, rough and bumpy **(Moehoro et al., 2002)**.

Lipid core of plaques prone to rupture has a high concentration of cholesterol esters with a high proportion of polyunsaturated fatty acids **(Virmani et al., 2000)**.

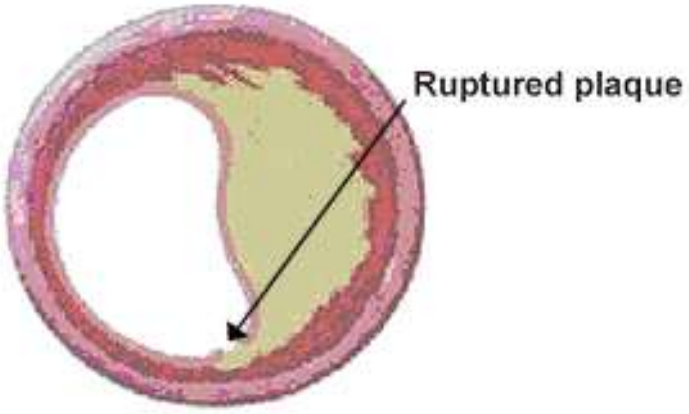
Fracture of fibrous cap occurs often at the shoulder of lipid rich plaque where macrophages enter the fibrous cap is believed to become thin because of the depletion of matrix components through a criteria of enzymes such as matrix – degrading proteinases and cysteine and aspartate proteases, and through reduction in the number of smooth muscle cell. Endothelial cells desquamation through activation of basement membrane degrading metalloprortienases appears to be involved **(Shah, 2003)**.

In addition to plaque rupture, plaque erosion has been described as one of the underlying mechanism in Acute coronary syndrome. Plaque erosions seem to be more common in women **(Farb and Tong, 1996)**.

When erosion occurs, thrombus adheres to the surface of plaque whereas, when plaque ruptures, thrombus involves the

deeper layers of the plaque, down to lipid core, when this latter situation is not accommodated by positive remodeling, it may contribute to the growth and rapid progression of the plaque **(Mickel et al. 2002).**

Fig1 Rupture of Plaque



Rupture of Plaque