Introduction:

Acute coronary syndromes are common phenomena nowadays. They are caused by plaque rupture and thrombosis leading to myocardial ischemia.

Percutaneous coronary intervention (PCI) is often the primary therapy. Before the era of glycoprotein (GP) IIb/IIIa inhibitors, PCI was associated with a major adverse cardiac event rate of 10% to 12%.[1–4] The GP IIb/IIIa inhibitor eptifibatide has been demonstrated to improve cardiac outcomes among patients with PCI by reducing the occurrence of major adverse cardiac events.[1] Despite this improvement in outcomes, micro-infarcts may still complicate PCI in the absence of angiographically evident vessel obstruction.

Thrombus and vascular debris may embolize and lead to plugging of the microvasculature, microvascular dysfunction, and eventually myocardial necrosis. GP IIb/IIIa antagonists at elevated local concentrations may enhance thrombus disaggregation by disrupting platelet crosslinking.[5,6] Indeed, higher levels of platelet GP IIb/IIIa receptor occupancy with eptifibatide have been associated with improved myocardial perfusion among patients with ST-elevation myocardial infarction. [7]Thus, local administration of eptifibatide may result in much higher local concentration, which may lead to increased levels

of platelet GP IIb/IIIa receptor occupancy, destabilization of platelet aggregates, and promotion of thrombus disaggregation in the epicardial artery and microvasculature, possibly offering the potential of improving myocardial perfusion. Eptifibatide has been shown to be safe in intracoronary administration in acute coronary syndromes.[8–10]

We hypothesized that local intracoronary bolus administration of eptifibatide & vasodilators in patients with acute coronary syndrome undergoing stent implantation might result in a better angiographic and clinical outcome.

Aim of the work:

The aim of the work is to prospectively assess the advantage of the local administration of GP IIb/IIIa inhibitor at the site of thrombus as compared to intracoronary administration via the guiding catheter to assess the potential benefits on the quality of reperfusion.

CHAPTER ONE

PCI FOR THROMBOTIC LESIONS

Pathology of Coronary Thrombosis:

Coronary atherosclerosis is by far the most frequent cause of ischemic heart disease, and plaque disruption with superimposed thrombosis is the main cause of ACS[11].

A non-occlusive or transiently occlusive thrombus most frequently underlies unstable angina with pain at rest and non-ST elevation myocardial infarction (non-STEMI), whereas a more stable and occlusive thrombus is most frequently seen in ST elevation MIs (STEMI), modified by vascular tone and available collateral flow.

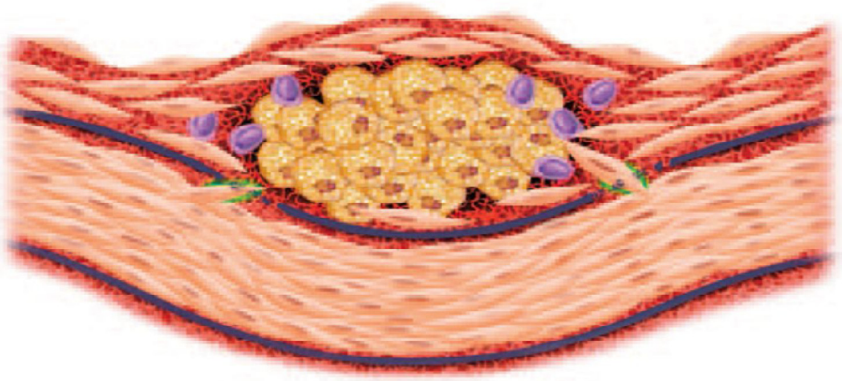

Fig. 1. Progression of atherosclerosis. Macrophages augment the expression of scavenger receptors in response to inflammatory mediators, transforming them into lipid-laden foam cells following the endocytosis of modified lipoprotein particles. Macrophage-derived foam cells drive lesion progression by secreting proinflammatory cytokines. T lymphocytes join macrophages in the intima and direct adaptive immune responses. These leukocytes, as well as endothelial cells, secrete additional cytokines and growth factors that promote the migration and proliferation of SMCs. In response to inflammatory stimulation, vascular SMCs express specialized enzymes that can degrade elastin and collagen, allowing their penetration into the expanding lesion. [16]

Rupture of a fibrotic cap overlying a plaque with large lipid-rich core underlies most thrombotic lesions [11–16] although superficial plaque erosion is the underlying mechanism of sudden cardiac death in one third of the cases and is more common in women and in the posterior descending artery [17].

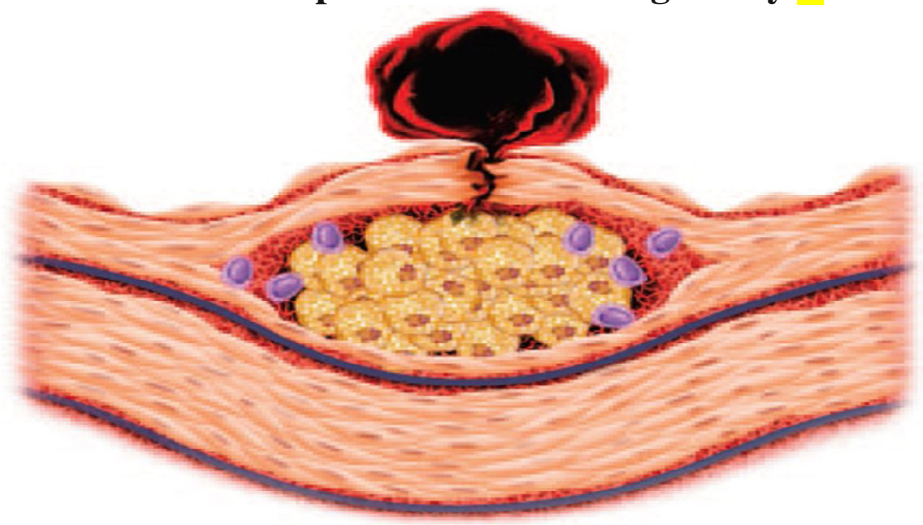

Fig.2. Thrombotic complication of atherosclerosis. Inflammatory mediators can inhibit collagen synthesis and evoke the expression of collagenases by macrophage foam cells within the intima. This imbalance diminishes the collagen content of the fibrous cap, rendering it weak and rupture-prone. In parallel, crosstalk between T lymphocytes and other cell types present within lesions heightens the expression of the potent pro-coagulant tissue factor. Thus, when the fibrous cap ruptures, as illustrated in this diagram, tissue factor induced by inflammatory signaling triggers the thrombus that causes most acute complications of atherosclerosis. Clinically, this may translate into an acute coronary syndrome.[16]

After plaque disruption, hemorrhage into the plaque, luminal thrombosis, and/or vasospasm may cause sudden flow obstruction [18]. Several factors appear to determine the thrombotic response to

plaque disruption/erosion [11]: (1) character and extent of exposed plaque components (local thrombogenic substrates), (2) degree of stenosis and surface irregularities that activate platelets (local flow disturbances), and the (3) thrombotic–thrombolytic equilibrium at the time of plaque disruption (systemic thrombotic tendency).

The clinical manifestation of an acute thrombotic event is determined by the balance between the propensity for thrombus formation and the efficacy of the endogenous thrombolytic processes. A low endogenous thrombolytic activity in ACS has recently been shown to be an independent predictor of poor outcomes.

The thrombus has a large component of densely packed fibrin but in unstable angina the non-occlusive thrombus tends to be mural and is covered by platelets [12] appearing grayish white on angioscopy [19]. The relative lack of therapeutic response to fibrinolysis in unstable angina [20] suggests that this fibrin is not easily accessed by therapeutic agents, although specific antiplatelet drugs may be able to influence events on the active surface. In the setting of STEMI, occlusive thrombi have a predominantly fibrin/ platelet component in the immediate zone of the disruption, but immediately distal to this, they are made up of a loose network of fibrin with intermeshed red cells [12]. On angioscopy, they appear reddish [19].

Thrombi can also cause myonecrosis by spontaneous embolization with occlusion of the

smaller branches distally [12]. Napodano et.al. [21] showed that 4.7% of the 400 patients with ACS were noted to have spontaneous distal embolization prior to percutaneous coronary intervention (PCI). Such embolized components are platelet rich [22].

Definition and Classification of Angiographic Thrombus:

On angiography, a thrombus is defined by the presence of a filling defect with either a total occlusion with convex, irregular, or hazy distal margins. Post injection, there is contrast retention or staining. It can also appear as a partial occlusion circumferentially outlined by contrast medium [23]. A thrombus can be further classified using the (TIMI) thrombus grade [24] defined as follows: TIMI thrombus grade 0, no cine angiographic characteristics of thrombus are present; in TIMI thrombus grade 1, a possible thrombus is present, with such angiographic characteristics as reduced contrast density, haziness, and irregular lesion contour; in TIMI thrombus grade 2, there is definite thrombus, with greatest dimensions ≤1/2 the vessel diameter; in TIMI thrombus grade 3, there is definite thrombus but with greatest linear dimension >1/2 but < 2 times the vessel diameter; in TIMI thrombus grade 4, there is definite thrombus, with the largest dimension ≥ 2 vessel diameters; and in TIMI thrombus grade 5, there is total occlusion and the size of thrombus cannot be assessed. The problem with such a classification is that in patients with STEMI, there is a high

incidence of total occlusion and therefore the prevalence of grade 5 or unknown thrombus size is over 50% of the patients as was shown in one series [25]. A modified thrombus grade was recently suggested by Scianos et.al. [25] where, grade 5 lesions were first reclassified into one of the other TIMI grade categories after flow achievement with either guide wire crossing or passage of a small deflated balloon. In the new scheme, grades 0–3 can be reclassified into small thrombus burden (STB) and grade 4 as large thrombus burden (LTB). With this method, most lesions (99.2%) could be classified into STB or LTB.

Prevalence of Angiographic Coronary Thrombosis in Acute Coronary Syndrome:

There is considerable variation in the reported incidence of angiographically detected coronary thrombus in patients with unstable angina, with figures varying from 1% [26] to 85% [27]. This inconsistency may be partly related to variability in the timing of angiographic study with respect to the last anginal attack; a low incidence of thrombus (1–12%) was reported in patients catheterized 30–90 days after the last attack [26–28], whereas the incidence was higher (52–85%) when angiography was performed soon after active symptoms [29]. Increasing levels of troponin T (tnT) also correlate with a higher occurrence of visible intracoronary thrombi from 2.9% in patients with tnT<0.01 µg/l to 15.7% in those with tnT>0.63 µg/l [30].

Irrespective of the timing of angiography or the relation to tnT, angiography lacks the resolution to detect smaller or mural thrombi [31] such as seen in unstable angina. Sherman et. al.[33] used intraoperative angioscopy at the time of CABG to examine the presence of thrombi in patients with rest angina. Angiography detected only one of seven thrombi while angioscopy detected thrombi in all the offending arteries. The fact that thrombi tend to be larger in STEMI may explain angiography's better sensitivity in this setting as opposed to unstable angina where thrombi can be mural and small.

Prognosis of Angiographically Detected Coronary Thrombi:

The presence of angiographically detected thrombosis in patients presenting with ACS is associated with a higher incidence of in-hospital [31-33] and long-term adverse cardiac events [35]. In general, patients who undergo angioplasty for unstable or post-infarction angina have abrupt closure of the treated vessel and ischemic complications more often than patients with stable angina [34, 35]. The mechanisms behind this relation also include the direct impact of thrombosis on myocardial necrosis and that the thrombus may be a marker of worse long-term outcomes since those patients have more extensive coronary artery disease with a propensity to develop future thrombotic events [30].

In patients with ACS, coronary thrombus can cause myocardial damage by spontaneous or PCI-induced occlusion of an epicardial vessel or its branch(s), or by spontaneous or PCI-induced distal embolization of plaque and thrombotic components. This results in myocardial infarction that can ultimately lead to congestive heart failure, ventricular dysrhythmias, and death. It is difficult to separate the contribution of the natural history of thrombosis from the aftermath of PCI since most patients with ACS are treated with coronary intervention. The unique design of the Fast Revascularization during In Stability in CAD trial [30] allowed us to get an insight into the separate contributions of the two mechanisms.

The negative prognostic impact of angiographic thrombus in the setting of PCI is best studied in patients suffering from STEMI where the thrombus burden is higher than in the other types of ACS. Several STEMI studies showed that PCI resulted in about 15% [21, 36] distal embolization rate. Patients with distal embolization, compared to those without, had lower procedural success rates [36, 37], lower left ventricular ejection fraction [36, 37], larger enzymatic infarcts with increased in-hospital [36, 37] and late [36] mortality rates. The size of the angiographic thrombus is also a negative prognostic marker; a large thrombus was shown to be an independent predictor of distal embolization [37], and correlated with worse final TIMI

flow/myocardial blush grades, as well as 2-year mortality and MACE rates [25].

Pharmacologic Management of Patients with Coronary Thrombosis:

In the setting of ACS or when faced with a thrombotic lesion for which PCI is being considered, adjunctive pharmacologic therapy delivered intravenously or via the intracoronary route should aim at the prevention of in-lab thrombo-embolic events associated with PCI, and the reversal of such events if they occur. Several classes of pharmacologic agents can be used to achieve those goals and include anti-thrombins, anti-platelets, vasodilators, and possibly free-radical scavengers.

Intravenous Anti-thrombins. **Unfractionated heparin (UFH) is an indirect thrombin inhibitor that has been used as an adjunct to PCI even in the setting of stable angina. However, because of several limitations [38] such as its unpredictable stability, its relative inability to inhibit clot-bound thrombin, its pro-thrombotic properties related to poor control of von Willebrand factor release, as well as platelet activation and rebound of thrombin generation after discontinuation, alternate anti-thrombins were investigated.**

Low molecular weight heparins (LMWH) such as enoxaparin have a more predictable pharmacological profile than UFH, removing the need for close therapeutic drug monitoring because

of reduced nonspecific protein binding and reduced neutralization by platelet factor 4. Other properties, such as reduced induction of von Willebrand factor release and reduced platelet activation, are of importance in PCI, during which endothelial denudation, plaque disruption, and implantation of stents are systematically followed by platelet activation and aggregation. Furthermore, LMWHs exhibit a greater inhibition of thrombin generation compared with UFH due to a higher anti-Xa to anti-IIa ratio; they also produce an enhanced release of tissue factor pathway inhibitor. Although the ESSENCE [39] and TIMI 11B [40] trials showed that in the setting of a mainly conservative strategy for ACS, enoxaparin was superior to UFH with respect to cardiovascular endpoints, their efficacy when intravenously administered during PCI was not superior to that of UFH [41].

Direct antithrombins inhibit thrombin without requiring the cofactor antithrombin and can block both fluid phase and clot-bound thrombin. Bivalirudin, the most studied agent in this class, was compared to an UFH + glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors strategy in ACS [42] and STEMI [43] patients. The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) was a randomized trial where 13,819 patients with ACS were assigned to one of three antithrombotic regimens: UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor,

or bivalirudin alone. Angiography was performed during the initial hospitalization in 99% of patients at a median of 19.6 h after admission, after which 56% of the patients underwent PCI. Stents were used in 93% of patients undergoing PCI, 65% of whom received drug eluting stents. Bivalirudin alone, as compared with UFH plus a GP IIb/IIIa inhibitor, was associated with a non-inferior rate of the composite ischemia end point and significantly reduced major bleeding rates [42].

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) was a trial that randomized 3,602 patients with ST segment elevation myocardial infarction who presented within 12 h after the onset of symptoms and who were undergoing primary PCI to treatment with heparin plus a GP IIb/IIIa inhibitor or to treatment with bivalirudin alone. Bivalirudin alone, as compared with heparin plus GP IIb/IIIa inhibitor, resulted in similar ischemic complications but lower major bleeding rates. The lower major bleeding rates noted with bivalirudin were felt to have resulted in a significantly lower 30-day rates of death from cardiac causes and death from all causes [43]. However, bivalirudin, as compared with heparin plus GP IIb/IIIa inhibitors, resulted in a significant 1.0% absolute increase in stent thrombosis within the first 24 h. This may be explained by adenosine diphosphate-induced platelet activation before maximal thienopyridine

blockade of the P2Y12 receptor or by residual thrombin activity after the discontinuation of bivalirudin.

It is also important to note that 63.9% and 65.8% of the patients in the bivalirudin arms of the ACUITY and the HORIZONS-AMI trials respectively received some form of heparin prior to randomization. Therefore, neither trial truly tested bivalirudin alone (without pretreatment with heparin) as compared to UFH + GP IIb/IIIa.

Intravenous Antiplatelets. **GP IIb/IIIa inhibitors are frequently administered to patients with ACS undergoing PCI, a strategy supported by several randomized clinical trials [44–47]. Abciximab, Tirofiban and Integrilin are currently approved in the USA and are directed against the GPIIb/IIIa receptors on the surface of human platelets, blocking the final common pathway for platelet aggregation and preventing aggregation regardless of the initial activating stimulus. They have rapid onset of action and result in a high level of inhibition of platelet aggregation in most patients when measured in vitro.**

In addition to preventing aggregation, potent antiplatelet agents, such as abciximab might also have some limited clot destabilizing potential by altering the balance between the fibrinogen and platelets which together form a clot. Abciximab binds to the platelet GPIIb/IIIa receptor with approximately 1,000 times greater affinity than fibrinogen, which forms the linkages between