

# ANTIPLATELET AND ANTITHROMBOTIC THERAPY IN NON ST ELEVATION ACUTE CORONARY SYNDROME: A review of current literature

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## ABSTRACT

The most important pathological mechanism in non-ST elevation Acute Coronary Syndrome (ACS) is the formation of a platelet rich thrombus on an atherosclerotic plaque. The understanding of this mechanism has changed the management of ACS with time. Until recently, the combination of aspirin and unfractionated heparin constituted the main antithrombotic therapy in ACS with a 46% reduction in vascular events, as reported by the Antithrombotic Trialists Collaboration. However, even with this regimen the recurrences of ischemic events in patients with ACS remained high. Now with the advent of newer drugs i.e., adenosine diphosphate (ADP) receptor antagonists and glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, the out come of patients with ACS have significantly improved. The CURE trial clearly demonstrated the benefits of the combination of aspirin and clopidogrel in reducing major cardiovascular events by 20%. GP IIb/IIIa inhibitors, block the final common pathway of platelet aggregation. Agents like eptifibatide and tirofiban in large studies have demonstrated to cause reduction in 30 days risk of death and myocardial infarction. The risk reduction was greatest in patients with a baseline-elevated troponin, dynamic ST changes, recurrent angina, diabetes and in patients undergoing percutaneous revascularization. In view of the current evidence, appropriate selection of the antiplatelet and antithrombotic agents is the key for reduction in death and major adverse cardiac events in patients with ACS.

**KEY WORDS:** Non ST Segment Elevation Acute Coronary Syndromes (NSTE ACS), Anti-platelet Therapy, Anti-thrombotic Therapy

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## INTRODUCTION

Disruption of an inflamed atherosclerotic plaque leads to a complex pathologic process that is central to the initiation of acute coronary syndrome<sup>1</sup>. It leads to platelet adhesion and platelet activation followed by platelet aggregation. Platelet adhesion is the initial process of thrombus formation, and it starts with plaque rupture or erosion. Platelet adhesion is mediated mainly via the platelet glycoprotein IIb receptor through its interaction with von Willebrand's factor<sup>2</sup>. Platelet activation is a complex process and involves several pathways (Figure 1). Platelet activation leads to a

configurational change in platelets, and from a smooth discoid appearance, they become spiculated. Following this configurational change, degranulation of alpha dense granules takes place inside the platelets<sup>3</sup>. This releases the prothrombotic, inflammatory and chemical mediators that propagate, amplify and sustain the process of thrombosis. Finally, platelet activation leads to the activation of glycoprotein IIb/IIIa (GP IIb/IIIa) receptor, which is responsible for platelet aggregation and fibrinogen binding, thus resulting in the formation of a thrombus. Formation of an occlusive thrombus results in the development of ST segment elevation Acute Coronary Syndrome (ACS), while a non-occlusive thrombus is the causation of a Non-ST segment Elevation (NSTE) ACS<sup>1</sup>.

Proper understanding of the pathogenesis of NSTE ACS has led the physicians to change their approach to management from the use

of more anticoagulants to the use of more antiplatelet therapy. For a long time aspirin and Unfractionated Heparin (UFH), remained the mainstay of treatment of NSTE ACS<sup>4</sup>. Now newer antiplatelet agents, i.e., Adenosine Diphosphate (ADP) receptor antagonists and GP IIb/IIIa receptor inhibitors, have proven to provide significant therapeutic benefits when used in addition to aspirin and heparin<sup>5-7</sup>. This article will summarize the rationale for the recommended antiplatelet and antithrombotic therapies in the treatment of NSTE ACS, in the light of current available literature.

**Aspirin**

Aspirin acts by inhibiting platelet cyclooxygenase-1. It does so by irreversible acetylation of this enzyme, thus preventing the formation of thromboxane A<sub>2</sub> that in turn stimulate platelet aggregation (Figure-1)<sup>8</sup>. Aspirin also has anti-inflammatory properties,

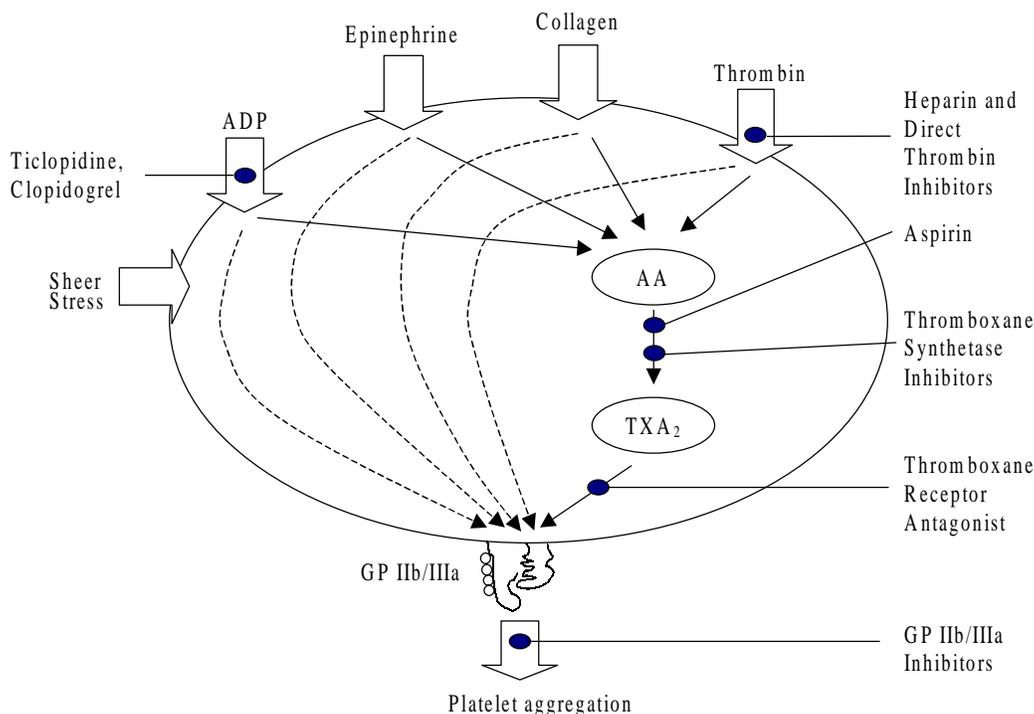


Figure 1: Mechanisms of platelet activation and aggregation.

Platelet activation is an important early step in the Pathophysiology of thrombus formation. Multiple agonists including thromboxane A<sub>2</sub> (TXA<sub>2</sub>), adenosine diphosphate (ADP), thrombin, epinephrine, and collagen can activate platelets. Following activation, degranulation of platelets occur which results in the release of prothrombotic factors. Platelet activation also leads to a conformational change in the platelets and the glycoprotein IIb/IIIa (GP IIb/IIIa) receptors are activated. These receptors bind to fibrinogen and activation of these receptors is the final common pathway for platelet aggregation. AA = Arachidonic Acid.

which probably also contributes to its clinical effectiveness in ACS.

Aspirin is rapidly absorbed from the stomach and upper small intestine. It acts rapidly and achieves a peak plasma level within 30 to 40 minutes of ingestion. Enteric-coated preparations may take up to 3 to 4 hours to reach peak plasma levels. Its plasma half-life is 15 to 20 minutes. Despite its rapid clearance from the circulation, aspirin provides platelet inhibition for the lifespan of each platelet.<sup>9,10</sup>

Multiple randomized studies have clearly established the benefits of aspirin in the management of patients with ACS. The Veterans affair trial (n = 1338) demonstrated a 41% reduction in death or myocardial infarction (MI) (10.1% vs 5% p= 0.004) in patients who received 12 weeks of aspirin, in a dose of 325 mg per day<sup>11</sup> with mortality reduction from 3.3% to 1.6% (p = 0.054). In the Canadian multicenter trial (n = 555), aspirin in a larger dose (325 mg four times daily) was used for an average of 18 months after an episode of unstable angina. This trial demonstrated a 30% reduction in death or MI with aspirin, at two years of follow up. The reduction in death alone was 43% (p = 0.035)<sup>12</sup>. In the Montreal Heart study (n = 479), aspirin was used for only 6 days during the acute phase. It reduced death or MI by 63% compared to the placebo (6.3% vs 2.6%; p = 0.04).<sup>4</sup> In the Research Group in Instability in Coronary Artery Disease (RISC) study, aspirin in a lower dose of 80 mg daily, for one year reduced death or MI by 49%, for up to 12 months (21.4% vs 11%; p = 0.0001)<sup>13</sup>.

Antithrombotic Trialists Collaboration conducted a meta-analysis of 287 studies. It involved 135,000 patients in comparisons of antiplatelet therapy versus control and 77,000 in comparisons of different antiplatelet regimens. This meta-analysis reported a 22% reduction in the composite end point of vascular death, MI, or stroke (13.2% vs 10.7%; p < 0.0001) in the high-risk group of patients with acute MI or with history of past MI. Among subset of patients with unstable angina, there was a 46% reduction in vascular events.<sup>14</sup>

Considering a large body of evidence in fa-

vor of aspirin, in the 2002 update of ACC/AHA guidelines for the management NSTEMI ACS, aspirin remains a class I indication among these patients<sup>15</sup>. Aspirin should be avoided in patients who are allergic to it or who have other contraindications e.g., active bleeding peptic ulcer.

Despite its significant beneficial effect the incidence of recurrent event, remain high among patients with NSTEMI ACS. This is because thromboxane A<sub>2</sub> is just one of 90 agonists that can stimulate platelet aggregation. Due to this fact, aspirin is considered as a weak antiplatelet agent. This highlights the need for newer and more potent agents, which either can replace or be used in addition to aspirin in patients with NSTEMI ACS to reduce the incidence of short and long-term recurrent events.

#### ***Unfractionated & Low molecular weight heparin***

Heparin is the most widely used anticoagulant. Unfractionated Heparin (UFH) is a glycosaminoglycan composed of a mixture of polysaccharides of varying molecular weights.<sup>16</sup> Heparin activates antithrombin III that in turn inactivates thrombin, and activated factors IX, X, XI, and XII of coagulation cascade. It also modulates inhibition of thrombin with heparin cofactor II, and blocks thrombin activation by plasmin. Heparin possesses antiplatelet properties as well. It inhibits von Willebrand's factor and thrombin mediated platelet aggregation.<sup>17</sup> Heparin with fewer sugar units or Low Molecular Weight Heparin (LMWH), are fractions of UFH produced by chemical or enzymatic depolymerization of the polysaccharide chains. The average molecular weight of LMWH is 4000 to 6000 daltons, with an overall range of 2000 to 16000 in varied preparations.<sup>18</sup> LMWH have less effect on thrombin but possess the ability to inhibit activated factor X of coagulation cascade. The anti-factor Xa: Anti IIa, ratio of LMWHs varies according to the preparation and is approximately 2 to 4:1.<sup>19</sup>

The LMWH has greater bioavailability than UFH, it has higher anti-factor Xa:IIa activity ratio and possesses a more predictable antico-

agulant effect.<sup>19,20</sup> LMWH is usually administered subcutaneously in fixed doses, without a need to monitor activated Partial Thromboplastin Time (aPTT). In contrast, UFH usually requires intravenous infusion with constant monitoring and adjustment of dosages. Moreover, LMWH is associated with fewer side effects as compared to UFH.<sup>19</sup>

The first trial using UFH was published in 1981.<sup>21</sup> In this, trial 400 patients were randomly allocated to heparin, atenolol, both or neither. Results were available from 214 patients and it was noted that during 7-day treatment, MI occurred in 3% of patients receiving UFH, compared to 15% in those who were not on heparin. Theroux and colleagues reported a significant reduction in composite of death, MI or refractory ischemia from 26% in the placebo group to 9% with heparin alone, 17% with aspirin alone and 11% with the combination of aspirin and UFH.<sup>4</sup> The RISC trial demonstrated that combination of aspirin and UFH had the lowest event rate at all follow up times.<sup>13</sup> A meta-analysis of relevant trials revealed that addition of UFH to aspirin in the treatment of ACS, resulted in a trend for a lower rate of composite of death or MI during inpatient therapy. This effect was lost at follow up weeks to months later. It was concluded that patients with unstable angina should acutely be treated with an antithrombin agent in addition to an antiplatelet agent.<sup>22</sup>

Several trials have tested LMWHs among patients with NSTEMI ACS. In an initial study, 219 patients were randomized to aspirin alone, aspirin plus UFH or aspirin plus LMWH. The greatest benefit in the reduction of recurrent angina, nonfatal MI and need for urgent revascularization was achieved in the aspirin plus LMWH group. This composite end point and major bleeding occurred in 59%, 63% and 22% in the study groups respectively ( $p < 0.0001$ ).<sup>23</sup> In the FRISC (Fragmin during Instability in Coronary artery disease) trial, a LMWH (dalteparin) was compared to placebo in patients with NSTEMI; aspirin was administered to both groups. At day 6 there was significant reduction in death or MI in the dalteparin

group (4.8% placebo vs 1.7% dalteparin;  $p = 0.001$ ). A low dose dalteparin was continued for 35 to 45 days. The reduction in endpoints in the dalteparin group was much less at 40 days and at 150 days with no significant difference in the endpoints between the two groups.<sup>24</sup>

In FRISC II study, patients with NSTEMI ACS were randomized to dalteparin or placebo for a minimum of 5 days and to early invasive or ischemia guided treatment. Patients were subsequently randomized to receive dalteparin or placebo for 90 days. The composite endpoint of death or MI, in the ischemia guided treatment arm was significantly lower with dalteparin at 30 days (3.1% vs 5.9%;  $p = 0.002$ ), but not at three months (6.7% vs 8.0%;  $p = 0.17$ ). However the composite of death and non fatal MI in the early invasive group was 9.4% versus 12.1% in the ischemia guided patients (relative risk [RR], 0.78; 95% confidence interval [CI], 0.62 to 0.98).<sup>25</sup>

Efficacy of LMWH against UFH has been tested in different trials. The FRIC (FRagmin In unstable Coronary artery disease) trial randomized 1,482 patients with NSTEMI ACS to dalteparin or UFH and there was no significant difference in the composite endpoint of death, MI or recurrent angina in the two groups (7.6% UFH vs 9.3% dalteparin,  $p = 0.33$ ).<sup>26</sup> Similarly, in the FRAXIS (FRAXiparine in Ischemic Syndromes) trial 3,468 patients were randomized to receive UFH or fraxiparine (a LMWH) for 7 days or fraxiparine for 14 days. There was no significant difference among different groups with respect to the primary outcome of death, MI, refractory/recurrent angina at day 14.<sup>27</sup>

Another large LMWH and UFH comparison study, the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave Coronary Events) trial, randomized 3,171 patients and demonstrated a significant reduction in death, MI or recurrent angina at 14 days in the enoxaparin group compared to UFH group (16.6% vs 19.8%  $p = 0.019$ ). This significant benefit was sustained at 30 days ( $p = 0.016$ ) and at one year (32.0%

vs 35.7%;  $p = 0.022$ ).<sup>28,29</sup> Enoxaparin was again compared with UFH in the TIMI 11B (Thrombolysis in Myocardial Infarction) trial. Treatment duration was 3 to 8 days as inpatient and then enoxaparin was continued for 35 days as outpatient while the UFH group received placebo. At 14 days there was a 15% reduction in the composite endpoints of death, MI or recurrent angina with enoxaparin (14.2% vs 16.7%;  $p = 0.029$ ). This difference was maintained at 43 days.<sup>30</sup> In a meta-analysis of ESSENCE and TIMI 11B studies, a significant reduction in the composite end points of death, MI and recurrent angina was demonstrated at 43 days with enoxaparin as compared to UFH (15.6% vs 18.8%;  $p = 0.0005$ ).<sup>31</sup>

In addition to the above-mentioned trials, the ongoing SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularization & GLYcoprotein IIb/IIIa [eptifibatide] inhibitors) trial is designed to evaluate the efficacy and safety of enoxaparin versus UFH as first line management in high risk NSTEMI ACS patients who are also likely to receive treatment with a GP II/IIIa inhibitor. The results of this large trial will give us further insight in the management of high-risk patients with NSTEMI ACS.<sup>32</sup> Considering the beneficial effects of LMWH in patients with NSTEMI ACS, the 2002 update of ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction, has recommended the use of LMWH in addition to antiplatelet therapy as a Class 1 indication.<sup>15</sup>

### **Adenosine diphosphate (ADP) receptor antagonists**

Two thienopyridines (ticlopidine and clopidogrel) are currently available as ADP receptor antagonists. These agents inhibit platelet 2-methylthio-ADP-binding receptor. This leads to inhibition of ADP induced exposure of the fibrinogen-binding site of the platelet GP IIb/IIIa receptor.<sup>33</sup> Cumulatively, these actions result in prevention of ADP-induced platelet aggregation. These drugs also blunt platelet aggregation in response to other stimuli whose actions are mediated through ADP re-

leased from endogenous platelet granules.<sup>34</sup> As the mechanism of action of the antiplatelet effects of aspirin and ADP antagonist differ, there is a potential that combination of these two agents may provide additive benefit.

Ticlopidine acts through its active metabolites.<sup>35</sup> It has a delayed onset of action, taking up to 48 to 72 hours which limits its usefulness in acute situations. Bleeding time take up to 5 to 7 days to become maximally prolonged.<sup>36</sup> Its effects on platelets are irreversible and require up to one week for dissipating completely after stopping the drug. In contrast, the full antiplatelet effect of clopidogrel is achieved in only 2 hours after the administration of a 300-mg loading dose.<sup>37</sup> Ticlopidine requires twice-daily administration of 250 mg tablets, while the dose of clopidogrel is 75 mg per day.

The adverse effects of ticlopidine include diarrhea, abdominal pain, nausea and vomiting. Side effects that are more sinister include neutropenia in approximately 2.4% of patients, severe neutropenia in 0.8% of patients and rarely thrombotic thrombocytopenic purpura.<sup>38</sup> Neutropenia is rarely fatal, and it usually resolves within 1 to 3 weeks of the discontinuation of therapy. TTP is a life threatening complication and carries a high mortality. Ticlopidine therapy requires monitoring of complete blood counts every 2 weeks for first 3 months. Clopidogrel on the other hand has a much more favorable adverse effect profile.<sup>39</sup> In particular, the avoidance of neutropenia, even over an extended follow up period, represents a major advantage of clopidogrel over ticlopidine. TTP has also been reported with the use of clopidogrel, occurring within 14 days of the initiation of therapy.<sup>40</sup>

Both ticlopidine and clopidogrel have been used successfully in clinical trials to prevent stroke and MI, and for prevention of stent closure and graft occlusion. In an open label trial, ticlopidine was compared to placebo in 662 patients with unstable angina, there was a 46% reduction in primary endpoint of death or MI with ticlopidine (13.6% vs 7.3%;  $p = 0.009$ ).<sup>5</sup> This benefit with ticlopidine was observed after two weeks of treatment. Clopidogrel was

compared against aspirin in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial.<sup>39</sup> In this, trial 19,185 patients were randomized to receive aspirin 325 mg per day or clopidogrel 75 mg per day, for a period of 1 to 3 years. The relative risk of ischemic stroke, MI or vascular death was reduced by 8.7% in favor of clopidogrel ( $p = 0.043$ ). The result of this trial provided the evidence that clopidogrel is at least as effective as aspirin.

The CURE (Clopidogrel in Unstable angina Recurrent Events) trial tested the hypothesis that the combination of clopidogrel and aspirin is superior to aspirin alone in the prevention of death, MI and stroke in patients with NSTEMI ACS.<sup>41</sup> It was a randomized double blind, placebo-controlled trial of short and long-term therapy with clopidogrel plus aspirin versus placebo plus aspirin. Following randomization there was no restriction on the use of revascularization procedures and other medications. Overall, 12,652 patients were recruited at 482 hospitals in 28 countries. Treatment with placebo or clopidogrel (300 mg as loading dose followed by 75 mg daily) was started within 24 hours of admission of patients with NSTEMI ACS. The results of this trial showed a significant reduction in the composite endpoint of death, MI or stroke with clopidogrel and aspirin versus aspirin alone (9.3% vs. 11.4%, RR 0.80, 95% CI 0.72-0.90;  $p < 0.001$ ). In addition, clopidogrel was associated with significant reduction in the rate of in hospital severe ischemia and revascularization, as well as need for thrombolytic therapy or intravenous GP IIb/IIIa inhibitors. A reduction in recurrent ischemia was noted within first few hours of randomization, it was manifested as a 23% reduction in MI (5.2% vs 6.7%, RR 0.77, 95% CI 0.67-0.89).

There was a relative 35% increase in the risk of bleeding in patients receiving the combination of clopidogrel and aspirin (2.7% in placebo vs. 3.7% with clopidogrel,  $p = 0.003$ ). However, there was no significant increase in life threatening bleeds or intracranial hemorrhage. The risk of bleeding was increased in

patients undergoing coronary artery bypass surgery (CABG) within first 5 days of stopping clopidogrel, but no significant increase in bleeding complication was noted if clopidogrel was stopped  $> 5$  days prior to CABG.

The PCI-CURE study demonstrated that in patients with NSTEMI ACS, receiving aspirin and undergoing percutaneous coronary intervention (PCI), a strategy of clopidogrel pretreatment followed by at least one month and probably longer term therapy is beneficial in reducing major cardiovascular events by 30% compared with placebo (4.5% with clopidogrel vs. 6.4% with placebo, RR 0.70, 95% CI 0.50-0.97;  $p = 0.03$ ).<sup>42</sup>

These trials provide strong evidence for the addition of clopidogrel to aspirin in patients with NSTEMI ACS, those who are managed conservatively as well as those undergoing PCI, especially stenting. Duration of therapy with combination of clopidogrel and aspirin is still debatable, however in light of CURE trial; this should be continued for at least 9 months from the time of admission. The association of increased risk of bleeding with this combination warrants the withholding of clopidogrel therapy at least 5 days prior to an elective CABG. The ACC/AHA guidelines have also recommended the use of clopidogrel as a Class 1 indication, in patients who are sensitive to aspirin or have major gastrointestinal intolerance.<sup>15</sup>

#### **Direct Thrombin Inhibitors**

Thrombin catalyzes the transformation of fibrinogen to fibrin and is a potent agonist for platelet aggregation. It promotes formation of clot through platelet aggregation. Direct Thrombin Inhibitors (DTI) prevent thrombin mediated platelet activation and aggregation.<sup>43</sup> DTIs specifically block both fluid-phase and tissue bound thrombin and, therefore, reduce thrombin activity more effectively than heparin.<sup>44</sup> DTIs do not bind to plasma proteins and heparinases do not inactivate them. DTIs have a more predictable anticoagulant response than UFH.<sup>44</sup> These drugs have been extensively investigated in the setting of NSTEMI ACS and PCI.

Hirudin is a prototype DTI. It is a naturally occurring polypeptide, which was first isolated from the salivary glands of medicinal leeches. It is now being prepared through recombinant DNA technology.<sup>45</sup> Peptide analogues of hirudin include hirugen and Hirulog (bivalirudin), whereas synthetic derivatives include argatroban, efegatran, and inogatran. Hirudin is a potent and selective inhibitor of thrombin. It binds thrombin in 1:1 fashion at the substrate recognition site and the catalytic site. Its dissociation rate is extremely slow, which makes it an essentially irreversible inhibitor of thrombin. It has a half-life of approximately 60 minutes after intravenous administration and its main route of excretion is renal.<sup>45</sup> Hirudin has a narrow therapeutic window, and is associated with a significant risk of bleeding at higher doses as compared to UFH.<sup>46</sup>

Bivalirudin (hirulog) is a synthetic 20-amino acid polypeptide. Like hirudin, it also binds to the substrate recognition and the active site of thrombin molecule. It also has a linker region with optimal length to allow binding of both inhibitory sites.<sup>47</sup> It has a short half-life of 35 minutes because of cleavage by thrombin of the active-site binding peptide. Bivalirudin is excreted primarily via non-renal mechanisms.<sup>47</sup> In the clinical trials, it has proven to be safer than UFH in terms of bleeding complications.<sup>48</sup> The synthetic univalent DTIs (argatroban, efegatran, and inogatran) have been evaluated in phase 1 and 2 ACS trials.<sup>49,50</sup> These agents bind only to the active site of thrombin and have a short half-life. They appear to be more potent inhibitors of fibrin bound thrombin than hirudin and bivalirudin.<sup>51</sup>

Hirudin and hirulog have been tested among patients with NSTEMI ACS. The largest phase III clinical trial with a DTI was the Global Use of Strategies to Open Occluded Coronary Arteries II (GUSTO II) trial.<sup>52</sup> The study was performed in two parts because of premature discontinuation of the original study due to an increase in hemorrhagic strokes. The GUSTO IIb trial enrolled 8,011 patients with NSTEMI ACS. Patients were randomized to UFH or hirudin. After a 72-hour infusion, the primary endpoint

of death or MI by 30 days occurred in 9.1% of heparin treated patients versus 8.3% of hirudin treated patients ( $p = 0.22$ ). Patients who received hirudin had a higher rate of bleeding, transfusions, and intracranial hemorrhage compared with those receiving heparin.

The Organization to Assess Strategies for Ischemic Syndromes (OASIS) II trial randomized 10,141 patients with NSTEMI ACS to a 72-hour infusion of hirudin or heparin.<sup>53</sup> This study also demonstrated a nonsignificant difference between hirudin and heparin in the primary outcome of death or MI at seven days (3.6% vs 4.2%). Hirudin was associated with a significantly increased risk of major bleeding (1.2% vs 0.7%).

Bivalirudin on the other hand demonstrated a benefit over UFH in the Thrombin Inhibition in Myocardial Infarction (TIMI) 8 trial. The sponsors prematurely terminated this trial; it compared a 72-hour infusion of bivalirudin with UFH in patients with NSTEMI ACS. The target enrolment was 5,320 patients but only 133 patients were randomized before study was terminated. There was a significant reduction in the risk of death and MI with bivalirudin compared with UFH at 14 days (2.9% vs 9.2%).<sup>54</sup> The Thrombin Inhibition in Myocardial Infarction (TIMI) 7 trial, was a randomized, double-blind study, which compared four doses of hirulog in patients with unstable angina.<sup>55</sup> The patients received a 72-hour infusion of hirulog at one of four doses: 0.02 ( $n = 160$ ), 0.25 ( $n = 81$ ), 0.5 ( $n = 88$ ), and 1.0 ( $n = 81$ ) mg/kg/hr. The primary endpoint of death, MI, recurrent ischemic pain at rest with ECG changes and rapid clinical deterioration at 72 hours was not different among the four groups. However, secondary endpoint of death or non-fatal MI through hospital discharge occurred in 10% of patients treated with 0.02 mg/kg/hr compared with 3.2% of patients with three higher doses of hirulog ( $p = 0.008$ ). Aspirin was used in all groups of patients.

The Direct Thrombin Inhibitor Trialists' Collaboration reported the results of a review of major randomized trials of DTIs compared with UFH in patients with unstable coronary

disease.<sup>56,57</sup> Overall, there was 15% reduction in death or MI at the end of treatment with DTIs compared with UFH (4.6% vs 5.4%; Odds Ratio (OR), 0.85; 95% CI, 0.77-0.94;  $p = 0.001$ ). Patients with NSTEMI/ACS had a 20% reduction in the risk of death or MI (3.7% vs 4.6%; OR, 0.80; 95% CI, 0.70-0.92). The greatest benefit of DTIs compared to heparin appeared to be in patients undergoing PCI during study period, where there was a 32% reduction in death or MI.

These several randomized trials provide good evidence that DTIs have equivalent efficacy as compared to UFH. In some instances, they have been proven superior to UFH. This equivalence and superiority comes at a cost of excess bleeding, which sometimes offsets any benefit of these agents. The randomized trials of DTI in patients with NSTEMI/ACS were performed before the widespread use of clopidogrel and LMWH. Further evidence is required to determine the efficacy and safety of DTIs in context with current antithrombotic strategies before they can be used in routine clinical practice in patients with ACS. Currently the ACC/AHA guidelines for the management of patients with unstable angina and NSTEMI/MI, recommends the use of hirudin for anticoagulation in patients with heparin-induced thrombocytopenia.<sup>15</sup>

### ***Glycoprotein IIb/IIIa receptor inhibitors***

GP IIb/IIIa is a platelet surface receptor that consists of two distinct and different subunits, an alpha chain, and a beta chain. It is also known as the platelet fibrinogen receptor. When platelets are activated, the two individual chains of GP IIb/IIIa receptor undergo a conformational change. This change increases its affinity to bind fibrinogen and other ligands. The binding of molecules of fibrinogen to receptors on different platelets results in platelet aggregation. This mechanism represents the final common pathway for platelet aggregation.<sup>58</sup> The aggregation potential of platelets can be seen in the number of GP IIb/IIIa receptors per platelet. There may be as many as 100,000 GP IIb/IIIa receptors per

platelet; 80,000 of which are on the platelet surface and, spaced approximately 20 nanometers (nm) apart. Another 20,000 or more of these receptors, which may also be located inside the platelets, are externalized during activation.<sup>59</sup> GP IIb/IIIa receptor antagonists act by occupying the receptors, and thereby prevent fibrinogen binding and platelet aggregation.

There are various GP IIb/IIIa antagonists available. These agents possess significantly different pharmacokinetic and pharmacodynamic properties. Currently three GP IIb/IIIa inhibitors are most widely used in the clinical practice. These are abciximab, eptifibatid, and tirofiban.<sup>60</sup> Abciximab is a Fab fragment of humanized murine antibody. It is not specific for the GP IIb/IIIa receptor and binds to a broader group of integrins, such as vitronectin ( $\alpha_v\beta_3$ ) receptor on endothelial cells and MAC-1 receptor on leucocytes.<sup>61,62</sup> Presently the clinical relevance of occupancy of these receptors is not known. It binds very tightly to the GP IIb/IIIa receptor. Thus, the antiplatelet effect last much longer than the infusion period. Platelet aggregation gradually returns to normal 24 to 48 hours after discontinuation of the drug.

Thus if bleeding occurs with abciximab, stopping the drug will not reverse the antiplatelet effect immediately and platelet infusion is required to achieve haemostasis.

Eptifibatid is a cyclic heptapeptide and tirofiban is a nonpeptide molecule. These are competitive and highly specific inhibitors of GP IIb/IIIa receptor. The level of platelet inhibition is directly related to the drug level in the blood. The half-life of these agents is 2 to 3 hours and platelet aggregation returns to normal in 4 to 8 hours after discontinuation of the drug.<sup>63,64</sup>

Several trials have demonstrated the effects of GP IIb/IIIa inhibition in reducing the incidence of death, MI, recurrent angina and urgent revascularization, in patients with NSTEMI/ACS. Tirofiban was studied in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) and Platelet Receptor Inhi-

bition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trials.<sup>7,65</sup> The PRISM trial compared the combination of tirofiban plus aspirin with heparin plus aspirin in 3,232 patients with NSTEMI ACS, or with positive stress test or with angiographically documented coronary disease. It demonstrated a 33% relative risk reduction in the composite end points of death, MI or refractory ischemia at the end of 48 hours infusion (5.6% with heparin vs. 3.8% with tirofiban;  $p = 0.01$ ). At 30 days this difference was not significant, but a trend toward reduction in the rate of death or MI was present with tirofiban (7.1% vs 5.8%;  $p = 0.11$ ), and a significant reduction in the mortality rate was observed (3.6% vs 2.3%;  $p = 0.02$ ). Patients with elevated troponin levels enjoyed the most benefit with tirofiban.<sup>66</sup>

In the PRISM-PLUS trial 1,915 patients with NSTEMI ACS, were randomized to tirofiban alone, UFH alone or the combination of UFH and tirofiban. The tirofiban alone arm was prematurely discontinued because of excess mortality. The trial showed a 32% reduction in the composite endpoint of death, MI or refractory ischemia at 7 days ( $p = 0.004$ ) and a 30% reduction in death or MI, at 30 days with tirofiban and UFH ( $p = 0.03$ ).<sup>65</sup> Patients with a TIMI risk score of more than four, and who underwent PCI, achieved the most reduction in the endpoints.

In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression, Using Integrilin Therapy (PURSUIT) trial, involving 10,948 patients with NSTEMI ACS, eptifibatid reduced the incidence of death or nonfatal MI from 15.7% to 14.2% ( $p = 0.042$ ) at 30 days.<sup>67</sup> In this trial, a greater benefit with eptifibatid was observed in patients undergoing early PCI than other treatment strategies.

Abciximab has primarily been studied, in PCI trials with and without associated ACS. The Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) study randomized 2,099 patients with high risk ACS undergoing PCI to abciximab or placebo, in addition to aspirin and heparin.<sup>68</sup> There was a 35% reduction in

the primary endpoint of death, MI, repeat revascularization and procedure failure resulting in stent or intra-aortic balloon pump placement, in patients randomized to abciximab compared with placebo (8.3% vs 12.8%;  $p = 0.008$ ). This benefit was maintained at 3 years.<sup>69</sup>

The Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) study enrolled patients at a lower risk than EPIC study.<sup>70</sup> The patients were randomized to abciximab with standard heparin, abciximab with low dose heparin, or placebo with standard heparin. A 57% reduction in the primary outcome of death, MI or urgent revascularization was observed in patients who were randomized to abciximab plus low dose heparin ( $p < 0.001$ ).

Patients with unstable refractory angina were studied in the Chimeric c7E3 Anti Platelet Therapy in Unstable REfractory angina (CAPTURE) trial.<sup>71</sup> After angiographic identification of a culprit lesion suitable for angioplasty, patients were randomized to either abciximab or placebo administered for 20 to 24 hours before the procedure and one hour thereafter. At 30 days 29% reduction in death, MI or urgent revascularization was noted in the abciximab group ( $p = 0.012$ ). This benefit was greatest in patients with elevated troponin levels.<sup>66</sup>

The trial, which assessed abciximab without use of PCI in patients with NSTEMI ACS, was the Global Utilization of Streptokinase and t-PA for Occluded coronary artery trial IV in Acute Coronary Syndromes (GUSTO IV ACS) trial.<sup>72</sup> It enrolled 7,800 patients with high risk ACS; they were randomized to placebo, an abciximab bolus and 24 hours infusion, or an abciximab bolus and 48 hours infusion. Use of early PCI was actively discouraged. At 30 days, death or MI occurred in 8% of patients taking placebo, in 8.2% of patients taking 24-hour abciximab, and in 9.1% of patients taking 48 hours abciximab; these differences were not statistically significant. There was lack of benefit with abciximab in all subgroups, including those with elevated troponin. The study suggested that abciximab at the dosing regi-

men used in GUSTO-IV ACS is not indicated in the management of patients with NSTEMI ACS in whom early PCI is not planned.

A meta-analysis of GP IIb/IIIa antagonists of all six large randomized placebo controlled trials, involving 31,402 patients with NSTEMI ACS not routinely scheduled to undergo coronary revascularization, reported a 9% relative reduction in death or MI when used as upstream therapy in patients with ACS ( $p = 0.015$ ).<sup>73</sup> No benefit was observed in women. In the subgroup of patients who underwent revascularization within 30 days of receiving GP IIb/IIIa therapy, the Odds Ratio for death and MI was 0.89 (95% CI 0.80-0.98). Patients who did not undergo revascularization the OR for death and MI was 0.95 (95% CI 0.86-1.05, NS). Bleeding complications were significantly more in patients who received GP IIb/IIIa inhibitors (2.4% vs 1.4%;  $p < 0.0001$ ). The meta-analysis suggested that GP IIb/IIIa inhibitors are of substantial benefit in patients with NSTEMI ACS who undergo PCI; they are of modest benefit in patients who are not routinely scheduled to undergo PCI (but who may do so), and they are of questionable benefit in patients who do not undergo PCI.

The Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI18) trial also demonstrated that patients with NSTEMI ACS, who present with elevated troponin levels, have diabetes and a TIMI risk score of  $> 4$ , were benefited the most from GP IIb/IIIa inhibitors if they undergo early revascularization.<sup>74,75</sup> Overall there was a relative risk reduction of 22% in composite endpoints of death, MI, or rehospitalization for ACS at six month, in patients with ACS who received tirofiban and were randomized to early invasive strategy compared to early conservative therapy. Patients with elevated troponin levels of  $> 0.01$  ng/ml at baseline had 56% ( $p < 0.001$ ) relative reduction in the incidence of primary endpoints and the occurrence of death and MI were reduced by 53% ( $p = 0.002$ ) at 30 days and the benefit was persistent at six month follow-up.<sup>74</sup> Patients with troponin lev-

els of  $< 0.01$ ng/ml had no difference in outcome with either strategy.

According to the current evidence from TACTICS-TIMI18 and several other trials in patients with NSTEMI ACS, use of GPIIb/IIIa inhibitors with an early invasive strategy reduces the risk for major adverse cardiac events. This effect is more pronounced in patients with elevated baseline troponin levels, diabetes, TIMI risk score of  $> 4$  and with ST-segment changes. Use of upstream GP IIb/IIIa inhibitors in placebo controlled trials also demonstrated reduction in death or MI, especially in patients with elevated troponin levels and in those with TIMI risk score of  $> 3$ , and this was irrespective of the use of PCI in these patients. However, use of abciximab in patients with NSTEMI ACS, who are not planned to undergo PCI, is considered as a Class III indication.<sup>15</sup> Use of GP IIb/IIIa receptor inhibitors with or without PCI, in low risk patients has failed to demonstrate any significant improvement in the outcome of these patients.

### **Oral Anticoagulants**

Oral anticoagulants, like warfarin act through interference with vitamin-K dependent production of coagulation factors II, VII, IX, and X, which are produced by the liver. Warfarin is rapidly absorbed from the gut and has a high bioavailability. In circulation, it is bound to plasma proteins and its metabolism occurs in the liver. Various drugs can cause interactions or effect metabolic clearance of warfarin e.g., trimethoprim, metronidazole, and amiodarone potentiate the anti coagulant activity, while rifampicin inhibits it.<sup>76,77</sup> Number of genetic and dietary factors also interferes with drug disposition and its efficacy. Due to these reasons, there is individual variability in anticoagulant effect and safety. However, monitoring has been standardized with the introduction of international normalized ratio (INR), and results are now internationally exchangeable and comparable.<sup>78</sup> The efficacy and safety of warfarin is dependent on the intensity of anticoagulation and maximum time spent in the target range.<sup>76,77</sup> Randomized clini-

cal trials have assessed the efficacy of warfarin with or without aspirin in patients with acute coronary syndromes.

Full intensity anticoagulation (INR 2.8 to 4.2) with warfarin as monotherapy, after acute myocardial infarction was associated with a significant reduction in reinfarction and death, but this was at the cost of 4-fold increase in the risk of major bleeding.<sup>79,80</sup> A meta-analysis of few small trials comparing moderate to high intensity anticoagulation versus aspirin did not demonstrate a difference in efficacy, whereas bleeding was lower with aspirin.<sup>81</sup> The same meta-analysis demonstrated that a combination of medium to high intensity Oral Anticoagulation (OA) was promising. Coumadin Aspirin Reinfarction Study (CARS) demonstrated that fixed dose low intensity OA did not improve outcome.<sup>82</sup>

The Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT)-II trial enrolled patients with ACS and randomized them to moderate intensity OA (target INR 2 to 2.5) with low dose aspirin (80mg per day), high intensity OA (target INR 3 to 4), or low dose aspirin.<sup>83</sup> A significant risk reduction in the primary endpoints of MI, stroke or death was observed in patients receiving a combination of OA and aspirin compared to aspirin alone (4.8% vs. 9.2%  $p < 0.05$ ). A 45% risk reduction was observed when OA was compared to aspirin alone (5.2% vs. 9.2%,  $p < 0.05$ ). Significantly more major bleeding episodes were observed among patients receiving the combination of OA and aspirin (2.1%) than among those receiving OA alone (0.9%) or aspirin alone (0.9%).

The Organization to Assess Strategies for Ischemic Syndromes-II (OASIS-II) study was performed worldwide and showed a nonsignificant 10% reduction in the risk of death, MI, or stroke, in patients with ACS receiving a combination of moderate intensity OA and aspirin.<sup>84</sup> The Warfarin-Aspirin Reinfarction-II Study (WARIS-II) enrolled patients with acute MI and demonstrated a 29% relative risk reduction in combined endpoints of death, MI, and Stroke in patients receiving a combination

of moderate intensity OA (target INR 2 to 2.5) plus aspirin compared to aspirin alone. High intensity OA (target INR 2.8 to 4.2) alone reduced the risk by 19% compared to aspirin alone.<sup>85</sup> On the other hand the largest worldwide trial after MI to date, Combination Hemotherapy And Mortality Prevention (CHAMP), was aimed at a target INR of 1.5 to 2.5 and was neutral.<sup>86</sup>

Currently, according to the updated ACC/AHA guidelines for the management of ACS, low or moderate intensity OA is not recommended for routine use after hospitalization for NSTEMI ACS.<sup>15</sup> Although data on the combination of moderate intensity OA with low-dose aspirin is promising, but the decision to use this combination is usually individualized. This combination should be reserved for high-risk patients including those who suffer a cardiovascular event despite being on aspirin monotherapy. The potential benefits of this combination should be weighed against the risk of major life threatening bleeding associated with the use of oral anticoagulants. Warfarin should be prescribed, however, for NSTEMI ACS patients with established indications for warfarin, such as atrial fibrillation and mechanical prosthetic heart valves. Currently we do not have data comparing the safety and efficacy of dual antiplatelet therapy with moderate intensity OA and aspirin, further studies are required to address this issue.

## CONCLUSIONS

Appropriate use of antiplatelet and antithrombotic agents has shown to reduce morbidity and mortality in patients with NSTEMI ACS. According to updated ACC/AHA guidelines for the management of patients with unstable angina and NSTEMI MI, all patients with NSTEMI ACS should receive aspirin, unless contraindicated.<sup>15</sup> Clopidogrel should be substituted for aspirin in patients who are either sensitive to aspirin or in whom aspirin is contraindicated. Combination of aspirin and clopidogrel is now a class I recommendation in patients with NSTEMI ACS. This combination

should be started as early as possible in all patients regardless of PCI. Anticoagulation with LMWH or UFH should be used in combination with aspirin and clopidogrel. GP IIb/IIIa inhibitors should be administered in addition to heparin, aspirin, and clopidogrel, to patients in whom cardiac catheterization and PCI are planned. There is now enough evidence that suggest that eptifibatide and tirofiban can be administered in addition to aspirin, clopidogrel, and heparin in patients with high risk NSTEMI ACS in whom invasive management strategy is not planned. On the other hand, after the results of GUSTO IV ACS trial, abciximab administration in patients in whom PCI is not planned is now a class III recommendation according to the current guidelines.<sup>15,72</sup>

Currently the use of direct thrombin inhibitors is limited to patients who develop heparin-induced thrombocytopenia. Their efficacy has not been tested against dual antiplatelet therapy and GP IIb/IIIa inhibitors in randomized trials. Similarly, the role of long-term OA is also limited to high-risk patients with atrial fibrillation of prosthetic metallic valves.

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