The Role of Low-Molecular Weight Heparins in Non-ST Elevation Myocardial Infarction

Idrus Alwi

ABSTRACT
Non-ST elevation myocardial infarction (NSTEMI) is a subset clinical manifestation of acute coronary syndrome (ACS), which is usually caused by disruption of vulnerable atherosclerotic plaque, followed by thrombosis resulting various degree of occlusions in coronary arteries.

The exposure of tissue factors following the plaque rupture causes activation of coagulation cascades and formation of factor Xa. The thrombin formation will cause fibrin deposition, platelet activation and finally lead to the formation of a stable plaque. Given the central role of thrombin in the pathogenesis of ACS, an antithrombotic agent is an important element in therapy ACS.

Low-molecular-weight heparin (LMWHs) is one of antithrombotic agents which has been widely studied in various clinical trials and has been proven useful in clinical efficacy, safety and practical characteristics for ACS treatment. They have been found to improve clinical outcomes in acute coronary syndromes and to provide a more predictable therapeutic response, longer and more stable anticoagulation, and a lower incidence of UFH-induced thrombocytopenia.

Of the several LMWH agents that have been studied in large clinical trials, including enoxaparin, dalteparin, and nadroparin, not all have shown better efficacy than UFH. Enoxaparin is the only LMWH compound to have demonstrated sustained clinical and economic benefits in comparison with UFH in the management of unstable angina/non–ST-segment elevation myocardial infarction (NSTEMI).

Key words: LMWH, NSTEMI, acute coronary syndrome.

INTRODUCTION
Non-ST elevation myocardial infarction (NSTEMI) is a subset clinical manifestation of acute coronary syndrome (ACS), which is usually caused by disruption of vulnerable atherosclerotic plaque, followed by thrombosis resulting various degree of occlusions in coronary arteries. In contrast to STEMI that usually associated with total thrombus occlusion of coronary artery, the thrombus developed in NSTEMI usually is non-occlusive thrombus.

NSTEMI is defined based on clinical manifestation of chest pain (angina) with ECG features of ST depression, prominent T-wave inversion and positive results of necrosis marker (such as troponin) without any ST segment elevation.

The exposure of tissue factors following the plaque rupture causes activation of coagulation cascades and formation of factor Xa. The thrombin formation will cause fibrin deposition, platelet activation and finally lead to the formation of a stable plaque. Consider the important role of thrombin in pathogenesis of ACS, therefore antithrombotics are one of main treatment for ACS. Low-molecular-weight heparin (LMWHs) is one of antithrombotic agents which has been widely studied in various clinical trials and has been proven useful in clinical efficacy, safety and practical characteristics for ACS treatment.

PATHOGENESIS OF NSTEMI
NSTEMI is characterized by an imbalance between myocardial oxygen supply and demand. Decreased oxygen supply is the more often main mechanism than the increased oxygen demand. The most common causes of NSTEMI is decreased myocardium perfusion resulting from coronary narrowing caused by thrombus formation, which is usually non-occlusive, subsequent to rupture of an atherosclerotic plaque.
plaque is arterial inflammation. A less common cause is dynamic obstruction (i.e., focal epicardial coronary artery spasm, spasm on top of plaque or dynamic micro-vascular spasm/dysfunction), severe narrowing, or coronary artery dissection.

**MANIFESTATION OF NSTE MI**

Manifestation of unstable angina are: 1) rest angina, 2) new onset of severe angina (less than 2 months) and 3) increasing angina severity (the intensity, duration and/or frequency). The gradation of angina is established based on the Canadian Cardiovascular Society classification. NSTE MI usually manifests as a progressive angina, more severe angina at rest or equivalent angina.

Most patients do not realize other symptoms other than the chest pain, such as short of breath, sweating, or extreme fatigue which may be part of equivalent angina. The average NSTE MI patient does not seek medical care for approximately 2 hour after symptom onset. Reasons for this delay include a mismatch between expectation and actual symptoms and impression that symptoms are self-limited or are due to other chronic condition.

As many as one-half of all AMIs are clinically silent or unrecognized, and one third present with symptoms other than chest discomfort. Patients without chest discomfort are more likely to be older, to be women, to have diabetes mellitus, to have prior heart failure and to delay going to hospital. Unexplained dyspnea, even without angina, is a common symptom.12

**ANTICOAGULANT THERAPY IN PATIENTS WITH NSTEMI**

Anticoagulant therapy is essential to modify the ACS disease process and its complication. A combination of aspirin, anticoagulant and additional antiplatelet therapy represents the most effective therapy. Triple-anticoagulant treatment is used in patients with continuing ischemia or with high-risk features and in patients oriented to an early invasive strategy.

An increasing number of anticoagulants have become available for management of patients with NSTEMI. Although each agent or regimen (UFH, enoxaparin, fondaparinux, and bivalirudin [invasive strategy only]) satisfies criteria for effectiveness, it is often difficult to conclude that antithrombotic strategy is preferred over another, given differing study designs (blinded vs. unblinded; superiority vs. noninferiority) and equipotent dosing; differing patient populations (high risk vs. low risk), durations of therapy, and strategies (invasive vs. conservative); confounding by open-label and crossover use of anticoagulants; differing antiplatelet strategies; and differing clinical versus study protocol.

**LMWH MECHANISM IN COAGULATION CASCADE**

In ACS, thrombosis is initiated through exposure of tissue factors on disrupted plaque. The tissue factor/factor VIIa complex stimulates activation of factor X into factor Xa. Furthermore, factor Xa is also involved in prothrombinase complex (factor Xa, factor Va, Ca++ and phospholipid membrane, usually derived from the activated platelets). The tissue factor/factor VIIa complex also activates factor IX into IXa, which facilitates maintaining the thrombosis process.

Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) act together through complex formation with antithrombin III. LMWHs has greater inhibitory effect on factor Xa than factor IIa (thrombin); therefore, the anti-Xa:IIa inhibitory ratio is greater than 1. Hence, the inhibition of upstream coagulation cascades is greater and decreased thrombin formation relatively greater than UFH administration. Unfractionated heparin has anti-Xa:IIa inhibitory ratio of 1. Unfractionated heparin and LMWHs also inhibit coagulation through shading off the tissue factor pathway inhibitor (TFPI) of the endothelial cells. However, unlike the UFH, LMWHs does not cause TFPI.
depletion, which is associated with paradoxical prothrombotic condition during anticoagulant therapy in ACS.

### Table 1. Various LMWHs and antiXa/IIa ratio

<table>
<thead>
<tr>
<th></th>
<th>Anti-Xa (IU/mg dry substance)</th>
<th>Anti-IIa (IU/mg dry substance)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>103</td>
<td>25</td>
<td>4.1</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>120</td>
<td>30</td>
<td>4.0</td>
</tr>
<tr>
<td>Reviparin</td>
<td>130</td>
<td>36</td>
<td>3.5</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>167</td>
<td>64</td>
<td>2.6</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>100</td>
<td>54</td>
<td>1.9</td>
</tr>
<tr>
<td>Certoparin</td>
<td>106</td>
<td>45</td>
<td>2.4</td>
</tr>
<tr>
<td>UFH</td>
<td>193</td>
<td>193</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### LOW-MOLECULAR-WEIGHT HEPARIN

The LMWHs are obtained through chemical or enzymatic depolymerization of polysaccharide chains of heparin to provide chains with different molecular-weight distribution. Approximately 25% to 50% of the pentasaccharides containing LMWH chains contain more than 18 saccharide units, which inactivate both thrombin and factor Xa; the LMWH chains of fewer than 18 saccharide units inactivates factor Xa but not thrombin. Therefore, LMWHs are relatively more potent in inhibiting factor Xa than inactivating thrombin. Advantages of LMWH over UFH include decreased plasma protein binding and endothelial cells and dose-independent clearance, with long half-life. This results in LMWH that more easily predictable and become a permanent anticoagulants with subcutaneous administration once- or twice- daily, that usually does not require laboratory monitoring. Different preparations of LMWHs vary in mean molecular weight (ranging from 4,200 to 6,000 Daltons) and the factor anti-Xa and factor anti-IIa ratio (1.9 to 3.8).

NSTEMI trials using LMWH and aspirin (ASA) compared with ASA alone or with UFH have generally shown favorable results. Eight randomized trials have directly compared an LMWTH with UFH. Trials with dalteparin and nadroparin reported similar rates of death or nonfatal MI compared with UFH, whereas 5 of 6 trials of enoxaparin found point estimates for death or nonfatal MI that favored enoxaparin; the OR was 0.91 (95% CI 0.83 to 0.99). This incremental benefit of enoxaparin appeared to be driven largely by a reduction in nonfatal MI. With an early invasive strategy, outcomes with UFH and LMWH (enoxaparin) were similar.

The Enoxaparin versus Tinzaparin (EVET) trial directly compared 2 LMWHs, enoxaparin and tinzaparin, in 436 patients with UA/NSTEMI. Enoxaparin was associated with a lower rate of death/MI/recurrent angina at 7 and 30 day than tinzaparin. Bleeding rates were similar.

Four trials evaluated the potential benefit of prolonged administration of LMWH after hospital discharge, with little or no benefit beyond the acute phase. In addition to providing ease of administration and eliminating the need for monitoring, LMWHs stimulate platelets less than UFH and less frequently cause heparin-induced thrombocytopenia. They are associated with more frequent minor but not major bleeding. A post hoc analysis from the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIa Inhibitors (SYNERGY) trial suggested that some of the excess bleeding seen with enoxaparin could be explained by crossover to UFH at the time of PCI. It thus appears reasonable to maintain consistent anticoagulant therapy from the pre-PCI phase throughout the procedure itself. For patients in whom CABG is planned, it is recommended that LMWH be discontinued and UFH used during the operation.

### GUIDELINES OF LMWH IN NSTEMI BY ACC-AHA 2007 AND ESC 2007

**Recommendations of Anticoagulant Therapy in NSTEMI by ACC-AHA 2007**

Class I

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.

- For patients whom an invasive strategy is selected, regimens with established efficacy at a Level of Evidence: A include enoxaparin and UFH, and those with established efficacy at a Level of Evidence: B include bivalirudin and fondaparinux.

- For patients in whom a conservative strategy is selected, regimens using either enoxaparin or UFH (Level of Evidence: A) or fondaparinux (Level of Evidence: B) have established efficacy.

- For patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable. (Level of Evidence: B)

Class IIA

For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG is planned within 24 hours. (Level of Evidence: B)
Recommendation of Anticoagulant Therapy in NSTEMI by ESC 2007

Some recommendation of anticoagulant therapy based on ESC guidelines, i.e.:

- Anticoagulant is recommended for all patients in addition to antiplatelet therapy.
- Several anticoagulants are available i.e.: UFH, LMWH, fondaparinux and bivalirudin. The choice depends on the initial strategy (urgent invasive, early invasive or conservative).
- In an urgent invasive strategy UFH (I-C) or enoxaparin (IIa-B) or bivalirudin (I-B) should be immediately started.
- In an non-urgent situation, as long as decision between early invasive or conservative strategy is pending:
  - Fondaparinux is recommended on the basis of the most favorable efficacy/safety profile (I-A).
  - Enoxaparin with a less favorable efficacy/safety profile than fondaparinux should be used only if the bleeding risk is low
  - As efficacy/safety profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown; these anticoagulants cannot be recommended over fondaparinux (IIa-B).
  - At PCI procedures the initial anticoagulant should be maintained also during the procedure regardless whether this treatment is UFH (I-C), enoxaparin (IIa-B) or bivalirudin (I-B), while additional UFH in standard dose (50-100 IU/kg bolus) is necessary in case of fondaparinux (IIa-C)
  - Anticoagulants can be stopped within 24 hours after invasive procedure (IIa-C). In a conservative strategy, fondaparinux, enoxaparin or other LMWH may be maintained up to hospital discharge (IB).

REFERENCES


