INTRODUCTION

Acute thrombosis may affect the arteries, veins or microvasculature through different pathogenesis and impact a fatal condition. Total thrombosis of coronary artery may cause acute myocardial infarct and in cerebral artery may cause stroke. Relative non fatal conditions refer to deep vein thrombosis in legs or occlusion in microvasculature of the fingers.

In the US, coronary artery disease has been the most frequent cause of death despite the advanced development in primary and secondary prevention of coronary artery disease (CAD). In the early 21st century, it was presumed that 1.1 million US citizens would have AMI or recurrence of cardiac events and 1/3 of them would die. Complete data from year of 1997 indicated mortality according to age was 82.8 per 100,000 people. In the African-American group the mortality was higher compared to those among white American group (119.9 vs 112.8 per 100,000 population). Men were more common than women (114.2 vs 57.6 per 100,000). In the year of 1999 economic burden reached $185,8 million and indirect burden due to diminished income and productivity reached $326.6 million.

Cerebrovascular disease (CVD) in the US and Europe has been 3rd leading cause of death and most frequent cause of long term disability. Most of the stroke were ischemic/infarct (85%) due to occlusion or emboli. In the middle-east this had been reached 70% of total cases of stroke. Risk factor and life style changes program had decreased the incidence of stroke. On the other hand mean age of population in the western countries had been increased; therefore the absolute number of stroke had been increasing and reached 700,000 incidence of stroke per year. In the US it has been presumed that 1 million people per year will have stroke in 2005.¹

PATHOPHYSIOLOGY AND PATHOGENESIS

In arterial thrombosis, myocardial ischemia and unstable angina is caused by increasing oxygen demand and inadequate oxygen supply. Primary myocardial ischemia is due to blood vessel obstruction and secondary myocardial ischemia refers to increasing oxygen demand in special condition such as fever, thyrotoxicosis, tachyarytmia or decreasing oxygen supply like one that we can find in anemia, hypoxemia and polycytemia.²

Platelet then will be activated and form thrombin that will end in thrombus formation. If the thrombus is large it can make acute vessel occlusion followed by tissue infarct. But if the thrombus is relatively small in size, fibrinolysis will occur and residual thrombus will become atherosclerotic lesion and finally will narrow vascular lumen and increase shear stress (Table 1).²,⁴

Unlike in arterial thrombosis, the role of vessel wall or endothelial lesion in vein thrombosis is not very important. The main factors are stasis/ disturbance of blood flow and coagulation factor activation.⁴

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Low molecular weight heparin (LMWH) is a sulphate-glycosaminoglycan compound with molecular weight (MW) less than 8000 Da. It could be made from fractionation or depolymerisation of heparin. It has potential more than 70 unit/mg of anti factor Xa and a ratio of anti factor Xa : IIa e” 1.5.

Heparin itself is a natural anionic of polysaccharide which is extracted from pig intestine or lung of cows. There are 8 LMWH from all over the world which are recommended to clinical application. All were obtain from chemical process or enzymatic depolymerisation from heparin with molecular weight range from 3,000 to 7,000 Da and ratio of anti Factor Xa : IIa ranging from 1.5 to 4.

**LMWH and Ischemic Stroke**

Ischemic stroke can be caused by various disease entities, thus, the use of anti thrombotic agent properly for prevention and treatment will need pathophysiologic approach from each etiologic group. Cerebral infarct occurs after blood flow in certain area in the cerebral is decreased under critical level to maintain tissue metabolism. About 10 % of ischemic stroke were caused by severe stenosis (> 70%) of carotid artery. Non stenosis of atherosclerosis plaque may cause transient ischemic attack (TIA) or stroke by providing source of emboli from artery to artery. Emboli from the heart chambers or the valves can make occlusion of cerebral arteries and cause wide area of cortical stroke. Subcortical lacunar infaract occurred due to lipohyalinolysis and small artery microatheroma. Thrombosis of arteries has been the most frequent cause of ischemic stroke where the platelet would adhesively stick to the disrupted vessel wall then followed by platelet aggregation and thrombus formation.

Pharmacologic approach for prevention and treatment including the use of anticoagulants, anti platelet aggregation and fibrinolysis.

A double blind, placebo-controlled study has been conducted by Kay et al involving 312 patients from 2,750 patients with diagnosis of acute ischemic stroke. Evaluation of 306 patients who were given therapy at 48 hours after the stroke onset : high dose nadroparin (2 X 4100 factor Xa), low dose of nadroparin (2 x 4100 factor Xa) and placebo for 10 days. It was concluded that the group of high dose of nadroparin was superior compare to placebo (p=0.005) with impression that 1 death or physical dependence could be avoided from 5 patients.

Saxena et al studied the effect of heparin on 3,169 (17%) acute ischemic stroke patients with atrial fibrillation from 18,451 “International Stroke Trial“ patients. They were given subcutaneous standard heparin of 5,000 IU bid (n=773), 12,500 IU bid (n=784) and without heparin (n=1612) for 14 days starting from 48 hours after the stroke onset. Half of the patients were randomly given aspirin 300 mg per day. It was concluded that recurrence of stroke in the first 14 days was lower according to amount of heparin. On the other hand it was also difficult to accept because the incidence of intracranial hemorrhage increased significantly in higher dose of aspirin (1.2% vs 0.4%). There was no difference of mortality on 14th days (9% vs 9.2%) and mortality or physical dependence in 6 months (62.9%) between the two groups. The benefits in the heparin group was less number of incidences of pulmonary emboli (PE) in 14 days (11.7% vs 12%). The groups of low dose heparin and aspirin showed the least incidence of stroke recurrence and early mortality (decreased of
0.9% and 1.3%) and the risk of hemorrhage was related to increased dose of heparin.7,8

Heparin in Acute Embolic Stroke Trial (HAEST) study was a multi-centered, double-blind and double-dummy to observe the effect of LMWH (Dalteparin 100 IU/kg SC bid) or aspirin 160 mg in 14 days. There was no significant difference between the two groups on the incidence of recurrent of stroke and secondary events such as asymptomatic or symptomatic intracranial hemorrhage in 48 hours or death. There was no significant difference on functional criteria at 14th day and after 3 months as well.9

Adams et al studied the effect of early heparinoid LMW/Daparinoid (in the first 24 hours) compared to placebo in stroke patients with severe stenosis or occlusions (>50%) of ipsilateral internal carotid artery. This was a double-blind, placebo-controlled study involving 229 from 1,041 patients underwent carotid artery imaging. Benefits were observed in the 7th day and 3rd month in the group who received danaparoid compared to placebo based on Barthel index (53.8% vs 38.0%). More benefits was seen in the 7th day and 3rd month in patients who received danaparoid but there was no difference in progression or recurrence of stroke.10

Reevaluation on five studies involving 705 patients with acute ischemic stroke. Four studies compared heparinoid (Danaparoid) and one study compared enoxaparin to standard heparin. The results was 55/414 (13%) patients who received heparinoid or LMWH had deep vein thrombosis compared to 65/291 (22%) heparin standard patients. There was significant decreased of incidence of vein thrombosis but the data was too small to evaluate outcome such as mortality or intracranial hemorrhage.

Meta-analysis of 11 double-blind controlled studies on LMWH and heparinoid gave the similar results with IST where LMWH had higher risk of major intracranial and extra cranial hemorrhage without significant decreased in mortality and morbidity. The benefit observed was the decrease in deep vein thrombosis incidence (OR 0.27%, 95% confidence interval of 0.08-0.96) and symptomatic pulmonary emboli (OR 0.34 with 95% confidence interval of 0.17-0.69). The conclusion from the meta-analysis was that LMWH is not recommended in ischemic stroke as routine treatment until further studies obtain sufficient data to support it.8

RAPID study which started in 2002 in Europe would evaluate classical IV heparin vs aspirin in non lacunar type of stroke, 12 hours post stroke and TAIST which studied the pragmatical LMWH and aspirin. The results would be published and hopefully could evaluate thoroughly this model for the first time.8,20

Among the disappointing results about the use of heparin and LMWH and heparinoid in ischemic stroke (except for decreasing the incidence of deep vein thrombosis, pulmonary emboli but increased incidence of hemorrhage), the consensus of ACCP regarding antithrombotic therapy may be basic approach of ischemic stroke and the role of heparin/LMWH. According to 6th consensus of ACCP on antithrombotic therapy, the use of anticoagulants were recommended in11:

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Venous Thrombosis</th>
<th>Defect of Blood, Protein and Platelet</th>
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<tbody>
<tr>
<td>Atherosclerosis</td>
<td>General surgery</td>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>Cigarette smoking</td>
<td>Orthopaedic surgery</td>
<td>Sticky platelet syndrome</td>
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<tr>
<td>Hypertension</td>
<td>Arthroscopy</td>
<td>Cancer procoagulant (CP)</td>
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<td>Diabetes Mellitus</td>
<td>Immobility</td>
<td>Protein S defects</td>
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<td>Low-density lipoprotein cholesterol</td>
<td>Malignancy</td>
<td>Protein C defects</td>
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<tr>
<td>Hypertriglyceridemia</td>
<td>Sepsis</td>
<td>APC resistance (factor V Leiden)</td>
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<td>Positive family history</td>
<td>Congestive Heart Failure</td>
<td>Antithrombin defects</td>
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<td>Left ventricular failure</td>
<td>Nephrotic syndrome</td>
<td>Heparin cofactor II defects</td>
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<td>Oral contraceptives</td>
<td>Obesity</td>
<td>Plasminogen</td>
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<td>Estrogens</td>
<td>Varicose veins</td>
<td>Tissue plasminogen activators</td>
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<td>Lipoprotein(a)</td>
<td>Postphlebitic syndrome</td>
<td>Plasminogen activator inhibitor defects</td>
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<td>Polycythemia</td>
<td>Oral contraceptives</td>
<td>Factors XII defects</td>
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<td>Hyperviscosity syndromes</td>
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<td>Dysfibrinogenemia</td>
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<td>Leukostasis syndromes</td>
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<td>Hyper Homocystinemia</td>
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1. Ineligible patients for thrombolytic therapy, receiving aspirin (160-325 mg/day) started at 48 hours after stroke onset and may combine with low dose of heparin SC for deep vein thrombosis prevention.

2. Patients with cardiac emboli and ischemic stroke of large arteries, progressive ongoing thromboembolies, it is recommended to give early anticoagulants.

3. Prevention of DVT and PE in patients with restricted mobility can be given low dose heparin SC, LMWH or Daparonoid (1A) if there is no contraindication.

4. Patients with cerebral vein sinus thrombosis is recommended to have UFH (un fractionated heparin) (1A) or LMWH (1C) followed by oral anticoagulants for 3 to 6 months (INR target of 2.5, range of 2.0-3.0) (1C)

**ACUTE CORONARY SYNDROME (ACS)**

The term ACS refers to clinical condition of unstable angina (UA), non Q wave acute myocardial infarct and Q wave acute myocardial infarct. Patient complaints of chest pain/ischemic pain on ECG evaluation can be classified into two groups: 1)."Without ST elevation", 2). With “ST elevation”. Patient who has no ST elevation can be categorized into 2 groups: unstable angina or non Q myocardial infarct which can be differentiated by the presence of cardiac marker in the blood.12

The conditions that had been mentioned above are precipitated by disruption of atherosclerotic plaque which would be followed by platelet activation. The most fragile plaque is the one with nucleus containing lipid, macrophage and lymphocytes and covered by thin fibrin layer consist of collagen and smooth muscle. In unstable angina and sudden cardiac arrest the thrombus is non occlusive while in acute myocardial infarct it is occlusive.

**LMWH IN UNSTABLE ANGINA AND NON Q WAVE MYOCARDIAL INFARCT**

For the first time, FRISC (Fragmin during instability in coronary artery disease) study involving 1,056 patients with UA and NQMI were given dalteparin with aspirin or aspirin alone in acute phase (1st-6th day) . Dalteparin with placebo were given in chronic phase (until 40th day). They were observed until 4 – 5 months post therapy. Indicators of evaluation were mortality, AMI and the need of revascularization. The group on dalteparin showed less mortality, cardiac event and need of revascularization on the 6th day (5.4% vs 10.3%, p=0.005) and was steady until the 40th day (p=0.005). However, this benefit disappeared on the 150th day (p=0.18).12,13

FRIC (Fragmin in unstable coronary artery disease) is the first study which compared LMWH and UFH with the same design as FRICS. The evaluations were done on 6th day and 45th day (acute and chronic phase). There were 1,482 patients with UA/NON STEMI on 1st to 6th day received dalteparin or standard heparin and followed by given dalteparin and placebo until 45th day. Based on mortality risk indicator, there were no significant difference between MI and recurrent angina until 6th day (9.3% vs 7.65%, p=0.33). The mortality was even higher in group of dalteparin compare to UFH (1.5% vs 0.4%, p=0.0057). The same result was seen on 6th to 45th day evaluation with group of placebo.12,14

FRAXIS (Fraxiparin in Ischemic syndromes) study involving 3,468 patients with 3 parallel treatment: UFH until 6th day, LMWH until 6th day, continued by placebo until 14th day. Reevaluation on the 6th day, 14th day and 3 months showed no significant difference in mortality, acute myocardial infarct, recurrent angina and need of revascularization between group of UFH, short course of LMWH and long treatment of LMWH.12,13 In addition, the mortality rate and AMI tended to be higher than group receiving nadroparin.12

Study on enoxaparin in UA and NQMI was carried out in ESSENCE (Efficacy and safety of subcutaneous Enoxaparin in Non Q wave coronary events) study and
TIMI 11 B (Thrombolysis in myocardial infarction) study. ESSENCE was a double blind, double dummy, placebo controlled study involving 3,171 patients who were given LMWH 1mg/kg body weight SC, bid or continuous infusion of UFH. Therapy was given minimum of 2 days and maximum of 8 days. Coronary events were evaluated in the period of 30 days. All patients received aspirin 100-325 mg.

There were less coronary events on 14th day in group of LMWH compare to UFH (16.6% vs 19.8%, p=0.019). The same result was shown in the 30th day evaluation (19.8% vs 23.3%, p=0.016).

The need of revascularization procedure until 30th day lower in group of LMWH (6.5% vs 7.0%) although bleeding events were higher in group of LMWH specially because of echimosis at location of needle puncture (18.4% vs 14.2%, p=0.001). It was concluded that treatment of LMWH (enoxaparin) with aspirin was more effective than UFH with aspirin in the early phase of UA or NQMI.13,15

TMII 11B is a study similar to ESSENCE, except that the patients received bolus of 30 mg of enoxaparin, in the group of LMWH and the evaluation was done until 43rd day. In the beginning of study, patients were randomly given UFH or LMWH for 8 days then followed by enoxaparin and placebo until 43rd day. On the 14th and 43rd day, the group of enoxaparin indicated the benefit of decreasing combined coronary events which were written in order 14.2% vs 16.7% p=0.03 and 19.7% vs 17.3%, p=0.061.13,14,16 Meta-analysis of ESSENCE and TMII 11B showed enoxaparin was consistently related to 20% decreased of mortality and fatal ischemic compared to UFH until 43rd day.13,16,17

The 6th Consensus of ACCP recommended treatment of heparin and LMWH (dalteparin, nadroparin or enoxaparin) for in-hospitalized patients with UA on aspirin. (Grade 1A). On the other hand, ACC/ACA in 2002 recommended for UA and Non STEMI to give the following anticoagulant treatment:

1. LMWH SC or infusion of UFH, in addition to aspirin therapy or clopidogrel (class I/grade A)
2. Enoxaparin is more recommended than UFH in patients with UA or NQMI unless if CAGB would be done in 24 hours (class 2, grade A).12

LMWH and QMI/ST Elevation

The role of UFH and LMWH as additional therapy in post thrombolysis is aimed to prevent the re-occlusion and recurrent ischemic event by maintaining anticoagulant effect.24 However, several studies showed controversial results and inconclusive. GUSTO IIa and TMII 9A studies were attenuated earlier due to significant intra cerebral bleeding in the group who received heparin.18

On the other hand, treatment of rt-pa resulted in more than ½ of the patients with the occlusion had been improved, while streptokinase resulted less than 1/3 of the patients and not all the artery could be opened successfully. Re-occlusion was occurred in 5-10% cases during hospitalization. (25% occurred in 1st day) and reached 30-40% in the 1st year and 50% of them were asymptomatic.18,19 Glick and friends studied the use of enoxaparin for 21 days and UFH for 5 days in patients with AMI post thrombolytic therapy and found coronary events in order 14% vs 43% (p<0.001) and significant decreased of re-infarction (p=0.001) during 5 weeks of observation since the occurrence of infarct.13

There were 4 studies involving anticoagulant (heparin) after fibrinolysis: GISSI-2, ISIS-3 and DUCCS which compared group received heparin and no heparin. There was no additional benefit shown on giving heparin in patient who were already be given aspirin and fibrinolysis. GUSTO study showed no significant difference between subcutaneous heparin therapy and intravenous after fibrinolysis. HART II is an ongoing study specific for LMWH would evaluate enoxaparin vs UFH as additional therapy of fibrinolysis.18

Based on information mentioned previously, ACC/AHA classified role of heparin in QMI in class II. On the other hand, 6th consensus of ACCP recommended giving treatment of low dose of heparin no less than 7500 IU SC every 12 hours or LMWH in patients with AMI until they leave the hospitals to prevent deep vein thrombosis unless if there is contraindications (1A). Meanwhile in patients who received rt-pa, r-PA, TNK-PA, SK or APSAC; and have high risk of systemic emboli or VTE the treatment of LMWH or heparin is also recommended. (Grade 2A), If the patients do not receive fibrinolysis but at the same time have high risk of systemic emboli or PE, the treatment of heparin is recommended (Grade 2A).

CONCLUSION

Thrombosis in coronary artery and specially in stroke involving various kind of etiologies and pathogenesis where it was found that 85% of stroke were ischemic stroke.

Acute myocardial infarct is still the leading cause of death, while stroke is the most frequent cause of long
term disability causing increase direct and indirect economic burden.

The role of LMWH in ischemic stroke is still controversial and inconclusive unless for some special conditions that it might be taken into consideration such as prevention of VTE, PE and progressive cardiac emboli or involving large artery (2B) or the patient with restricted mobility (1A) if there is no contraindication.

The role of LMWH together with aspirin or clopidogrel in UA and NQMI has given benefit to decreased combined coronary events (1A), while enoxaparin is more recommended than any other LMWH (2A).

The role of LMWH in AMI/ST elevation AMI/QMI as additional therapy after thrombolysis has not been proven to give beneficial result, for some reasons such as post fibrinolysis with high risk of VTE and systemic emboli, treatment of LMWH or UFH is recommended (2A), or at least with low dose of UFHJ (1A) or patients without fibrinolysis but have risk of systemic emboli and PE, the treatment of UFH is also recommended (2A).

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