Jurnal Sains Kesihatan Malaysia **6** (1) 2008: 23-34

Bleeding Risk Factors with Enoxaparin for Patients with NSTEMI/UA in HUKM

(Faktor Risiko Pendarahan Berkaitan dengan Enoxaparin di Kalangan Pesakit NSTEMI/UA di HUKM)

NORAIDA MOHAMED SHAH, AZMI SARRIFF & ROSNANI HASHIM

ABSTRACT

Low-molecular-weight heparins (LMWHs) are antithrombotic agents utilised in the treatment of acute coronary syndromes. They have been shown to be more effective than unfractionated heparins (UFHs) in reducing ischeamic events, which include death, myocardial infarction (MI) and urgent revascularisation. Enoxaparin is one of the products of LMWHs. Its safety and efficacy has been proven in the ESSENCE and TIMI IIB studies. This study was carried out to identify risk factors that may affect bleeding complications associated with the use of enoxaparin for non-ST-elevation MI (NSTEMI) or unstable angina (UA) in Universiti Kebangsaan Malaysia Hospital (HUKM). This observational, longitudinal study was conducted on patients who were admitted to the Coronary Care Unit (CCU), Coronary Rehabilitation Ward (CRW), Medical 1 and Medical 2 wards at HUKM and initiated on enoxaparin for NSTEMI/UA from 22nd of March until 22nd of April 2004. A total of 40 patients were included in the study with median age of 65 years, male to female ratio of 3:1, diagnosed with NSTEMI (55%) and UA (45%). 45% of patients developed an episode of bleeding and among them 83.3% (15 patients) characterised by haematuria. Higher percentages of women (80%) and those with creatinine clearance of < 30ml/min (100%) had incidence of bleeding as compared to men (50%) and those with creatinine clearance ≥ 30 ml/min, respectively (p < 0.05 for both parameters). Age, enoxaparin dose and duration of therapy, smoking and concomitant aspirin/ticlopidine therapy did not significantly affect the incidence of bleeding. In conclusion, renal impairment and gender were associated with bleeding in relation with the use of enoxaparin that may require dose adjustments.

Key words: Enoxaparin, NSTEMI/UA, Risk factors, Bleeding

ABSTRAK

Heparin berberat molekular rendah (LMWH) adalah agen antitrombotik yang digunakan dalam rawatan sindrom koronari akut. LMWH adalah lebih efektif

daripada heparin tanpa fraksi (UFH) dalam mengurangkan kejadian iskemik, termasuklah kematian, infarksi miokardial (MI) dan revaskularasi segera. Enoxaparin adalah salah satu produk LMWHs. Keselamatan dan keberkesanannya telah dibuktikan oleh kajian – kajian ESSENCE dan TIMI IIB. Kajian ini dijalankan untuk mengenal pasti faktor-faktor risiko yang boleh memberi kesan kepada komplikasi pendarahan yang dikaitkan dengan penggunaan enoxaparin untuk infarksi miokardial tanpa peningkatan ST (NSTEMI) atau angina tidak stabil (UA) di Hospital Universiti Kebangsaan Malaysia (HUKM). Kajian jenis pemerhatian ini dijalankan ke atas pesakit-pesakit yang dimasukkan ke Unit Jagaan Koronari (CCU), Wad Pemulihan Koronari (CRW), Wad Perubatan 1 dan Wad Perubatan 2 di HUKM yang menerima enoxaparin untuk NSTEMI/UA dari 22 Mac hingga 22 April 2004. Seramai 40 pesakit telah dikaji dengan median umur 65 tahun, nisbah lelaki kepada perempuan 3:1 yang didiagnos dengan NSTEMI (55%) dan UA (45%). Sejumlah 45% pesakit mengalami episod pendarahan di mana 83.3% (15 pesakit) dicirikan dengan haematuria. Lebih ramai wanita (80%) and pesakit yang mempunyai klearan kreatinin < 30 ml/min (100%) mengalami pendarahan berbanding dengan lelaki (50%) dan mereka yang mempunyai klearan kreatinin ≥ 30 ml/min, masing-masing (p < 0.05 untuk kedua-dua parameters). Umur, dos enoxaparin dan tempoh penggunaannya, merokok dan pengambilan bersama aspirin/ticlopidine didapati tidak mempunyai hubungan yang bererti dengan kejadian pendarahan. Sebagai kesimpulan, kerosakan ginjal dan jantina adalah berkait dengan pendarahan yang mempunyai hubungan dengan penggunaan enoxaparin dan mungkin memerlukan pengubahsuaian dos.

Kata kunci: Enoxaparin, NSTEMI/UA, Faktor risiko, Pendarahan

INTRODUCTION

Cardiovascular disease is a leading cause of death in Malaysia. In year 2000, 33,623 patients were admitted into the government hospitals for acute coronary syndromes (Malaysian Clinical Practice Guidelines on UA/NSTEMI 2002). Patients with ischaemic discomfort presented with or without ST segment elevation on electrocardiogram (ECG) is classified under acute coronary syndromes (ACS). Patients without ST-segment elevation are experiencing either unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI). UA/NSTEMI is normally caused by atherosclerotic coronary artery disease and is associated with an increased risk of cardiac death and myocardial infarction (MI). Differentiation between these two is based on the presence or absence of cardiac markers. Patients with unstable angina will have normal creatine kinase, CK-MB and cardiac troponins but for NSTEMI, these cardiac enzymes will normally be raised (Braunwald et al. 2002).

Intravenous UFH or generally known as heparin is an anticoagulant utilised not only for UA/NSTEMI but also for the treatment of other thromboembolic disorders such as deep-vein thrombosis, pulmonary embolism and acute myocardial infarction. Generally, the goal of heparin therapy is to prevent extension of existing thrombi and recurrent thromboembolism with a minimal risk of bleeding (Hirsh et al. 1995). Activated partial thromboplastin time (aPTT) is a laboratory test advocated to monitor the anticoagulant effect of heparin. It measures the activity of thrombin, Factor Xa and Factor IXa in the clotting cascade (Sparks 1996).

Inadequate starting dose of heparin, delay in obtaining and/or responding to the aPTT results and inappropriate heparin dose adjustments are problems associated with the use of heparin (Gunnarsson et al. 1995). On the other hand, low molecular weight heparins (LMWHs) are derived from UFH, which is separated into fragments based on molecular weight. LMWH differs from UFH with respect to molecular weight, antithrombotic and pharmacokinetic properties, monitoring requirements and adverse effects profile (Wittkowsky 2000). The antithrombotic effect of LMWH is more predictable (Verheugt 1999) and does not prolong the aPTT (Wittkowsky 2000 & Weitz 1997). Other advantages of LMWH over UFH include improved bioavailability, predictable anticoagulant response, dose independent clearance mechanism and longer half-life (Verheugt 1999 & Weitz 1997). Furthermore, LMWH is associated with less bleeding as opposed to UFH (Weitz 1997).

LMWH has been extensively studied and utilised for the prevention and treatment of thromboembolic diseases (Wittkowsky 2000). Its use is established for the prevention and treatment of venous thromboembolism (Wittkowsky 2000 & Weitz 1997) and has been proven effective and safe in ACS. LMWH utilised as an antithrombotic agent in ACS has been linked with reduction in ischaemic events, including death, MI and the need for urgent revascularisation (Ageno & Turpie 2002).

Results from the FRISC (Fragmin During Instability in Coronary Artery Disease- using dalteparin), FRIC (Fragmin in Unstable Coronary Artery Disease- using dalteparin), FRAXIS (Fraxiparine in Ischemic Syndrome- using nadroparin), ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in non-Q-wave Coronary Events) and TIMI IIB (Thrombolysis in Myocardial Infarction- using enoxaparin) studies have supported the safety and efficacy of LMWHs in patients with ACS (Ageno & Huisman 2001 & Villareal 2001).

Despite the evidence described above, there are currently no data evaluating the safety and efficacy of LMWHs in patients who are obese and patients with severe renal impairment (creatinine clearance [CrCL] ≤ 30 ml/min). A retrospective subgroup analysis of these patients was performed from the combined database of TIMI IIB and ESSENCE studies. It was found that enoxaparin reduced the rate of the combined end point of death, MI or urgent revascularisation in patients who were or were not obese and patients with no renal insufficiency. However,

patients with severe renal impairment treated with enoxaparin or UFH have a higher risk of clinical events, major and any haemorrhages as compared to patients without severe renal impairment (Spinler et al. 2003).

The utilisation of SC enoxaparin for the management of NSTEMI/UA in Malaysia is relatively new and has replaced the use of IV UFH. This has ignited an interest to study its pattern of use in patients with NSTEMI/UA at the Universiti Kebangsaan Malaysia Hospital (HUKM) and identify relevant issues that may affect its utilisation, which include bleeding risk factors.

The research hypothesis of this study is that patients with renal impairment have a higher risk of developing haemorrhages with SC Enoxaparin. The aim of this study is to describe the pattern of utilisation of SC Enoxaparin for NSTEMI/UA in HUKM and identify risk factors that may affect bleeding complications with SC Enoxaparin.

EXPERIMENTAL METHODS

The research is an observational, longitudinal study of patients admitted to Coronary Cardiac Unit (CCU), Coronary Rehabilitation Ward (CRW), Medical Ward 1 and Medical Ward 2 at HUKM initiated on LMWH therapy for NSTEMI/UA at any period between 22nd of March to 22nd of April 2004. Patients were identified prospectively from screening through the medication charts.

Demographic data and enoxaparin utilization, which include indication for its use, dosing regimen, duration of therapy, progression of symptoms (chest pain, shortness of breath, ECG changes and other symptoms), as well as incidence and type of side effects that occurred were documented. Patients' laboratory and medication profile were also noted.

RESULTS

A total of 40 patients were studied and all received SC enoxaparin for NSTEMI/UA. The majority of patients were male (75%) and 42.5% of the patients were Malay. The median age of the patients studied was 65 years. Previous cardiac history was seen in 35% of the patients. Fifty five percent of the patients studied were initially diagnosed with non-ST-elevation MI (NSTEMI) while the remaining had unstable angina (UA). All except 5 patients received aspirin concomitantly with enoxaparin (Table 1).

Patients with NSTEMI/UA in this study received SC enoxaparin 40mg, 60mg or 80mg every 12 hours. On average, patients received a total of six doses of enoxaparin. As for the duration of therapy, seven patients (17.5%) were administered with enoxaparin for less than 48 hours (Table 2).

TABLE 1. Baseline characteristics of patients (n = 40)

Mean age (yr)	61.6 (range of age: 35-83y)
Gender	
Male	30 (75%)
Female	10 (25%)
Race	
Malay	17 (42.5%)
Chinese	14 (35%)
Indian	7 (17.5%)
Others	2 (5%)
Previous cardiac history	14 (35%)
Type II diabetes mellitus	21 (52.5%)
Hypertension	31 (77.5%)
Hypercholesterolemia	15 (37.5%)
Family history of cardiac disease	11 (27.5%)
Current smoker	13 (32.5%)
Initial diagnosis	22 (55%) NSTEMI, 18 (45%) UA
Raised baseline cardiac markers	22 (55%)
ECG changes	26 (65%)
ST-segment elevation	3 (7.5%)
ST-segment depression	9 (22.5%)
T-wave inversion	19 (47.5%)
New Left Bundle Branch Block (LBBB)	2 (5%)
Presence of Q-wave	9 (22.5%)
Time to first dose (h)	Median 4.33h (range: 1.5-55.5h)
Concomitant medication with SC enoxaparin	
Aspirin	35 (87.5%)
Ticlopidine	4 (10%)
Clopidogrel	1 (2.5%)
NSAIDs	1 (2.5%)

Bleeding occurred in 18 patients (45%), whereby majority was due to haematuria or blood in the urine (15 patients; 83.3%). Two patients experienced upper gastrointestinal bleeding while one patient had bleeding from the femoral catheter.

As for kidney profile of the patients studied, six patients (15%) had creatinine clearance less than 30 ml/min. These patients experienced an episode of bleeding

TABLE 2. Dosing and duration of enoxaparin therapy

Dosing	
40 mg bd	3 (7.5%)
60 mg bd	29 (72.5%)
80 mg bd	8 (20%)
Number of doses	Mean: 6 (range: 1-12 doses)
Duration of therapy	Mean: 2.8 days
< 2 days	12 (30%)
2 - 8 days	28 (70%)

whereas only 12 out of 34 (35.3%) patients with creatinine clearance of > 30 ml/min had signs of bleeding during the period of hospital stay. Using Pearson Chi Square test, it was found that there is a significant difference in bleeding incidence between patients with creatinine clearance of < 30 ml/min and > 30 ml/min ($p < 0.01$) (Table 3).

TABLE 3. Factors affecting incidence of bleeding in patients on SC enoxaparin

	Bleeding	No bleeding	Significance
Kidney function			
GFR < 30 ml/min ($n = 6$)	6 (100%)	0 (0%)	
GFR > 30 ml/min ($n = 34$)			$p < 0.01$
	12 (35.3%)	22 (64.7%)	
Gender			
Male ($n = 30$)	15 (50%)	15 (50%)	
			$p < 0.05$
Female ($n = 10$)	8 (80%)	2 (20%)	

As for the influence of gender on bleeding incidence, 80% (8 out of 10) female patients while 50% (15 out of 30 patients) male experienced an episode of bleeding. Using similar statistical analysis of Pearson Chi Square test, it was found that there is significant difference in bleeding incidence between male and female patients ($p < 0.05$).

Bleeding occurred most frequently in patients aged between 65 to 75 years of age (7 out of 18 patients; 38.9%). However, there was no statistically significant difference in the occurrence of bleeding based on the patients' age. Similarly, dosing and duration of enoxaparin therapy, smoking status as well as concomitant therapy with aspirin or ticlopidine had no statistically significant difference on bleeding incidence.

Out of the 18 patients studied whereby bleeding occurred during administration f enoxaparin, 12 patients (66.7%) had Naranjo scale of 2 [possible adverse drug

reaction (ADR)], 4 patients (22.2%) with Naranjo scale of 3 (also possible ADR) and the remaining 2 patients (11.1%) with a scale of 5 (probable ADR).

DISCUSSION

In this study, all 40 patients received SC enoxaparin as the antithrombotic agent for the treatment of NSTEMI/UA. None received nadroparin (Fraxiparine®), the only other LMWH available at HUKM apart from enoxaparin (Clexane®). In this hospital, nadroparin is only utilised for prophylaxis of deep vein thrombosis.

Patients either diagnosed as NSTEMI (55%) or UA (45%) but not patients with ST-elevation MI (STEMI) were included in this study. However, 5 patients diagnosed with NSTEMI showed presence of Q-wave on the ECG. Both ESSENCE and TIMI IIB trials enrolled patients with unstable angina or NQMI and patients with ST-elevation MI (STEMI) were excluded (Antman et al. 1999).

Baseline characteristics of the patients in this study were almost similar to the patients included in the ESSENCE and TIMI IIB studies. The median age of patients in this study was 65 years, similar to the median age in the TIMI IIB study. Risk factors for coronary artery disease, previous cardiac history and types of ECG changes if present were also analysed similarly as for patients from the ESSENCE and TIMI IIB studies.

In this study, patients did not receive an initial 30 mg IV bolus SC enoxaparin, which is similar to the protocol set by the ESSENCE study (Cohen et al. 1997). The dosing resembled more of a standard dose regimen since patients would either receive 40 mg, 60 mg or 80 mg enoxaparin subcutaneously every 12 hours with majority (72.5%; 29 patients) receiving the 60 mg dosing. This was mainly due to a higher percentage of patients (60%) being in the weight range of 56-75 kg. The three patients that received 40 mg of SC enoxaparin every 12 hours weigh 40 kg, 49 kg and 70 kg respectively. In the ESSENCE study, patients received 1mg/kg of SC enoxaoparin every 12 hours (Cohen et al. 1997). In TIMI IIB study, patients in the enoxaparin group received an initial IV bolus of 30mg enoxaparin followed by 1mg/kg SC enoxaparin every 12 hours (Antman et al. 1999a).

In this study, 35 patients (87.5%) received oral aspirin 150mg daily. However, all patients received 100-325 mg of oral aspirin daily in both ESSENCE and TIMI IIB studies (Cohen et al. 1997 and Antman et al. 1999b).

The median duration of therapy in this study was for 3 days with an average of 6 total doses of enoxaparin. There was no definite time for termination of enoxaparin but most prescribers would opt for a total of 6 doses. The duration of therapy remained subjective and depended on the prescribers' judgment. Based on ESSENCE and TIMI IIB studies, patients received SC enoxaparin for a median duration of 2.6 and 4.6 days respectively. In the ESSENCE study, the minimum duration of therapy was 48 hours and the maximum was for 8 days. In this study, 7 patients (17.5%) receiving enoxaparin for less than 48 hours were still included.

A total of 45% of patients (18 patients) on enoxaparin in this study developed an episode of bleeding with majority of them (83.3%, 15 patients) due to haematuria. However, only 7 patients had haematuria with 250 red blood cells per microlitre of urine. Three of these 7 patients had enoxaparin discontinued. In both ESSENCE and TIMI IIB studies, macroscopic haematuria is classified as a minor haemorrhage, which does not necessitate termination of enoxaparin. On the other hand, in both studies, major haemorrhage was described as bleeding resulting in death, transfusion of at least 2 units of blood, a fall of haemoglobin of at least 30g/l, retroperitoneal, intracranial or intraocular damage (Antman et al. 1999b). In this study, only 2 patients could be described as experiencing major haemorrhage. One patient had a total of 7 units of packed cells transfused as he aspirated coffee ground secretions from Ryles tube and had malaenic stools. His haemoglobin had dropped from 157 g/l on the day of admission to 77 g/l on day 9 of his hospital stay. Another patient had 2 units of fresh frozen plasma transfused as he was bleeding from the femoral catheter inserted for his regular haemodialysis. Thus, as a whole, if bleeding is classified similarly as in the ESSENCE and TIMI IIB trials, 17.5% of the patients studied (7 patients) developed minor haemorrhage while 5% (2 patients) experienced major haemorrhage. The incidence of minor haemorrhage was 10.6% and 9.4%, while the incidence of major haemorrhage was 1.5 and 1.1% in the TIMI IIB and ESSENCE study respectively (Antman et al. 1999b). The higher percentage of both minor and major bleeding seen was probably due to other confounding factors like severity of illness and presence of other concomitant diseases that may affect bleeding with enoxaparin that were not determined in this study.

Several risk factors that may affect the incidence of bleeding in this study were analysed. These include the effect of gender, age, dosing, smoking, kidney function and concomitant aspirin/ticlopidine therapy in the incidence of bleeding. Only kidney function and gender were found to have a significant effect on the incidence of bleeding that occurred in the patients studied. All six patients (15% of total subjects) with creatinine clearance of less than 30 ml/min experienced an episode of bleeding. In this study, being female was also found to increase the risk of bleeding. Age, enoxaparin dose and duration of therapy, smoking and concomitant aspirin/ticlopidine therapy did not significantly affect the incidence of bleeding.

Patients with renal impairment (creatinine clearance < 30 ml/min or a serum creatinine level ≥ 2 mg/dl) (Spinler et al. 2003 & Becker et al. 2002) were excluded in the ESSENCE and TIMI IIB studies. LMWHs are not recommended in patients with renal failure due to risk of accumulation, which might lead to major bleeding (Becker et al. 2002). However, in the ESSENCE and TIMI IIB studies, 2% (143 patients) of the study population actually had severe renal impairment (creatinine clearance ≥ 30 ml/min) either due to unavailable serum creatinine levels or miscalculated creatinine clearance values. A retrospective subgroup analysis of the safety and efficacy of enoxaparin and UFH who are obese and renally impaired

was conducted from the combined database of the ESSENCE and TIMI IIB trials. It was found that the renally impaired patients had a high rate of the primary composite end points of death, myocardial infarction and urgent revascularization at 43 days whether treated with enoxaparin or UFH. This group of patients was also found to experience an approximately 6-fold increase in the risk of major bleeding compared to patients without renal impairment (Spinler et al. 2003).

There are no specific dosage-reduction guidelines although the manufacturer recommended prescribing enoxaparin with caution in patients with renal insufficiency and is generally inadvisable in patients with severe renal impairment (Rhone-Poulenc Pharmamceuticals 1998).

A study conducted by Becker et al. (2002) on the influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin in patients with NSTEMI found that the trough and peak anti-Xa activity together with its apparent clearance were not affected by patients' age, gender or body weight in fixed, weight-adjusted dose of 1.0-1.25 mg/kg. However, patients with severe renal impairment (creatinine clearance of < 40 ml/min) showed higher anti-Xa in plasma and higher incidence rate of major haemorrhagic events. The author suggested either to reduce the dose to 0.5-0.75 mg/kg or to monitor anti-Xa serum levels to avoid dangerous levels of anticoagulation in this group of patients.

Collet et al. (2001) conducted a study to evaluate the optimal dose of SC enoxaparin according to renal function in patients with unstable angina at high risk of bleeding. Enoxaparin dose was reduced empirically based on the creatinine clearance and subsequently adjusted based on the level of anti-Xa measured after the third dose to achieve a target value of 0.5-1.0 IU/ml. It was found that the optimal dose depended on the renal function and in patients with creatinine clearance of < 30 ml/min, the dose should be reduced to 64% of the standard dose of 1 mg/kg every 12 hours.

Nagge et al. (2002) conducted a systematic research of MEDLINE, EMBASE and International Pharmaceutical Abstracts to identify prospective articles comparing differences in the pharmacokinetics of LMWHs in patients with varying degrees of renal function. They concluded that based on available evidence, patients with creatinine clearance of 30 ml/min or less should not be excluded from receiving LMWHs despite the accumulation of anti-Xa heparin activity seen with enoxaparin. However, no conclusive recommendations could be made for the dosing of this agent in patients with renal insufficiency.

Only one patient in this study was on regular chronic haemodialysis and was administered with SC enoxaparin at a dose of 0.92 mg/kg (60 mg every 12 hours, weight 65 kg). This patient developed bleeding characterised by oozing from the femoral catheter and was transfused with 2 units of fresh frozen plasma. Brophy et al. (2001) carried out a study on patients with end-stage renal disease (ESRD) on long-term haemodialysis administered with enoxaparin. They found that dosing adjustments were unnecessary in this group of patients. This was

because ESRD had minimal effect on the pharmacokinetics of enoxaparin based on anti-Xa activity.

When assessing bleeding incidence using Naranjo scale, most of the patients (88.9%) demonstrated a probable adverse drug reaction (ADR) of bleeding due to enoxaparin alone. Failure to show a possible or definite instead of a probable ADR was mainly due to the inclusion of kidney impairment (creatinine clearance of < 30ml/min) and concomitant use of aspirin that could on their own caused the reaction.

There are some limitations in this study. Due to the short duration and the prospective nature of the study, the sample size is very small, consisting of 40 patients only. Therefore, the power of analysis is limited. A longer period of study incorporating a larger number of patients would be necessary to evaluate the safety and efficacy of enoxaparin in the treatment of NSTEMI/UA in this setting. Various confounding factors like the severity of illness and concomitant diseases that may affect the outcome and bleeding incidence of patients administered with enoxaparin were not addressed in this study. Furthermore, the results of this study were compared with published studies that have different inclusion and exclusion criteria rendering a direct comparison not entirely appropriate.

Another limitation in determining the frequency of bleeding in patients with renal insufficiency is lack of control group with renal impairment who did not receive enoxaparin. This is important as renal insufficiency by itself is a risk factor for bleeding. Renal failure is known to depress erythropoiesis by reducing erythropoietin production and promotes accumulation of toxins that leads to bone marrow suppression (Brady & Brenner 1994). Furthermore, no monitoring of anti-Xa level was carried out in this study. Anti-Xa levels do not correspond to efficacy but may help to predict bleeding by determining if accumulation of enoxaparin occurred (Gerlach et al. 2000).

Further prospective studies are required to address issues pertaining to the use of enoxaparin, including the need to monitor anti-Xa activity monitoring and/or dose adjustment in patients with severe renal impairment.

CONCLUSION

Renal impairment and gender were significant risk factors that may predispose patients to bleeding with enoxaparin. In this study, age, enoxaparin dose, duration of therapy, smoking status and concomitant use of aspirin and ticlopidine did not significantly affect bleeding incidence.

REFERENCES

Ageno, W. & Huisman, M. V. 2001. Arterial indications for the low molecular weight heparins : Current control trials. *Cardiovascular Medicine* 2: 233-239.

Ageno, W. & Turpie, A. G. G. 2002. New advances in the management of acute coronary syndromes : 4. Low-molecular-weight heparins. *Canadian Med. Assoc. J.* 166(7): 919-924.

Antman, E. M., McCabe, C. H., Gurfinkel, E. P., Turpie, A. G., Bernink, P., Salein, D., de Luna, A. B., Fox, K., Lablanche, J. M., Radley, D., Premmereur, J. & Braunwald, E. 1999a. Enoxaparin prevents death and cardiac ischemic events in unstable angina/ non-Q-wave myocardial infarction (TIMI) IIB trial. *Circulation* 100: 1593-601.

Antman, E. M., Cohen, M., Radley, D., McCabe, C., Rush, J., Premmereur, J. & Braunwald, E. 1999b. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI IIB-ESSENCE meta-analysis. *Circulation* 100: 1602-8.

Becker, R. C., Spencer, F. A., Gibson, M., Rush, J. E., Sanderink, G., Murphy, S.A., Ball, S. P. & Antman, E. M. 2002. Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. *Amer. Heart J.* 143: 753-9.

Brady, H. R. & Brenner, B. M. 1994. Acute renal failure. In K. J. Isselbacher, E. Braunwald, R. G. Petersdorf, J. D. Wilson, J. B. M., A. S. Fauci. (Eds.) *Harrison's Principles of Internal Medicine*, 13th ed, New York: McGraw-Hill, 1265-74.

Braunwald, E, Antman, E. M., Beasley, J. W., Califf, R. M., Cheitlin, M. D., Hochman, J. S., Jones, R. H., Kereiakes, D., Kupersmith, J., Levin, T. N., Pepine, C. J., Schaeffer, J. W., Smith, E. E. 3rd, Steward, D. E., Theroux, P., Gibbons, R. J., Alpert, J. S., Faxon, D. P., Fuster, V., Gregoratos, G., Hiratzka, L. F., Jacobs, A. K. & Smith, S. C. Jr. 2002. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina) ACC/AHA 2002. *Guideline Update for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction.* ACC/AHA Practice Guidelines. *J. Am. College Cardiol.* 40(7): 1366-1374.

Brophy, D. F., Wazny, L. D., Gehr, T. W., Comstock, T. J. & Venitz, J. 2001. The pharmacokinetics of subcutaneous enoxaparin in end-stage renal disease. *Pharmacotherapy* 21(2): 169-174.

Cohen, M., Demers, C., Gurfinkel, E. P., Turpie, A. G., Fromell, G. J., Goodman, S., Langer, A., Califf, R. M., Fox, K. A., Premmereur, J. & Bigonzi, F. 1997. For the efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events study group : A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *New England J. Med.* 337: 447-52.

Collet, J. P., Montalescot, G., Choussat, R., Lison, L. & Ankri, A. 2001. Enoxaparin in unstable angina patients with renal failure, *Int. J. Cardiology* 80: 81-82.

Gerlach, A. T., Pickworth, K. K., Seth, S. K., Tanna, S. B. & Barnes, J. F. 2000. Enoxaparin and bleeding complications : A review of patients with and without renal insufficiency. *Pharmacotherapy* 20(7): 771-775.

Gunnarsson, P. S., Sawyer, W. T., Montague, D., Williams, M. L., Dupuis, R. E. & Caiola, S. M. 1995. Appropriate use of heparin: empiric vs nomogram-based dosing, *Archives of Internal Medicine* 155(5) : 526-532.

Hirsh, J., Raschke, R., Warkentin, T. E., Dalen, J. E., Deykin, D. & Poller, L. 1995. Heparin: Mechanism of action, pharmacokinetics, dosing, monitoring, efficacy and safety. *Chest.* 108 (Suppl.): 258S-275S.

Kwang Leng, D. Q., Zambahari, R., Siang Tong, K., Tan, K., Kah Lin, K., Jamaluddin, A. N., Kui-Hian, S., Yusoff, K., Wan Ahmad, W. A., Jeyaindran, S., Chandran, K., Raman, K. S. & Menon, R. K. 2002 Malaysian Clinical Practice Guidelines on UA/NSTEMI. Kuala Lumpur: Ministry of Health Malaysia, National Heart Association of Malaysia, Academy of Medicine Malaysia.

Nagge, J., Crowther, M., Hirsh, J. 2002. Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arc. Int. Med*. 162: 2605-9.

Sparks, K. S. 1996. Are you up to date on weight-based heparin dosing? *Am. J. Nursing* 96(4): 33-36.

Spinler, S. A., Inverso, S. M., Cohen, M., Goodman, S. G., Stringer, K. A. & Antman, E. M. 2003. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment : Analysis from the ESSENCE and TIMI IIB studies. *Am. Heart J*. 146: 33-41.

Verheugt, F. W. A. 1999. Acute coronary syndromes : Drug treatments. *Lancet* 353 (Suppl. II): 20-23.

Villareal, R. P. 2001. Unstable angina and non-ST-segment elevation myocardial infarction, perspective on combination therapy. *Texas Heart Inst. J*. 28: 276-87.

Weitz, J. I. 1997. Low molecular weight heparins. *New England J. Med*. 337(10): 688-697.

Wittkowsky, A. K. 2001. Thrombosis: The clinical use of drugs. In M. A. Koda-Kimble and L. Y. Young (Eds.). *Applied Therapeutics: The clinical use of drugs*. Philadelphia : Lippincott Williams & Wilkins, 14.4-14.5

Noraida Mohamed Shah
Rosnani Hashim
Jabatan Farmasi
Fakulti Sains Kesihatan Bersekutu
Universiti Kebangsaan Malaysia
Jalan Raja Muda Abdul Aziz
50300 Kuala Lumpur

Azmi Sarriff
Pusat Pengajian Sains Farmasi
Universiti Sains Malaysia
11800 Minden Pulau Pinang

Corresponding author: noraida_mohamedshah@yahoo.com
Received: July 2007
Accepted for publication: October 2007