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REVIEW

The Use of Low-Molecular Weight Heparins in Acute Coronary Syndromes

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Abstract: Acute coronary syndrome (ACS) comprises of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). ACS is the consequence of a sudden rupture of the coronary artery plaque and the immediate formation of thrombosis around the plaque. The presence of coronary occlusion and thrombus might result in cardiac muscle damage and loss of effective cardiac output, leading to cardiac failure. Anticoagulants, therefore, play an important role in medical management for ACS. This article assesses the role of low molecular weight heparin (LMWH) in ACS based on current available data in clinical trials and clinical practice guidelines from the American College of Cardiology (ACC)/the American Heart Association (AHA) and the American College of Chest Physicians (ACCP) antithrombotic and thrombolytic therapy consensus guidelines. Overall, the use of enoxaparin is generally preferred over other LMWHs when LMWH is indicated, and there is strong support for its role across the continuum of treatment for ACS patients.

Keywords: acute coronary syndromes, low molecular weight heparin, anticoagulants

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Introduction

Acute coronary syndromes including unstable angina and myocardial infarctions are forms of coronary heart disease that brought approximately 733,000 patients to U.S. hospitals in 2006.[1] In contrast to chronic stable angina, acute coronary syndromes are the result of an imbalance between myocardial oxygen demand and supply primarily due to an occlusive or partially occlusive coronary artery thrombus. They represent life-threatening situations that require immediate medical care. The spectrum of acute coronary syndrome includes unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI). The classification of ACS type depends on EKG changes and presence of biomarkers. The presence of ST segment elevation on EKG readings differentiates STEMI from UA and NSTEMI. Increases in biomarkers such as troponin I or T or creatinine phosphokinase distinguishes NSTEMI from UA.[2]

Anticoagulation should be initiated early after presentation of ACS when the cause is a coronary artery thrombus to arrest thrombus growth and prevent recurrence of ischemia. Several studies have evaluated the use of low molecular weight heparin (LMWH) in patients with ACS that are managed with either conservative or invasive therapy. The potential benefit of using LMWHs in ACS can be attributed to their pharmacological properties. LMWHs are produced by chemical or enzymatic depolymerization of UFH resulting in sulfated glycosaminoglycan chains that are shorter in length with less variation in chain lengths compared to UFH. As a result, LMWHs have greater anti-Xa:IIa inhibition activity, more predictable dose-response relationship, improved subcutaneous bioavailability, dose-independent clearance, longer half-life, and lower risk of thrombocytopenia than UFH.[3] The ability to administer LMWH subcutaneously without frequent monitoring and subsequent dosage adjustments make LMWHs attractive alternatives to UFH in the management of ACS. In addition, they are resistant to inhibition by activated platelets.[4]

Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction

In the studies that have compared LMWH to UFH in patients managed with early conservative therapy, the results generally favor LMWH over UFH. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study was the first trial that directly compared enoxaparin with UFH in a randomized, double-blind, placebo-controlled study that enrolled 3,171 patients with angina at rest or non-Q-wave myocardial infarction. Patients were randomized to receive enoxaparin 1 mg/kg SQ every 12 hours with IV placebo bolus and infusion or IV UFH bolus (usually 5,000 units) followed by continuous infusion and SQ placebo injections. The UFH continuous infusion was dose-adjusted to achieve aPTT according to a pre-approved institutional heparin-dosing nomogram (typically 55–85 seconds). Patients were randomized within 24 hours of presentation and trial medications were administered for a minimum of 48 hours and up to a maximum of 8 days (average 2.6 days). All patients received 100–325 mg of oral aspirin daily. At 14 days, the risk of death, myocardial infarction, or recurrent angina was significantly lower in the enoxaparin group versus those treated with UFH (16.6% vs. 19.8%, respectively; $P = 0.019$). The risk of this composite endpoint remained significantly lower in the enoxaparin group at 30 days (19.8% vs. 23.3%; $P = 0.016$). Also at 30 days, the rate of coronary revascularization was significantly less frequent among patients treated with enoxaparin than those treated with UFH (27% vs. 32.2%, respectively; $P = 0.001$). There were no statistically significant differences in the rate of serious hemorrhagic complications between the two groups. However, the enoxaparin patients experienced more bleeding complications overall than those treated with UFH (9.5% vs. 4.4%, respectively, during acute phase and 18.4% vs. 14.4%, respectively, at 30 days, $P = 0.001$) due to an increase in minor hemorrhagic events, such as injection site ecchymosis.[5]

Thrombolysis in Myocardial Infarction (TIMI 11B) trial is another trial that looked at the effects of enoxaparin compared to the standard treatment with UFH in both an acute and outpatient phase for prevention of cardiac ischemic events in patients with UA/NSTEMI. The primary outcome was a combination of all-cause mortality, recurrent MI, or urgent revascularization. The secondary outcome was the individual elements of all-cause mortality, recurrent MI or urgent revascularization, and the combination of death or nonfatal MI. The

main safety outcome was major hemorrhage. A total of 3,910 patients were enrolled in a two-year period across ten countries in a double-blinded study and randomized to one of two anti-thrombin treatments. All patients were taking aspirin and received either UFH or matched placebo IV infusion and enoxaparin or matched placebo SQ injection depending on the randomization. The standard UFH treatment consisted of a minimum of three days and a maximum of eight days with a bolus of 70 units/kg, and an initial infusion rate of 15 units/kg/hr. The aPTT was monitored with a target range of 1.5–2.5 times control. The enoxaparin treatment dose for safe use consisted of an initial IV bolus of 30 mg followed by SQ injections of 1 mg/kg every 12 hours. Those who completed the acute phase were then enrolled in the outpatient phase to continue the study of enoxaparin effects for an additional 43 days. Patients previously on UFH were given placebo SQ injections, whereas patients previously on enoxaparin continued with 40 mg every 12 hours if they weighed <65 kg or 60 mg every 12 hours if they weighed ≥65 kg. The acute phase consisted of either an average of 3 days of UFH or an average of 4.6 days of enoxaparin treatment. At 48 hours, there was a difference in primary outcome events with rates of 7.3% in UFH patients and 5.5% in enoxaparin patients ($P = 0.026$). At day 8, the primary outcome events were 14.5% in UFH patients and 12.4% in enoxaparin patients ($P = 0.048$). From the study, it was determined that 21 events could be avoided per 1,000 patients treated with enoxaparin. Similarly, the secondary outcome also resulted in a decrease of events with rates of 5.9% in UFH groups, and 4.6% in enoxaparin groups ($P = 0.073$), although it was not statistically significant. A total of 2,364 patients continued into the outpatient phase. Data of time to first event of primary end point from day 1 through day 43 showed enoxaparin to be more effective on day 8, but from day 14 to day 43, there were no further benefits of enoxaparin compared to UFH. On day 43, the incidence of the primary end point was 19.7% for UFH and 17.3% for enoxaparin ($P = 0.048$), which showed no further decrease in events. Only benefits from initial treatments were sustained through day 43. As for rates of major hemorrhage, there were no significant differences between the two groups in both phases, but for minor hemorrhage, enoxaparin resulted in a higher rate of events that consisted of either ecchymosis at the injection site or a hematoma at the site of a sheath inserted for cardiac catherization. The results of the TIMI 11B illustrated that enoxaparin for the acute management of UA/NSTEMI is superior to UFH in cardiac patients mostly for treatment of the acute phase.[6]

Results of other studies also support the use of enoxaparin as an alternative to UFH. The Antithrombotic Combination Using Tirofiban and Enoxaparin II (ACUTE II) study illustrated the safe use of combination therapy of the GIIb/IIIa inhibitor, tirofiban, with enoxaparin relative to combination therapy of tirofiban with UFH. In the study, all patients received 160–325 mg of aspirin and 0.4 μg/kg/min of tirofiban over 30 minutes for a loading dose followed by a maintenance infusion of 0.1 μg/kg/min. There were 525 patients at 54 participating sites who were randomized to receive either 5,000 units IV bolus of UFH followed by 1,000 units/hour UFH (210 patients) adjusted to an aPTT of 1.5–2.5 times the control or 1.0 mg/kg subcutaneous injection of enoxaparin (315 patients) every 12 hours for at least 24 hours to as long as 96 hours.[7] In the Aggrastat to Zocor trial (A to Z trial) 3,987 patients were randomized to receive initial aspirin doses of 150–325 mg followed by a 75–325 mg dose daily and either the same dose of enoxaparin as the ACUTE II trial, or UFH dose that was weight based in which patients weighing ≥70 kg received 4000 units IV bolus followed by 900 units/hr infusion or patients weighing <70 kg, 60 units/kg loading bolus followed by 12 units/kg/hr. The aPTT goal was 50–70 seconds instead of 1.5–2.5 times the control. In the A to Z trial, patients received 10 mg/kg of tirofiban over 3 minutes followed by an infusion of 0.1 mg/kg/minute of a minimum of 48 hours and a maximum of 120 hours.[8] The ACUTE II study concluded the combination of aspirin, tirofiban and enoxaparin had fewer significant bleeding events compared to the combination with UFH whereas the A to Z trial supported that enoxaparin, although it may not necessarily be superior, may be used as an alternative to UFH.[7,8]

The use of other LMWHs including dalteparin, nadroparin, and tinzaparin has also been evaluated in the setting of UA/NSTEMI.[9–12] In the only trial that compared one LMWH to another LMWH, the Enoxaparin Versus Tinzaparin Trial (EVET), it was found that the enoxaparin group had lower

Table 1. Trials of LMWH in UA/NSTEMI.

Study	Number of patients	LMWH group	Control group
ESSENCE[5]	3,171	Enoxparin 1 mg/kg SQ BID for ≤4 days	UFH 5000 U bolus, infusion dose adjusted to aPTT 55–85 sec for ≥48 hrs
TIMI 11B[6]	3,910	Enoxaparin 30 mg IV bolus, 1 mg/kg SQ BID for ≤8 days	UFH 70 U/kg IV bolus, 15 U/kg/h for ≥3 days to aPTT 1.5–2.5 × control
ACUTE II[7]	525	Enoxaparin 1 mg/kg SQ BID ≤4 days	UFH 5000 U IV bolus, 1000 U/h for ≤4 d to aPTT 1.5–2.5 × control
A to Z[8]	3,987	Enoxaparin 1 mg/kg SQ BID for ≤5 days	UFH 4000 U IV bolus, 900 U/h if ≥70 kg; 60 U/kg bolus, 12 U/kg/h if <70 kg; aPTT 50–70 sec
EVET[12]	438	Enoxaparin 1 mg/kg SQ BID for 7 days	Tinzaparin 175 IU SQ QD for 7 days
FRIC[14]	1,482	Dalteparin 120 IU/kg SQ BID for 6 days, then 7500 IU SQ QD for 6–45 days	UFH 5000 U IV bolus, 1000 U/h to aPTT 1.5 × control for 48 hours, then placebo for 6–45 days
FRISC[9]	1,506	Dalteparin 120 IU/kg SQ BID for 6 days, then 7500 IU QD for 35–45 days	Placebo
FRISC II[10]	2,105	Dalteparin 120 IU/kg SQ BID for >5 d, then 5000 IU if F >80 kg or M >70 kg or 7500 IU if above weight for 3 months	Placebo
OASIS-5[15]	20,078	Enoxaparin 1 mg/kg SQ BID	Fondaparinux 2.5 mg SQ QD

rates of the composite endpoint of death, nonfatal myocardial infarction, or recurrent angina at 7 days and 30 days than the tinzaparin group (12.3% vs. 21.1%, respectively; $P = 0.015$ and 17.7% vs. 28.0%, respectively; $P = 0.012$). As for hemorrhage, both groups had similar rates although they were higher compared to those in the ESSENCE and TIMI 11B trials.[12] Other trials have shown that dalteparin is more effective than placebo.[9,10] Due to limited studies directly comparing different LMWHs, one LMWH is generally not substituted in place of another. Enoxaparin is generally the preferred LMWH because it has substantial evidence supporting its use.[13]

Extended therapy of LMWH beyond the acute phase treatment of UA and NSTEMI has also been evaluated. In the Fragmin in Unstable Coronary Artery Disease (FRIC) study, there was no significant difference in the combined endpoint of death, myocardial infarction, or recurrent angina in patients that received 7,500 IU once daily of dalteparin than those patients that received placebo SQ injections in the same period of 6–45 days after acute treatment of dalteparin or UFH, respectively.[14] Similar findings were also reported in the TIMI 11B trial, such that continuation of enoxaparin for another 35 days into the outpatient setting did not confer additional benefit over placebo despite having demonstrated acute phase superiority to UFH.[6] In addition, the enoxaparin group experienced higher rates of major hemorrhage than the placebo group (2.9% vs. 1.5%, $P = 0.021$) at day 43. In contrast, in the Fragmin During Instability in Coronary Heart Disease (FRISC) study, patients who received home treatment of 7,500 IU dalteparin SQ once daily after acute phase treatment with dalteparin showed a significant reduction in the combined endpoint of death, new myocardial infarction, occurrence of revascularization, and the need for intravenous heparin at 40 days compared to patients who received placebo SQ injections at the hospital and at home (20.5% vs. 25.7%, respectively; $P = 0.011$).[9] Subanalysis of this study suggested that the benefit seen with home treatment of enoxaparin was confined to non-smokers, patients with NSTEMI, lower body-mass index, or with at least one high risk indicator

Table 1 (*Continued*)

Primary efficacy outcome	Efficacy %			Major bleed %		
	LMWH	Control	*P* value	LMWH	Control	*P* value
30 day death, infarction, recurrent angina, TIMI major bleeding	19.8	23.3	0.016	6.5	7.0	ns
14 day death, infarction, recurrent angina, TIMI major bleeding	14.2	16.7	0.03	1.5	1.0	0.143
96 hour death, infarction, ischemia, TIMI major bleeding	9.2	9.0	ns	0.3	1.0	0.57
30 day death, infarction, recurrent angina, ischemia, TIMI major bleeding through 24 hours after tirofiban discontinued	12.7	14.2	0.16	3.0	2.2	0.13
7 day death, infarction, recurrent angina	12.3	21.1	0.015			ns
6 day and 6–45 day death, infarction,	9.3	7.6	0.42	1.1	1.0	ns
recurrent angina, major bleeding	12.3	12.3	0.96	0.5	0.4	ns
6 day and 40 day death, infarction,	5.4	10.3	<0.001	0.8	0.3	ns
recurrent angina, IV heparin, major bleeding	20.5	25.7	0.011	0.3	0.3	ns
30 day and 90 day death, infarction,	19.5	25.5	0.001			
recurrent angina, major bleeding	29.1	33.4	0.031	3.3	1.5	
9 day death, infarction, ischemia	5.7	5.8	0.007	4.1	2.2	<0.001

such as age >70, previous myocardial infarction, diabetes mellitus, and concurrent treatment for heart failure. The potential benefit of extending dalteparin use beyond acute phase was also reported by the investigators of the Fragmin and Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) study.[10] At 30 days, patients who received fixed-dose dalteparin twice a day experienced a lower rate of death and myocardial infarction than patients who received placebo injections after an acute phase treatment with dalteparin in both groups (3.1% vs. 5.9%, respectively; $P = 0.002$). At 3 months, there was a non-significant decrease in death and myocardial infarction and this continued at 6 months. Due to dissimilarity in the type of LMWH used in each trial and differences in dosing regimen, there is no conclusive agreement on the benefit of extending LMWH use beyond the acute phase treatment of UA or NSTEMI.[10]

More recently, the use of enoxaparin in the management of UA and NSTEMI have been evaluated against a factor Xa inhibitor, fondaparinux. Efficacy and safety of fondaparinux in the treatment of non-ST segment elevation ACS were evaluated in OASIS-5. This is a randomized, double-blind, double-dummy trial that compared daily subcutaneous injection of 2.5 mg fondaparinux against twice daily subcutaneous injection of 1 mg/kg of enoxaparin for up to 8 days in 20,078 patients with UA or NSTEMI. The primary outcome of death, myocardial infarction, or refractory ischemia at 9 days occurred at similar rates in the two groups (5.8% with fondaparinux and 5.7% with enoxaparin). The rate of major bleeding at 9 days was significantly lower with fondaparinux than with enoxaparin (2.2% vs. 4.1%, respectively, $P < 0.001$). When bleeding risk is considered with the primary endpoint, the composite of death, myocardial infarction, refractory ischemia, or major bleeding occurred less frequently in patients treated with fondaparinux than patients treated with enoxaparin at 9 days (7.3% vs. 9.0%, respectively, $P < 0.001$). Fondaparinux significantly reduced mortality rates at 30 days (2.9% vs. 3.5%, $P = 0.02$) and at 180 days (5.8% vs. 6.5%, $P = 0.05$). The results of this study suggested that fondaparinux is not inferior to

Table 2. Trials of LMWH in STEMI.

Study	Number of patients	LMWH group	Control group
ASSENT-3[19]	4,078	Enoxaparin 30 mg IV bolus, then 1 mg/kg SQ BID for ≤7 days	UFH 60 U/kg IV bolus (max 4000 U), followed by infusion 12 U/kg/h (max 1000 U/h) for 48 h, or with abciximab IV bolus 40 U/kg (max 3000 U), followed by infusion 7 U/kg/h (max) adjust to target aPTT 50–70 sec
ASSENT-3 PLUS[20]	1,639	Enoxaparin 30 mg IV bolus, then 1 mg/kg (max 100 mg for 1st 2 doses) SQ BID for ≤7 days	UFH 60 U/kg IV bolus (max 4000 U), then 12 U/kg/h (max 1000 U/hr) for 48 h, adjusted to aPTT 50–70 sec
ExTRACT-TIMI 25[21]	20,479	Enoxaparin 30 mg IV bolus for age <75, then 1 mg/kg for age <75 yr or 0.75 mg/kg for age ≥75 yr (max 100 mg for age <75 yr or max 75 mg for age ≥75 yr for first 2 doses) SQ BID for ≤7 days	UFH 60 U/kg IV bolus (max 4000 U), then 12 U/kg/h (max 1000 U/h) for ≥48 h, adjusted to target aPTT 50–70 sec
FRAMI[22]	776	Dalteparin 150 IU/kg SQ BID (in hosp)	Placebo
ASSENT PLUS[23]	439	Dalteparin 120 IU SQ BID for 4–7 days	UFH 4000–5000 U IV bolus, 800 or 1000 U/h for body wt < or > 67 kg to aPTT 50–75 sec
CREATE[24]	15,570	Reviparin 3436 IU <50 kg, 5153 IU for 50–75 kg, 6871 IU for >75 kg SQ BID for 7 days	Placebo

enoxaparin in reducing death, myocardial infarction or refractory ischemia and is associated with a substantially lower risk of major bleeding, therefore reducing long term mortality and morbidity.[15]

ST-Segment Elevation Myocardial Infarction

Anticoagulation plays an important role in patients with STEMI, including those who are undergoing percutaneous coronary intervention (PCI). Currently, UFH is the primary anticoagulant used in STEMI patients, although it may not be the most effective and safe choice. Many studies have been performed to compare UFH against LMWHs and resulted in data that exhibited superiority of some LMWHs over the standard UFH. Data in these trials have shown decreased rates of deaths and myocardial infarction events, but higher rates of bleeding have been seen with enoxaparin in particular.[16,17] According to the 2007 ACC/AHA guidelines, it is recommended that patients who are undergoing medical reperfusion should be treated with aspirin plus one of the following anticoagulants: Enoxaparin (Level of Evidence: A), fondaparinux (Level of Evidence: B), or UFH (Level of Evidence: C).[18] Of all the LMWHs, enoxaparin is the only one that is currently FDA-approved for used in STEMI patients.

Three major trials in particular were pivotal in evaluating the use of enoxaparin in combination with other thrombolytics that are standard treatments for reperfusion. In the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-3) study, 6,095 patients with an acute MI were randomized to receive one of the following: full-dose tenecteplase and enoxaparin (initial 30 mg IV bolus followed by 1 mg/kg SQ q12h) for 7 days, half-dose tenecteplase and weight-based UFH with abciximab infusion for 12 hours, or full-dose tenecteplase and weight-based UFH for 48 hours only. All patients received aspirin 150–325 mg daily. The primary efficacy endpoints of this study were mortality at 30 days, reinfarction, and refractory ischemia. The primary safety endpoints were major bleeding or intracranial hemorrhage. The enoxaparin and abciximab groups had lower incidences of primary efficacy endpoints than the UFH treatment group (11.4% vs. 15.4%, $P = 0.0002$; and 11.1% vs. 15.4%, $P < 0.0001$, respectively). For the primary efficacy endpoints plus safety endpoints,

Table 2 (*Continued*)

Primary efficacy outcome	Efficacy %			Major bleed %		
	LMWH	Control	*P* value	LMWH	Control	*P* value
30 day death, in-hospital reinfarction, in-hospital refractory ischemia	11.4	15.4	0.0002	3.0	2.2	ns
30 day death, in-hospital reinfarction, in-hospital refractory ischemia	14.2	17.4	0.08	4.0	2.8	0.17
30 day death, in-hospital reinfarction, in-hospital refractory ischemia	9.9	12	<0.001	2.1	1.4	<0.001
9 day Left ventricular thrombus plus arterial thromboembolism	14.2	21.9	0.03	2.9	0.3	0.006
TIMI 3 Flow	69.3	62.5	0.163	3.7	4.6	ns
7 day death, reinfarction, stroke	9.6	11.0	0.005	0.9	0.4	<0.001

the enoxaparin and abciximab groups also had lower incidences compared to UFH (13.7% vs. 17.0%, $P = 0.0037$; and 14.2% vs. 17.0%, $P = 0.01416$, respectively). There were no statistically significant differences between the groups for major bleeding.[19]

In the ASSENT-3-Plus trial, enoxaparin was specifically studied in elderly (>75 years of age) patients for the purposes of analyzing the efficacy and safety of its use in this population. This is important since an increase in age directly correlates to an increased risk of an MI. Patients enrolled in this study were randomized to receive one of the following: Tenecteplase plus UFH, tenecteplase plus enoxaparin, or half-dose tenecteplase with abciximab and low-dose UFH. Duration of therapy differed between the treatment arms, such that enoxaparin SQ was administered for a maximum of 7 days in contrast to 48 hours of IV UFH. The primary endpoints were the same as those in the original ASSENT-3 trial. The authors of this study found that enoxaparin had a 14.2% rate of primary endpoint incidence vs. 17.4% for UFH ($P = 0.080$). There was a significant increase in intracranial hemorrhagic events in patients older than 75 years of age in the enoxaparin group (2.2% vs. 0.97%, $P = 0.047$).[20]

The Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment—Thrombolysis in Myocardial Infarction (ExTRACT-TIMI 25) trial is the largest study to date to compare enoxaparin with IV infusion of UFH. The regimen for enoxaparin was 30 mg IV bolus followed by 1 mg/kg SQ injection twice daily up to 8 days while UFH was given for a maximum of 48 hours. This study enrolled 20,479 STEMI patients who previously received fibrinolysis and aspirin or alternative antiplatelet drugs. Patients who were older than 75 years old or had a creatinine clearance less than 30 ml/min had their enoxaparin dose adjusted according to the ACC/AHA guidelines. The primary efficacy endpoint of this study was all cause-mortality or non-fatal recurrent myocardial infarction at 30 days after randomization. The primary safety endpoint was major hemorrhage. The authors found that there was a 17% reduction in relative risk in the primary endpoints at 30 days in the enoxaparin group compared with UFH group ($P < 0.001$). Even at the 48-hour time point, there was already a 33% reduction in the risk of non-fatal MI with enoxaparin compared to UFH ($P = 0.002$). However, enoxaparin was linked to a statistically significant increase in bleeding

compared to UFH (2.1% vs. 1.4%, respectively, $P < 0.001$). Relative incidences of intracranial hemorrhage or minor bleeding events were not statistically significant between the two groups. Combined rates of death, MI, and major bleeding events resulted in superiority of an overall clinical benefit with enoxaparin over UFH (11.0% vs. 12.8%, $P < 0.001$).[21]

Another LMWH, dalteparin, has been evaluated in fibrinolytic-treated-STEMI patients in several studies. In the FRagmin Acute Myocardial Infarction (FRAMI) study, 776 patients with an acute MI treated with streptokinase and aspirin were enrolled to assess the efficacy of dalteparin with a dosing of 150 IU/kg body weight administered SQ every 12 hours during hospital stay. Risk reduction of thrombus formation was 0.63 with dalteparin therapy compared to placebo ($P = 0.02$). However, there were no statistically significant differences in the rates of arterial embolisms, reinfarctions, and mortality. Dalteparin treatment was directly correlated to an increased risk of hemorrhage compared to placebo (2.9% vs. 0.3%, respectively, $P = 0.006$).[22] The Assessment of the Safety and Efficacy of a New Thrombolytic agent (ASSENT)-Plus study had a cohort of 439 patients who were randomized to receive alteplase treatment along with either dalteparin (120 IU/kg SQ twice daily for 4–7 days) versus IV infusion of UFH for 48 hours. There were no differences between both treatment arms in the primary endpoint of TIMI grade 3 flow rates (69.3% vs. 62.5%, $P = 0.163$). During the treatment period, dalteparin was associated with significant lower reinfarction events compared to UFH (1.4% vs. 5.4%, $P = 0.01$). However, a "rebound effect" was seen with dalteparin after it was stopped when the study treatment period ended. This "rebound effect" led to more reinfarctions, contributing to similar rates of reinfarction at day 30 (6.5% versus 7.0%). There was no statistically significant difference in major bleeding between the two arms (3.7% vs. 4.6%). These trials may show some beneficial effects in the efficacy of dalteparin compared with UFH, but improvement in overall clinical outcome has not been demonstrated.[23]

Reviparin is another LMWH that has been studied against UFH as adjunctive therapy. In the Clinical trial of REviparin and metabolic modulation in Acute myocardial infarction Treatment Evaluation (CREATE), 15,570 patients with STEMI were randomized to receive either reviparin SQ twice daily (dosed according to weight and anti-Xa activity) or placebo for 7 days. Patients in both arms also received standard therapy. Primary endpoints included death, reinfarction, or stroke at 7 days and 30 days. Compared to the placebo group, patients in the reviparin group had significantly decreased rates of primary endpoints at 7 days (11.0% vs. 9.6%, $P = 0.005$, respectively). Differences remained at 30 days with significant decreases in mortality (13.6% reviparin vs. 11.8% placebo, $P = 0.005$) and reinfarction (2.6% reviparin vs. 2.0% placebo, $P = 0.01$), but there was no difference in rate of strokes between the two arms. There was also no difference in rates of life-threatening major bleeding.[24] As a consequence of this major trial, reviparin may be considered to be a useful adjunct in the future for patients with STEMI but more trials are necessary to support this data. Currently, reviparin is available in selected areas of Asia and Europe but has not yet been approved by the FDA in the United States.

In several trials, most notably the ExTRACT-TIMI 25 trial, the duration of therapy for anticoagulant use may play an important role in treatment management of STEMI patients. Currently, the ACC/AHA and ACCP guidelines on STEMI management recommend treatment duration of only 24–48 hours for UFH as an adjunct to thrombolytic therapy since no additional benefit was found after that duration.[18] In the ExTRACT-TIMI 25 study, treatment duration for IV UFH was at least for 48 hours while duration for enoxaparin was not extended beyond 8 days. At 48 hours, the significant benefit of enoxaparin over UFH was already seen with a 12% risk reduction in the endpoints of revascularization, death, and nonfatal MI ($P = 0.02$). However, higher incidences of major bleeding were seen in the enoxaparin group compared with the UFH group (1.4% vs. 1.0%, $P = 0.004$). In this study, treating patients beyond 48 hours with UFH was not found to have additional clinical benefit, but the opposite was true for enoxaparin. Extending treatment with enoxaparin from 2 days to up to 8 days proved to have additional clinical benefit in patients enrolled in this arm. However, a "rebound effect", similar to the one seen with dalteparin, was found after treatment ended at 8 days. Patients who were continued on enoxaparin after discharge did not have a rebound effect.[21]

Presently, for the management of STEMI, enoxaparin and revirapin are the only two LMWHs, that have demonstrated improvements in clinical efficacy as anticoagulants adjunct to fibrinolysis. However, more studies are needed to directly compare reviparin to the standard intravenous infusion of UFH therapy before one can consider it as a safe and effective alternative to UFH. Studies with dalteparin failed to demonstrate its superiority in clinical efficacy endpoints compared to UFH. Enoxaparin has been studied most extensively of the LMWHs and has shown clear clinical benefit in the treatment of patients with STEMI.

Conclusion

Clinical trials have shown that LMWH is effective in the treatment of patients presenting with ACS. The use of enoxaparin is generally preferred over other LMWHs when LMWH is indicated due to the body of evidence supporting its use. In UA or NSTEMI, the length of LMWH therapy is usually limited to the acute phase treatment. The 2007 ACC/AHA guidelines recommend the use of either enoxaparin or UFH in the conservative management of UA or NSTEMI (Level of Recommendation: Class I, Level of Evidence: A).[2] In contrast, the 2008 ACCP guidelines recommend the use of LMWH over UFH (Level of Recommendation: Grade 1, Level of Evidence: B).[25] For STEMI, enoxaparin is recommended over UFH if given for more than 48 hours.[6,19] Overall, there is strong support for using enoxaparin across the continuum of treatment for ACS patients.

Abbreviations

ACC, American College of Cardiology; ACCP, American College of Chest Physicians; ACS, Acute coronary syndrome; AHA, American Heart Association; EKG, Electrocardiogram; FDA, Food and Drug Administration; IV, Intravenous(ly); LMWH, Low molecular weight heparin; MI, Myocardial infarction; NSTEMI, Non-ST-segment elevation myocardial infarction; SQ, Subcutaneous(ly); STEMI, ST-segment elevation myocardial infarction; UA, Unstable angina; UFH, Unfractionated heparin.

Disclosure

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