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Randomized Trial of Low Molecular Weight Heparin (Enoxaparin) Versus Unfractionated Heparin for Unstable Coronary Artery Disease

One-Year Results of the ESSENCE Study

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OBJECTIVES We sought to determine whether the observed benefits of enoxaparin were maintained beyond the early phase; a one-year follow-up survey was undertaken for patients enrolled in the Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q wave Coronary Events (ESSENCE) study.

BACKGROUND We have previously reported a significant benefit of low molecular weight as compared with unfractionated heparin (UFH) in the 14- and 30-day incidence of a composite end point of death, myocardial infarction (MI) or recurrent angina in patients with unstable angina or non–Q wave MI.

METHODS The study recruited 3,171 patients with recent-onset rest angina and underlying ischemic heart disease. All patients received oral aspirin daily and were randomized to receive enoxaparin subcutaneously every 12 h or UFH (intravenous bolus followed by continuous infusion) in a double-blind, double-dummy fashion for a median of 2.6 days.

RESULTS The incidence of the composite triple end point at one year was lower among patients receiving enoxaparin as compared with those receiving UFH (32.0% vs. 35.7%, $p = 0.022$), with a trend toward a lower incidence of the secondary composite end point of death or MI (11.5% vs. 13.5%, $p = 0.082$). At one year, the need for diagnostic catheterization and coronary revascularization was lower in the enoxaparin group (55.8% vs. 59.4%, $p = 0.036$ and 35.9% vs. 41.2%, $p = 0.002$, respectively).

CONCLUSIONS In patients with unstable angina or non–Q wave MI, enoxaparin therapy significantly reduced the rates of recurrent ischemic events and invasive diagnostic and therapeutic procedures in the short term with sustained benefit at one year. (J Am Coll Cardiol 2000;36:693–8) © 2000 by the American College of Cardiology

Coronary artery atherosclerotic plaque disruption with accompanying platelet adhesion and aggregation, as well as thrombosis, plays a fundamental role in the pathogenesis of unstable angina, acute myocardial infarction (MI) and sudden death (1). A meta-analysis (2) of several randomized clinical trials described a 44% relative risk reduction of MI or death with combined aspirin and unfractionated or low molecular weight heparin (LMWH) therapy in patients with unstable angina or non–Q wave MI. However, despite the dramatic short-term effect, most studies have been limited to short-term outcomes (2) or have failed to demonstrate sustained benefit of this antithrombotic regimen (3,4).

We have previously reported a significant benefit of LMWH as compared with unfractionated heparin (UFH), along with aspirin therapy, in the 14-day incidence of death, MI or recurrent angina in patients with unstable angina or non–Q wave MI (5). The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q wave Coronary Events (ESSENCE) trial demonstrated continued benefit of LMWH therapy administered for a median duration of 2.6 days in the primary composite end point at 30 days, with a trend toward lower death or MI rates and a significant reduction in the need for coronary revascularization.

To determine whether the observed benefits of enoxaparin plus aspirin, as compared with UFH plus aspirin, in patients with unstable angina or non–Q wave MI were maintained beyond the early (14 to 30 days) phase, a one-year follow-up survey was undertaken for all patients enrolled in the ESSENCE study.

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Abbreviations and Acronyms

CI	=	confidence interval
CK	=	creatine kinase
ECG	=	electrocardiographic
ESSENCE	=	Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q wave Coronary Events
LMWH	=	low molecular weight heparin
MI	=	myocardial infarction
OR	=	odds ratio
PCI	=	percutaneous coronary intervention
UFH	=	unfractionated heparin

METHODS

Patient group. The entry criteria for enrollment, study design and treatment protocol, as well as end point definitions, of the ESSENCE study have been described in detail (5). Briefly, 3,171 patients were enrolled at 176 centers in Canada, the United States, Europe and South America. Patients had recent-onset rest angina occurring within 24 h before randomization and were required to have evidence of underlying ischemic heart disease, as manifested by one of three criteria: 1) new ST segment depression of at least 0.1 mV, transient ST segment elevation or T wave changes in at least two contiguous leads; 2) documented previous MI or coronary revascularization procedure; or 3) results of noninvasive or invasive testing demonstrating ischemic heart disease. Written, informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of each participating hospital.

Study design and treatment protocol: primary analysis. Patients were randomized to receive (double-blind, double-dummy) either 1 mg/kg body weight of enoxaparin (Rhone-Poulenc Rorer Corp., Collegeville, Pennsylvania; 100 anti-factor Xa U/kg) subcutaneously every 12 h and an intravenous placebo bolus and infusion, or subcutaneous placebo injections and an intravenous bolus of UFH (usually 5,000 U), followed by a continuous infusion at a dose adjusted according to the activated partial thromboplastin time. Trial therapy was administered for a minimum of 48 h and up to a maximum of eight days. All patients received 100 to 325 mg/day of oral aspirin. All other medications, the decision to proceed with cardiac catheterization and the use of coronary revascularization were left to the discretion of the investigator.

The primary outcome of the trial was the composite triple end point of death, nonfatal MI (or reinfarction) or recurrent angina at 14 days.

Study methods and end point definitions: one-year follow-up. One-year follow-up was obtained in a retrospective manner, with each site responsible for telephone contact of all randomized patients (or their physicians), case report form completion and appropriate supporting documentation concerning end points and procedures performed. In the United States, a death registry was also employed in cases where patients were lost to follow-up. All information was verified independently by an end points committee whose members had reviewed all end points during the initial 30-day study period and who were unaware of treatment assignments.

For the one-year follow-up, the same composite triple end point of death, MI or recurrent angina was used, and the time to first composite triple end point was the primary outcome. Secondary aims were to assess the time to the first composite double end point of death or MI, cardiac catheterization or coronary revascularization and to assess the incidence of rehospitalization.

The confirmation of end points during the one-year follow-up was based on the following definitions. *Death* was defined as any death, regardless of cause. Cardiac arrest from which the patient was resuscitated was also classified as death. *De novo MI* was defined as 1) a total creatine kinase (CK) concentration of more than twice the upper limit of normal and an above-normal concentration of CK, MB fraction (CK-MB) (at least 3% of total CK); or 2) in the absence of CK or CK-MB measurements, new Q waves >0.04 s in at least two leads. *Perioperative MI* was defined as an elevation of total CK to five times the upper limit of normal or new Q waves >0.04 s in at least two leads. A diagnosis of MI after a percutaneous coronary intervention (PCI) was made if the total CK concentration increased to three times the upper limit of normal and at least 50% above the previous nadir value. *Recurrent angina* during the 30-day to one-year follow-up was defined as recurrent chest pain leading to revascularization or rehospitalization.

Statistical analysis. The analyses were done according to the intention-to-treat principle. Statistical comparisons between treatment groups were made using the time to event with the Kaplan-Meier survival technique (two-sided, log-rank test, alpha = 0.05). In measuring the time to an event for cases in which a patient had multiple end points, the first event was taken into account. All patients without events and lost to follow-up were censored at the time of study termination or last contact. In some cases where it was only possible to establish whether a patient was alive or dead, the confirmation date determined the length of follow-up for mortality. However, if an earlier date was known at which full information (and not simply mortality) was available, that date determined the length of follow-up in the analysis of all events. Subgroup analyses were performed using univariate Cox regression models, and treatment effects were estimated by a hazard ratio with the 95% confidence interval (CI).

RESULTS

Short-term outcome. Figure 1 shows the flow of patients through the trial. As reported previously (5), the incidence of the composite triple end point (death, MI or recurrent angina) at 14 days (primary end point) and 30 days was significantly lower among the patients assigned to enoxapa-

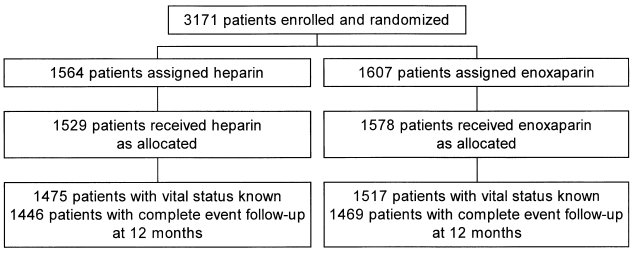

Figure 1. Trial profile.

rin than among those assigned to UFH (16.6% vs. 19.8%, p = 0.019, odds ratio (OR) 0.80, 95% CI 0.67 to 0.96; and 19.8% vs. 23.3%, p = 0.016, OR 0.81, 95% CI 0.68 to 0.96, respectively). The secondary composite end point of death or MI was reached at 30 days in 6.2% of the enoxaparin group as compared with 7.7% of the UFH group (p = 0.081, OR 0.79, 95% CI 0.59 to 1.03).

One-year outcome. Of the 3,171 patients enrolled, 87 (2.7%) died within the initial 30-day follow-up period. Only 16 patients (0.5%) had no follow-up information beyond 30 days. Complete one-year follow-up event information was available in 2,915 patients (91.9%) (91.4% in the enoxaparin group and 92.5% in the UFH group), and complete one-year vital status was available in 2,992 patients (94.4%) (94.4% in the enoxaparin group and 94.3% in the UFH group); thus, some degree of follow-up data beyond 30 days were available in 99.5% of patients.

Selected baseline characteristics and final diagnoses of the overall patient cohort are shown in Table 1, according to whether one-year follow-up information was available. As compared with patients with one-year follow-up, those with less than one-year follow-up had several lower risk characteristics, including younger age and more frequent presentation with no electrocardiographic (ECG) changes, and were more likely to have a final diagnosis (as determined by the local site investigator) of the qualifying chest pain of noncardiac origin (14.5% vs. 5.5%, p < 0.0001). There was no significant difference in any baseline variable between the two treatment groups among patients with one-year follow-up.

The incidence of the composite triple end point at one year was significantly lower in the enoxaparin group as compared with the UFH group (intention-to-treat analysis: 32.0% vs. 35.7%, p = 0.022, hazard ratio 0.87, 95% CI 0.77 to 0.98). Figure 2 shows the Kaplan-Meier estimates of the time to the first triple end point (death, MI or recurrent angina) and double end point (death or MI) in the 12 months after randomization.

Among the patients who received at least one dose of study medication, enoxaparin was also more effective than UFH (efficacy analysis: 32.0% vs. 35.9%, p = 0.018). Consistent with the 30-day finding (5), enoxaparin was significantly more effective than UFH in reducing the primary composite triple end point among several high risk subgroups, including those with previous aspirin use and those with any ECG changes at baseline or ST segment depression at baseline.

The trend toward a lower incidence of the secondary

Table 1. Baseline Characteristics and Final Diagnosis According to Whether Complete One-Year Follow-Up Information was Available

Characteristic	<1-Year Follow-Up	1-Year Follow-Up	p Value
Patients randomized (n)	256	2,915	
Patients treated (n)	240 (94%)	2,867 (98%)	
Median age (years [range])	58 (27–88)	65 (25–94)	0.0001
Median weight (kg [range])	80 (41–152)	78 (33–182)	0.044
Female	28%	34%	0.045
Risk factors			
Current smoker	36%	23%	< 0.0001
Hypertension	59%	54%	0.12
Hypercholesterolemia	40%	45%	0.15
Diabetes mellitus	23%	22%	0.81
Previous cardiac history			
Positive cardiac catheterization	45%	43%	0.001
MI	49%	46%	0.58
Coronary artery bypass graft surgery	22%	19%	0.52
Coronary angioplasty	25%	21%	0.013
Electrocardiographic changes	48%	57%	0.005
ST segment elevation	7%	7%	0.74
ST segment depression	15%	24%	0.001
T wave inversion	36%	39%	0.30
Final diagnosis			
Unstable angina	68%	69%	0.58
Non–Q wave MI	15%	21%	0.013
Evolving Q wave MI	3%	4%	0.52
Noncardiac chest pain	14%	6%	< 0.001

MI = myocardial infarction.

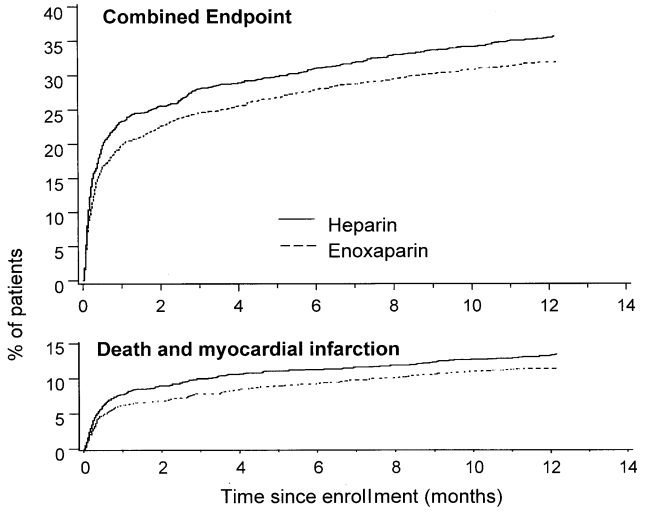

Figure 2. Kaplan-Meier plots of the time to a first event over a period of one year for the composite triple end point of death, MI or recurrent angina and for the composite double end point of death or MI.

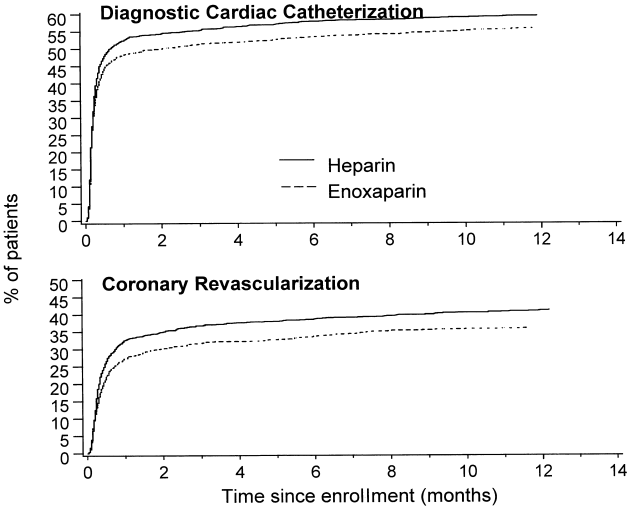

Figure 3. Kaplan-Meier plots of the time to a first diagnostic cardiac catheterization and the time to a first coronary revascularization over a period of one year.

composite end point of death or MI seen at 30 days in the enoxaparin group as compared with the UFH group remained at one year (11.5% vs. 13.5%, p = 0.082, hazard ratio 0.84, 95% CI 0.69 to 1.02).

Cardiac catheterization and revascularization. Thirty days after randomization, the need for diagnostic cardiac catheterization and coronary revascularization was significantly less among the patients assigned to enoxaparin than among those assigned to UFH (47.9% vs. 51.9%, p = 0.024 and 27.0% vs. 32.2%, p = 0.001, respectively).

At one-year follow-up, the requirement for diagnostic catheterization and coronary revascularization remained significantly less in the enoxaparin group as compared with the UFH group (55.8% vs. 59.4%, p = 0.036, hazard ratio 0.91, 95% CI 0.83 to 0.99 and 35.9% vs. 41.2%, p = 0.002, hazard ratio 0.84, 95% CI 0.75 to 0.94, respectively) (Fig. 3). In particular, patients assigned to enoxaparin as compared with UFH required PCI less frequently (18.5% vs. 22.8%, p = 0.004, hazard ratio 0.79, 95% CI 0.68 to 0.93).

Hospital admission. Among the 3,051 patients (96.2%) with complete medical resource data during the first 30 days, initial intensive care unit and total length of stay were similar among those patients assigned to enoxaparin and to UFH (mean [±SD] duration 2.8 ± 3.4 vs. 3.0 ± 3.8 days, p = 0.26; and 8.2 ± 6.4 vs. 8.5 ± 6.7 days, p = 0.28, respectively). From 31 days to one year, rehospitalization for any cause occurred in 27.9% of patients receiving enoxaparin and 28.3% of patients receiving UFN (mean [±SD] duration of intensive care unit and total length of hospital stay: 1.0 ± 4.8 vs. 1.3 ± 5.4 days, p = 0.24; and 4.7 ± 13.9 vs. 4.8 ± 12.8 days, p = 0.49, respectively).

DISCUSSION

Advantages of LMWH therapy. Although oral aspirin and intravenous UFH represent the current standard of care for patients admitted to the hospital with unstable angina or non–Q wave MI, this antithrombotic approach has a substantial failure rate: recurrent ischemic chest pain, MI or death occurs in 15% to 30%, and 15% to 25% of patients undergo coronary revascularization within 12 weeks of treatment initiation (2). This failure rate is likely due, in part, to the marked variability in dose response and dose-dependent clearance of UFH (6). In contrast, the reduced binding of LMWH to plasma proteins, endothelial cells and macrophages is associated with high bioavailability after subcutaneous injection, a longer plasma half-life, dose-independent clearance and a more predictable anticoagulant response. Further advantages of LMWH include greater resistance to inhibition by activated platelets, less platelet activation, reduced release of von Willebrand factor, minimal effect on microvascular permeability, a lower incidence of heparin-induced thrombocytopenia and no need for monitoring of activated partial thromboplastin time (6). Low molecular weight heparins also have a higher anti-factor Xa/IIa ratio and more tissue factor pathway inhibition, leading to greater inhibition of thrombin generation and activity (6).

Previous trials with LMWH. A significant advantage of combination LMWH and aspirin versus aspirin alone was demonstrated during the first six days of treatment in 1,506 patients in the FRagmin during InStability in Coronary artery disease (FRISC) study (3). This benefit was maintained during the following 35 to 40 days of ongoing once daily subcutaneous dalteparin therapy; however, by four to five months after the end of dalteparin treatment, the initial reduction in death, MI and need for coronary revascularization was no longer significant. Furthermore, on termination of treatment after six weeks, there was a trend toward an increased frequency of ischemic events in the dalteparin group in comparison with the placebo group, despite the concurrent use of aspirin.

The superiority of LMWH as compared with UFH was

first demonstrated by Gurfinkel et al. (7) in 219 patients with unstable angina. In a randomized, open-label trial, nadroparin plus aspirin was more effective than either UFH plus aspirin or aspirin alone in the reduction of in-hospital cardiac outcomes (7); no long-term data were collected in this pilot study. However, the FRAXiparine in Ischaemic Syndrome (FRAXIS) study of 3,468 patients with unstable angina or non–Q wave MI failed to demonstrate an advantage of subcutaneous nadroparin (administered for 6 ± 2 days or 14 days, respectively) over intravenous UFH (6 ± 2 days) during the short- (six or 14 days) or intermediate-term (three months) follow-up period (8).

Another direct comparison of UFH and LWMH therapy in 1,482 patients showed no difference in efficacy in the hospital phase of the FRagmin In unstable Coronary artery disease study (FRIC) (4). Furthermore, there was no benefit of continued use of once daily dalteparin as compared with aspirin alone up to 45 days after treatment initiation.

Results of ESSENCE. In contrast, the ESSENCE study demonstrated both early (14 and 30 days) and sustained benefit (one year) with a twice daily subcutaneous injection of enoxaparin as compared with continuous UFH infusion. ESSENCE is the first large-scale trial showing one-year benefit of antithrombotic therapy administered for a relatively brief duration of 2.6 days to patients with nonpersistent ST segment elevation acute coronary syndromes. Although the clinical benefit with enoxaparin was established early (relative risk reduction of 16% at 48 h and maintained at 14 and 30 days), the similar benefit of enoxaparin on the rates of recurrent angina, MI, death, cardiac catheterization and coronary revascularization, as well as rehospitalization from 31 days to one year, indicates no clinical evidence of greater late reactivation of disease after enoxaparin as compared with standard heparin therapy.

There was a 1.5% absolute reduction in 30-day and 2% absolute reduction in one-year death or MI rates with enoxaparin as compared with UFH in the ESSENCE study. This is similar to the absolute benefit seen over 30 days (1.6%) and six months (2%) in a meta-analysis of patients with unstable angina or non–Q wave MI from all of the randomized trials of intravenous platelet glycoprotein IIb/IIIa receptor antagonists as compared with, or in addition to, UFH (9). However, additional information regarding the magnitude of the benefit seen with enoxaparin is required, because the number of patients in the ESSENCE study is modest (n = 3,171) in comparison to the four IIb/IIIa receptor antagonist trials combined (n = 18,031).

Results of ESSENCE and TIMI 11B. The Thrombolysis In Myocardial Infarction (TIMI)-11B study (10) was a randomized, double-blind, placebo-controlled trial comparing the strategy of combined short-term (≥72 h) and intermediate-term (43 days) administration of enoxaparin versus UFH for patients with unstable angina or non–Q wave MI during the early phase. The results of this 3,910-patient trial confirm the benefit seen with enoxaparin over heparin in the ESSENCE trial, at 14 and 43 days, respectively. Furthermore, a meta-analysis of both trials (n = 7,081) demonstrates a significant reduction in the triple end point of death, MI or recurrent ischemia requiring urgent revascularization, as well as the double end point of death or MI up to 43 days (11); longer term (one year) follow-up in TIMI-11B is also consistent with the ESSENCE results (12).

Comparisons with other LMWHs. A number of reasons could account for the apparent inconsistency of efficacy findings between the trials evaluating dalteparin (FRIC) and nadroparin (FRAXIS) and the studies (ESSENCE and TIMI-11B) that have demonstrated an advantage over UFH. First, the LMWHs vary in their average molecular weight, patterns of distribution of glycosaminoglycan chains, anti-factor Xa/IIa ratio and release profile of tissue factor pathway inhibitor. Second, the anti-thrombotic doses of both the LMWHs and UFH were different in each of the clinical trials. Third, there were differences in trial design, including the time from the qualifying episode of chest discomfort to study enrollment, patient risk profile (e.g., proportion of patients with ECG changes, non–Q wave MI) and end point definitions (e.g., recurrent angina, MI). Thus, in addition to the play of chance, a number of factors could have played a role in demonstrating a significant and sustained advantage of enoxaparin (ESSENCE and TIMI-11B), whereas others failed to show a benefit of LMWH over UFH (FRIC and FRAXIS).

Future treatment. Particularly in view of the cost-effectiveness of enoxaparin (13,14), it is likely that optimal short-term treatment of high risk patients with acute ischemic coronary syndromes without persistent ST segment elevation in the near future will include a combination of oral aspirin, subcutaneous LMWH and intravenous glycoprotein IIb/IIIa receptor antagonists.

Despite the modest benefit of enoxaparin in the ESSENCE study, it is sobering to note that the event rates in patients who present without persistent ST segment elevation acute coronary syndromes remain high at both 30 days (20%) and one year (32%). Indeed, death or (re)infarction occur in 6 of 100 patients by 30 days, despite aspirin, short-term enoxaparin therapy and a coronary revascularization rate of 27%. An additional six deaths or MIs (per 100 patients) occur despite on-going aspirin therapy, and the revascularization rate is 9% from 31 days to one year. The high risk of recurrent ischemic events likely relates to the fact that the underlying lesion in the coronary artery remains active, with accompanying thrombin generation for many weeks after the initial plaque rupture, leading to the initial episode (15,16). Despite its modest antiplatelet activity, aspirin has only an indirect effect on thrombin generation or activity, and further clinical event prevention may require continued antithrombotic therapy after the initial phase of treatment. In addition, there is evidence from the FRISC II study to suggest that a more aggressive approach (early cardiac catheterization plus revascularization, when appropriate) to moderate to high risk patients

with unstable angina or non–Q wave MI leads to a lower incidence of six-month death and (re)infarction (17).

Role of enoxaparin in unstable angina or non–Q wave MI. Treatment with enoxaparin in addition to aspirin should be considered for at least 48 to 72 h in patients with unstable angina or non–Q wave MI to reduce the short- and long-term risk of recurrent angina, myocardial (re)infarction or death. This antithrombotic strategy will also lead to a lower requirement for diagnostic catheterization (approximately four less per 100 patients) and coronary revascularization (approximately one less coronary artery bypass graft surgeries and four less percutaneous procedures per 100 patients) by one year. The simple mode of administration without the need for anticoagulation monitoring, lower requirement for invasive diagnostic and therapeutic procedures, cost savings and superior short-term and sustained long-term efficacy make enoxaparin an attractive option in the treatment of patients with acute ischemic coronary syndromes presenting without persistent ST segment elevation.

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