Low Molecular Weight Heparin Decreases Rebound Ischemia in Unstable Angina or Non-Q-Wave Myocardial Infarction: The Canadian ESSENCE ST Segment Monitoring Substudy

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OBJECTIVES

The goal of this study was to determine whether enoxaparin was more effective than heparin in reducing recurrent ischemic episodes.

BACKGROUND

Continuous ST segment monitoring is a simple tool for assessment of ischemia and identifies patients with a worse prognosis. Little is known about the impact of low molecular weight heparin on ST segment shift.

METHODS

Patients were randomized to receive enoxaparin or heparin (mean 3.4 days). Three-lead ST segment monitoring was performed for the first 48 h (n = 220) and an additional 48 h (n = 174) after intravenous study drug discontinuation (mean 1.9 days later).

RESULTS

During initial monitoring, ischemia rates were similar among the heparin and enoxaparin groups (27.2% vs. 22.6%, p = 0.44); however, the time to first ischemic episode was earlier among heparin-treated patients (11 ± 11 vs. 25 ± 18 min, p = 0.001). After drug discontinuation, ischemic episodes occurred more frequently (44.6% vs. 25.6%, p = 0.009), and the total ischemic duration was greater among heparin patients (18 ± 39 vs. 5 ± 12 min/24 h, p = 0.005). Recurrent ischemia occurred more frequently after discontinuation in the heparin (46% vs. 31%, p = 0.043), but not the enoxaparin, group (18.4% vs. 25%, p = 0.33). Regardless of treatment, patients with ischemia were more likely to die or experience (re)infarction at one year (18.4% vs. 8.3%, p = 0.023).

CONCLUSIONS

ST segment shift occurs frequently in unstable angina/non-Q-wave myocardial infarction despite antithrombotic therapy and is associated with worse one-year prognosis. Enoxaparin is a more effective antithrombotic treatment than unfractionated heparin and leads to greater prevention of rebound ischemia. (J Am Coll Cardiol 2000;36:1507–13) © 2000 by the American College of Cardiology

Continuous ST segment monitoring is an effective and simple tool for assessment of ongoing or recurrent ischemia. Patients with unstable angina or non-Q-wave myocardial infarction (MI) who experience episodic ST segment shifts—mostly silent—have worse short- (1–10) and long-term (7,11,12) prognosis. Further, the prognostic value of ST segment shifts during continuous monitoring has been demonstrated in addition to other important variables, such as left ventricular function or angiographic extent of coronary artery disease (4,13).

Cycles of thrombosis and thrombolysis appear to mediate ischemic ST segment shifts in patients with acute coronary syndromes (14). However, despite anti-platelet and antithrombotic treatment, transient myocardial ischemia as detected by continuous electrocardiographic (ECG) monitoring occurs in 15% to 40% of patients with unstable angina or non-Q-wave MI (9,10,15).

We have previously reported a significant benefit of enoxaparin (a low molecular weight heparin [LMWH]) compared with unfractionated heparin (UFH) on the background of aspirin therapy in the 14-day incidence of death, MI or patients with recurrent angina with unstable angina or non-Q-wave MI (16). The purpose of this study was to determine whether enoxaparin was more effective in reducing recurrent ischemic episodes in patients with unstable angina or non-Q-wave MI. Specifically, the following three hypotheses were prospectively identified: 1) treatment with enoxaparin as compared with UFH will result in a significant reduction in the incidence of recurrent ischemia during the first 48 h; 2) patients treated with enoxaparin as compared with UFH will have fewer ischemic episodes during the 48 h after study drug discontinuation; and 3) regardless of study drug treatment, patients with, as compared with those without, ST segment shift during the first 48 h or during the 48 h after treatment discontinuation will have a higher death or nonfatal (re)infarction rate.
METHODS

Patient population and treatment. The entry criteria for enrollment, study design and treatment protocol and end point definitions in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study have been described in detail (16). Briefly, 3,171 patients with rest angina occurring within 24 h and evidence of underlying ischemic heart disease (manifested by new ECG changes or previously documented coronary disease) were randomized to receive (double-blind, double-dummy) enoxaparin (Rhone-Poulenc Rorer, Collegeville, Pennsylvania) or UFH for a minimum of 48 h. All patients received 100 to 325 mg of oral aspirin daily. All other medications, the decision to proceed with cardiac catheterization and the use of coronary revascularization were left to the discretion of the investigator.

Patients participating in the main study from 20 Canadian sites were also approached to participate in the ST segment monitoring substudy from September 15, 1995 to the end of the main trial in May 1996 (Fig. 1). Written, informed consent was obtained from all patients, and the study was approved by the institutional review board of each participating hospital.

ST segment monitoring. Three-channel (leads aVF, V2, V5) ST segment monitoring (Marquette Electronics, Milwaukee, Wisconsin) was performed on patients for the first 48 h after randomization and for an additional 48 h after intravenous study drug discontinuation. Analysis was performed initially by using an automated algorithm with all potential episodes of transient ST segment shift printed on paper. Data were subsequently reviewed by three cardiologists who were blinded to the clinical data and treatment assignment. The ST segment was measured 80 ms after the J point. Significant ST segment shift was defined as horizontal or downsloping ST depression $\geq 0.1$ mV below the baseline or upward ST elevation $\geq 0.1$ mV above the baseline lasting $\geq 1$ min in duration and separated from other episodes of ST segment shift by $\geq 1$ min. Patients with ST segment changes at baseline attributed to left ventricular hypertrophy with repolarization changes, bundle branch block and digoxin were excluded. In those patients with ST segment depression at baseline of 0.1 mV, a further depression of 0.15 mV (0.25 mV absolute) was required; similarly, baseline depression of 0.15 mV and 0.2 mV required further depression of 0.2 mV (0.35 absolute) and 0.3 mV (0.50 absolute), respectively, for qualification of an ischemic episode. Patients with $>0.25$ mV baseline ST depression were excluded. A similar approach was adopted for ST segment elevation episodes.

Clinical follow-up. The primary clinical outcome was the composite double end point of death or nonfatal myocardial (re)infarction at one year. One-year follow-up was obtained in a retrospective manner and was verified independently by an end point committee consisting of three cardiologists unaware of treatment assignment. Death was defined as any death, regardless of cause. Myocardial infarction, including periprocedural, was defined as previously reported (16).

Statistical analysis. Descriptive statistics (percentages for discrete variables, means with standard deviation or medians with 25th and 75th percentiles for continuous variables) were calculated for baseline characteristics, ECG and clinical outcomes. Comparison of baseline characteristics and clinical outcomes between patient groups was carried out using likelihood-ratio chi-square or Fisher exact test for differences in proportions of categorical variables and Wilcoxon rank-sum tests for differences in median values of continuous variables. Kaplan-Meier estimates were used to obtain event-free rates at one year, and a curve comparison was made using the log-rank test. Backward elimination logistic regression was utilized for prediction of one-year death or myocardial (re)infarction. Variables considered in the backward selection were: age, gender, body mass index, diabetes, diastolic blood pressure, smoking status (current and former), previous stroke, ST segment deviation on the baseline ECG, index MI and study drug treatment (enoxaparin or UFH).

The number and total duration of ischemic episodes were normalized by the duration of continuous ECG monitoring, and comparisons between treatments at the initial (first 48 h) and follow-up (48 h after study drug discontinuation)
monitoring periods were made using the Wilcoxon non-parametric sign test.

RESULTS

Patient participation. Figure 1 shows the flow of patients through the ST segment monitoring substudy. Two hundred and eighty-eight of 439 patients (66% of all potentially eligible patients) from 20 Canadian sites participating in the substudy were enrolled. Fifty-five patients (30 in the UFH and 25 in the enoxaparin group) were excluded due to confounding ECG factors or due to significant artifact on the ECG recording. Two hundred and sixty-three patients had ECG recordings (mean 1.9 h/patient), with a similar time interval between the two ECG monitoring periods (87 heparin, 76 enoxaparin) underwent follow-up 48-h monitoring beginning at the time of study drug discontinuation. One hundred and sixty-three patients (87 heparin, 76 enoxaparin) underwent initial 48-h monitoring at the time of study drug initiation, and 174 patients (92 heparin, 82 enoxaparin) underwent follow-up 48-h monitoring beginning at the time of study drug discontinuation. One hundred and sixty-three patients had ECG recordings during both monitoring periods (87 heparin, 76 enoxaparin), with a similar time interval between the two ECG recordings (mean 1.9 ± 1.8 and 1.9 ± 3.7 days) in both treatment groups. Study drug treatment duration was 3.3 ± 1.7 and 3.5 ± 1.8 days in the heparin and enoxaparin groups, respectively.

ST segment monitoring. During 18,721 h of monitoring (64 ± 24 h/patient), 87 patients (37.1%) had at least one episode of transient ischemia. Transient ischemic episodes with ST segment elevation occurred in 21 patients (9.1%). The rates of ischemia according to baseline ECG ST segment depression are presented in Table 1.

There were no significant baseline differences between the two treatment groups (Table 2). The use of beta-adrenergic blocking agents (77% vs. 72%, p = 0.3), calcium blockers (54% vs. 63%, p = 0.2) and nitrates (85% vs. 81%, p = 0.5) was comparable between the UFH and enoxaparin groups. The mean number, ST segment magnitude, duration and cumulative duration of ischemic episodes was 6.8 ± 8.0 and 3.3 ± 3.3 episodes, −0.17 ± 0.9 and −1.6 ± 0.6 mV, 14.3 ± 18.2 and 10.4 ± 1.32 min and 98.2 ± 143.6 and 34.8 ± 56.7 min in the UFH and enoxaparin groups, respectively. The heart rate preceding and at the onset of ST segment depression was 70 ± 24 and 77 ± 25 beats/min and 67 ± 17 and 74 ± 16 beats/min in the UFH and enoxaparin groups, respectively; 63% of UFH and 77% of enoxaparin-treated patients experienced a less than 10% increase in heart rate at the onset of ischemia.

The mean duration from the onset of the index episode of chest discomfort to initiation of ST segment monitoring and from study randomization to initiation of ST segment monitoring was similar among the two treatment groups (heparin 9.1 ± 8.5 h and enoxaparin 10.0 ± 9.8 h; and heparin 1.9 ± 4.1 h and enoxaparin 2.7 ± 7.1 h, respectively).

Initial 48-h ECG monitoring. Among those undergoing initial 48-h ST segment monitoring (n = 220, mean ± standard deviation 37 ± 15 h/patient), 31 of 114 (27.2%) heparin-treated patients and 24 of 106 (22.6%) enoxaparin-treated patients experienced at least one ischemic episode (p = 0.44). However, there was a shorter time to the first episode of ischemia after study drug initiation among heparin- as compared with enoxaparin-treated patients (11.3 ± 10.5 vs. 25.4 ± 18.3 min, p = 0.001). After adjustment for the overall duration of monitoring, the mean

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*Continuous variables are expressed as median (25th percentile, 75th percentile).
number of episodes and the adjusted total duration of episodes per 24 h was similar among heparin- and enoxaparin-treated patients (0.8 ± 2.0 vs. 0.3 ± 0.9 episodes/24 h, p = 0.41 and 12.0 ± 34.8 vs. 5.1 ± 17.0 min of ischemia/24 h, p = 0.35, respectively).

**Study drug discontinuation 48 h ECG monitoring.** During follow-up 48-h ST segment monitoring (n = 174, 27 ± 19 h/patient), 41 of 92 (44.6%) patients receiving heparin and 21 of 82 (25.6%) patients treated with enoxaparin experienced at least one ischemic episode (p = 0.009). The time to first ischemic episode after study drug discontinuation was shorter in the heparin group (13.9 ± 23.3 vs. 23.8 ± 21.1 min, p = 0.03). The mean number of episodes and episode duration was greater among patients treated with heparin (1.5 ± 3.0 vs. 0.4 ± 0.9 episodes/24 h, p = 0.005 and 18.0 ± 39.2 vs. 4.6 ± 12.4 min of ischemia/24 h, p = 0.005, respectively).

**Paired initial and study drug discontinuation 48-h ECG monitoring.** Among the 163 patients who underwent both initial and study drug discontinuation monitoring, ischemia was detected more frequently after the time of study drug discontinuation (41 [25.2%] initial vs. 59 [36.2%] follow-up). Ischemia was more frequently observed during both monitoring periods among the heparin as compared with the enoxaparin group (28 [32.2%] vs. 14 [18.4%], p = 0.045 and 40 [46.0%] vs. 19 [25.0%], p = 0.005, respectively). There was a shorter time to the first ischemic episode after study drug initiation among heparin-treated patients (12.3 ± 10.6 vs. 27.8 ± 17.8 min, p = 0.004). After study drug discontinuation there were a significantly greater number of heparin-treated patients with ischemia when compared with the initial monitoring period (46.0% vs. 31.0%, p = 0.043); in contrast, no increase was seen among the enoxaparin group (18.4% vs. 25.0%, p = 0.33). After adjusting for the duration of monitoring, there were a greater number of episodes and a trend towards greater episode duration compared with the initial monitoring period among heparin (1.6 ± 3.0 vs. 0.9 ± 2.1 episodes/24 h, p = 0.04 and 19.0 ± 40.1 vs. 14.5 ± 38.4 min, p = 0.06), but not enoxaparin, treated patients (0.4 ± 1.0 vs. 0.2 ± 0.6 episodes/24 h, p = 0.23 and 4.7 ± 12.8 vs. 3.7 ± 12.4 min of ischemia/24 h, p = 0.3).

**One-year death or MI.** Death or nonfatal (re)infarction occurred in 28 of 221 patients (12.7%); this one-year event rate was similar to that observed in the overall ESSENCE trial (12.1% in 3,171 patients). Regardless of study drug treatment, there was a trend towards higher rates of death or nonfatal MI (10 of 54 patients [18.5%] vs. 16 of 166 patients [9.6%, p = 0.079) or death alone (13.0% vs. 4.8%, p = 0.058) among patients with, as compared with those without, ST segment shift during initial monitoring. Patients with ischemia identified after study drug discontinuation were at higher risk for one-year death or infarction (13 of 62 patients [21.0%] vs. 11 of 112 patients [9.8%, p = 0.041) but not for mortality alone (8.1% vs. 6.3%, p = 0.8). ST segment shift occurring during either 48-h period of continuous ECG monitoring was associated with a higher one-year death or infarction rate (16 of 87 patients [18.4%] vs. 12 of 144 patients [8.3%, p = 0.023; Fig. 2).

One-year rates of diagnostic cardiac catheterization and coronary revascularization were similar among the heparin and enoxaparin groups (40.5% vs. 40.0%, p = 0.91 and 28.4% vs. 23.7%, p = 0.52, respectively). After adjustment for differences in baseline characteristics and other prognostic determinants of outcome in a multivariable model, the presence of ST segment shift during continuous monitoring was an important predictor of one-year mortality or (re)infarction (double end point). In addition to older age (odds ratio [OR] 2.1, 95% confidence intervals [CI] 1.3, 3.2) and history of diabetes mellitus (OR 3.3, 95% CI 1.3, 8.0), the following interactions were independent predictors of outcome: ST shift on baseline 12-lead ECG to ST shift on continuous monitoring (OR 4.5, 95% CI 1.7, 11.8) and study drug treatment to ST shift on continuous monitoring (OR 4.7, 95% CI 1.1, 20.4). This suggests that the predictive value of ST shift on the double end point is different depending upon whether the patient: 1) had ST shift on the prerandomization 12-lead ECG, or 2) received enoxaparin or UFH. As seen in Figure 3, the event rate is highest in the group that received heparin and had ST shift on continuous monitoring (25%, p = 0.0114). In contrast,
In this study all patients received a heparin preparation in addition to ASA, beta- or calcium-channel blockade and nitrates. Thus, even in an era of combination antiplatelet and short-term anticoagulant therapy, transient myocardial ischemia as detected by continuous ECG monitoring is associated with worse long-term prognosis.

In a randomized, single-blind comparison involving 219 patients, Gurfinkel et al. (15) showed a trend towards lower rates of silent ischemia ($\geq 2$ mm of ST segment shift) during 48 h of continuous ECG monitoring with LMWH (nadroparin) plus aspirin compared with aspirin alone (25% vs. 38%, $p = 0.1$); nadroparin was found to be superior to UFH plus aspirin in the reduction of silent ischemic episodes (25% vs. 41%, $p = 0.04$).

In this analysis, the rates of ST segment shift were not significantly different in the two treatment groups (5% absolute difference in favor of enoxaparin). However, with approximately 110 patients in each group, the power to detect a moderate (for example, 10% absolute, 30% relative) reduction was less than 30%. Nonetheless, the time to first ischemic episode was longer and the frequency and duration of episodes was lower among enoxaparin– as compared with heparin–treated patients, suggesting some additional degree of anti-ischemic benefit with enoxaparin. This benefit was evident clinically in the overall ESSENCE population where a 16% relative risk reduction in the composite end point of recurrent angina, MI or death was seen with enoxaparin by 48 h (16).

**Rebound ischemia.** To our knowledge, this is the first study to examine the impact of heparin withdrawal on ischemic episodes detected by continuous ST segment monitoring among the unstable angina/non-Q-wave MI population in the treatment setting of concomitant use of ASA. Theroux et al. (18) demonstrated early reactivation of unstable angina and MI occurring within the first 96 h (clustered around 10 h) after UFH discontinuation in those patients not receiving simultaneous aspirin therapy. In our analysis even in the presence of ASA, rebound ischemia occurred more frequently among patients withdrawn from heparin as compared with enoxaparin. In addition, the time to rebound ischemia was longer and the frequency and duration of ischemic episodes was less among patients withdrawn from enoxaparin therapy. This finding is consistent with the known pharmacokinetic advantages of LMWHs over UFH (19). The superiority of enoxaparin may be explained by: 1) the higher antifactor Xa to antifactor IIa ratio (3:1 vs. 1:1 with UFH), with relatively greater inhibition of thrombin generation while maintaining similar activity against thrombin inhibition, 2) stimulation of more tissue factor pathway inhibitor release, leading to greater inhibition of thrombin generation and activity, 3) less platelet activation and greater resistance to inhibition by activated platelets, and 4) reduced release of von Willebrand factor (19–21). The mean heart rate at the onset of ischemia was not substantially different from the heart rate preceding the ischemic episode in both treatment groups of this substudy.
groups and 70% of ischemic episodes were associated with a less than 10% increase in heart; this supports the concept that ischemia was more likely due to a decrease in coronary blood flow (e.g., recurrent thrombosis) than increased myocardial oxygen demand (e.g., increased heart rate related to physical activity).

**Prognostic value of ST segment shift.** The independent value of ST segment shift on continuous monitoring in predicting adverse outcomes at one year was particularly evident among those patients who demonstrated ST shift on the baseline 12-lead ECG and those who received UFH as compared with enoxaparin. In patients without recurrent ischemia, the risk of MI and death was relatively low and similar among the treatment groups and those with or without ST shift at baseline. On the other hand, patients with recurrent ischemia during continuous monitoring, particularly those with ST shift at baseline or treated with heparin, exhibited a higher risk for adverse outcome. This finding is similar to those of previous investigators utilizing continuous 2-channel (22) or vector-derived 12-lead ECG (23) ischemia monitoring or baseline troponin levels (24,25) to identify retrospectively those patients with unstable angina/non-Q-wave MI most likely to benefit from antiplatelet (glycoprotein IIb/IIIa receptor antagonist plus UFH ± aspirin) (22–24) or antithrombotic therapy (LMWH dalteparin plus aspirin vs. aspirin alone) (25). Thus, simple 3-lead continuous ECG monitoring also appears to be a useful noninvasive tool for further risk stratification and selection of high-risk patients who may require more potent antithrombotic therapy.

**Conclusions.** ST segment shift occurs frequently among patients with unstable angina and non-Q-wave MI despite antithrombotic therapy and is associated with worse one-year prognosis. The LMWH enoxaparin is a more effective antithrombotic treatment than UFH and leads to greater prevention of rebound ischemia.

**APPENDIX**

**Study Centers, Principal Investigators and Study Coordinators Participating in the Canadian ST Segment Monitoring Substudy:** York Central Hospital, Richmond Hill (E. Gangbar, L. Willoughby); Humber Memorial Hospital, Weston (M. Cheung, L. Yao, P. Girard); Centenary Health Center, Scarborough (N. Singh, B. Bozek); St. Michael’s Hospital, Toronto (S. Goodman, A. Langer, B. Nolf); Oshawa General Hospital, Oshawa (R. Bhargava, N. Kachra); Mississauga Hospital, Mississauga (T. Rebane, H. Hink); Peel General Hospital, Willowdale (B. Lubelsky, D. Burge); Bowmanville Memorial Hospital, Bowmanville (W. Heslop, N. Kachra); Joseph-Brant Memorial Hospital, Burlington (I. Darcel, P. Anderson); Curans Health Center, Thunder Bay (C. Lai, K. Kwiatkowski) and York County Hospital, Newmarket (A. Hess, M. Gaudet).

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