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A Novel Antithrombotic Agent in the Treatment of Cardiovascular Disease

Final results from the TIMI 11a and ESSENCE trials

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Antithrombotic therapy with heparin plus aspirin reduces the rate of ischemic events in patients with unstable coronary artery disease. Low molecular weight heparin has a more predictable anticoagulant effect than standard unfractionated heparin, is easier to administer, and does not require monitoring. The role of low molecular weight heparin is now clearly established in the treatment of unstable coronary artery disease based on impressive efficacy and safety of subcutaneous enoxaparin administration.

TIMI 11a

Dr. Elliot Antman (Brigham and Women's Hospital, Boston) presented the initial results of the TIMI 11a study comparing the safety and tolerability of two weight-adjusted regimens of enoxaparin administered subcutaneously in patients with unstable angina or non-Q-wave myocardial infarction.[1] In Dose Tier 1, 321 patients received an initial intravenous bolus of 30 mg of enoxaparin, followed by 1.25 mg/kg q12h, while in hospital. In Dose Tier 2, 309 patients received the 30-mg intravenous bolus, followed by 1.0 mg/kg q12h. Both dose tiers received subsequent self-administered subcutaneous injections of enoxaparin (40 mg q12h for body weight <65 kg or 60 mg q12h for body weight ≥65 kg) on an outpatient basis after hospital discharge to complete a total of two weeks of low molecular weight heparin therapy. The mean in- and outpatient treatment was 3 and 10 days, respectively.[2]

The major bleeding rate at 14 days was 6.5% in Dose Tier 1 and only 1.9% in Dose Tier 2. The vast majority of major hemorrhages were related to instrumentation (e.g., cardiac catheterization, revascularization). These rates were compared in an indirect fashion to the 3.2%, 14-day major hemorrhage rate seen in the TIMI IIIb study, where all patients with unstable angina and non-Q-wave infarction received standard, unfractionated intravenous heparin (in addition to placebo vs. moderate doses of tPA).[3] Thus, Dose Tier 2 of enoxaparin compares very favourably to intravenous unfractionated heparin with lower rates of major hemorrhage despite continued outpatient use of enoxaparin.

Compliance as assessed by patient interview and review of a daily diary was greater than 95% in the outpatient phase, suggesting that patients recovering from an acute coronary

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syndrome can self-administer low molecular weight heparin, at least over an initial 10 days following hospital discharge.

TIMI 11b

TIMI 11a was the pilot study for the recently started TIMI 11b study. TIMI 11b is a multicentre, randomized, double-blind, parallel group clinical trial designed to evaluate the efficacy and safety of uninterrupted subcutaneous treatment with enoxaparin in patients with unstable angina or non-Q-wave myocardial infarction. It will be conducted in 200 centres in North America, South America, and Europe. All patients will receive antiplatelet therapy with aspirin throughout the study. Two studies of antithrombotic therapy for unstable angina or non-Q-wave myocardial infarction will be compared in TIMI 11b: unfractionated heparin during the acute phase followed by placebo subcutaneous injections during the chronic phase vs. uninterrupted therapy with an initial bolus followed by subcutaneous enoxaparin during both acute and chronic phases. Dosing for the acute treatment phase (weight-adjusted) will commence with enrollment into the trial and will end at hospital discharge or on day 8 (whichever comes first). Dosing for the chronic treatment phase (fixed-dose) will commence at the time of hospital discharge or day 8 and will continue for an additional 35 days. The sample size for TIMI 11b is designed so that at least 3,500 patients will be randomized with 1,750 patients per treatment group. The primary endpoint will be a composite of death, recurrent myocardial infarction, and recurrent ischemia requiring revascularization. In addition, major bleeding and other adverse events will be carefully documented. It is anticipated that the study will complete enrollment and a 43-day follow-up in all patients by early 1998.

ESSENCE

Dr. Marc Cohen (Medical College of Pennsylvania and Hahnemann University Hospital, Philadelphia) presented the results of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) Study.[4,5] The ESSENCE Study was a randomized, double-blind, placebo-controlled, parallel-group, multicentre trial of 3,171 patients from 176 centres from 10 countries in North and South America and Europe. Patients with unstable angina or non-Q-wave myocardial infarction were randomized to receive standard unfractionated, dose-adjusted intravenous heparin or enoxaparin 1mg/kg q12h subcutaneously. All patients receive 325 mg of aspirin daily and maximal anti-ischemic therapy (nitrates and/or beta- and/or calcium channel blockers) as per local practice. The treatment phase was a minimum of 48 hours and a maximum of 8 days. Patients returned to their local centres for 14-day follow-up and were contacted by telephone to ascertain their 30-day status.

To be eligible for study enrollment, patients had to have had an episode of angina at rest within the previous 24 hours and definite evidence of underlying coronary artery disease. Coronary artery disease was defined by: the presence of ischemic ECG changes on hospital presentation; previous history of myocardial infarction or coronary revascularization (angioplasty or bypass surgery); or prior cardiac catheterization revealing ≥50% stenosis in ≥1 coronary artery. The primary endpoint of the ESSENCE Study was the composite 14-day occurrence of death, myocardial reinfarction or recurrent ischemia. Recurrent ischemia required an episode of chest discomfort: in association with ≥ 0.1 mV ST segment shift or new T-wave inversions in at least two contiguous leads; prompting the decision of the local investigator to proceed with coronary revascularization; or prompting rehospitalization.

Canadian investigators and their patients made an important contribution to enrollment in the ESSENCE Study. Canadian centres comprised 25% of all sites and provided the largest patient enrollment by a single country, representing 40% of the overall trial population. The median age in the trial was 64.5 years and 33% of participants were women. The baseline characteristics were similar between the two treatment groups and indicated a high-risk group of unstable angina/non-Q-wave MI patients: about 50% had a history of myocardial infarction; 21% had a previous angioplasty; 20% had previous bypass surgery; and just over 60% had a history of aspirin use. Although study inclusion required an episode of chest discomfort within 24 hours of randomization, 70% of patients were actually enrolled within 12 hours. The mean duration of treatment was 3.5 days in the heparin-treated and 3.7 days in the enoxaparin-treated group.

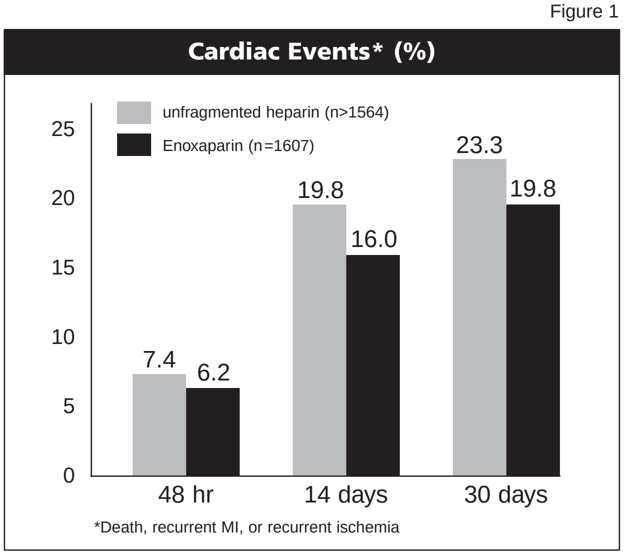
The primary composite endpoint of death, myocardial infarction, and recurrent angina at 14 days was significantly lower in the enoxaparin as compared to heparin-treated group (16.6% vs. 19.8%, p=0.019) (Figure 1), which represents a 16.2% relative risk reduction with enoxaparin. This beneficial effect of enoxaparin was sustained at the 30-day follow-up (19.8% vs. 23.3%, p=0.017).

While the study was not powered to detect a significant difference in the secondary endpoint of death or myocardial infarction, the relative risk reduction was comparable at 14 days (19.7%, p=0.131) with a trend towards a reduction in death and myocardial infarction at 30 days (6.2% vs. 7.7%, p=0.081) representing a 19.5% relative risk reduction.

Another important benefit was the reduced number of coronary revascularizations required in the group treated with enoxaparin as compared to heparin. Coronary artery bypass surgery (12.6% vs. 13.9%, p=not significant) and PTCA (14.9% vs. 18.9%, p=0.003) was required less frequently in the enoxaparin group.

Major hemorrhage (associated with death, transfusion of ≥2 units of blood, >30 g/L fall in hemoglobin, or retroperitoneal, intracranial, or intraoccular hemorrhage) occurred at a similar rate in the two treatment groups (6.5% vs. 7.0%, p=0.566). All types of hemorrhage were more frequent in the enoxaparin group (18.4% vs. 14.1%, p=0.001); however, this absolute difference of approximately 4% was primarily accounted for by injection site ecchymoses/hematomas where enoxaparin was administered.

Figure 1



Dr. Cohen concluded that enoxaparin significantly reduced the 14-day primary endpoint of death, myocardial infarction, and recurrent ischemia in patients with unstable angina and non-Q-wave infarction with evidence of a sustained significant reduction at 30 days. This superiority was achieved without an increase in major hemorrhage events. Although there was an increase in minor hemorrhage events in enoxaparin-treated patients, the majority of events were related to minor ecchymoses at the subcutaneous injection site.

Enoxaparin vs other low molecular weight heparins

Two other large-scale studies evaluating low molecular weight heparins and acute coronary syndromes have been previously published. The Fragmin During Instability in Coronary Artery Disease (FRISC) study evaluated the use of another low molecular weight heparin (dalteparin) given subcutaneously in combination with aspirin vs. aspirin alone.[6] While an impressive relative risk reduction of 48% in the composite endpoint of death or myocardial infarction (MI) was seen in the first 6 days of treatment, this European-based study differed from usual North American practice where aspirin and heparin are commonly used together. The Fragmin in Unstable Coronary Artery Disease (FRIC) study provided the first comparative evaluate of low molecular weight heparin (dalteparin) and unfractionated heparin in addition to aspirin.[7] In contrast to the larger ESSENCE Study this study of 1,482 patients did not find that dalteparin had benefit beyond that of unfractionated heparin in terms of the composite endpoint of death, MI, or recurrent angina at 6 days. There was no advantage to dalteparin over placebo by day 45 among those patients who continued home treatment. However, this trial was half the size of ESSENCE with low statistical power, it was unblinded, and the low molecular weight heparin (dalteparin) has a lower ratio of antifactor Xa to antithrombin activity (IIa) (2:1) (enoxaparin, 3:1). Therefore, it is difficult to be confident that other low molecular weight heparins besides enoxaparin will provide the same efficacy as seen in the ESSENCE study.

Preliminary cost analysis of the ESSENCE study

In a preliminary cost analysis of ESSENCE, Dr. Dan Mark (Duke University, North Carolina) presented promising cost data suggesting a dramatic savings with the use of enoxaparin as compared to unfractionated heparin in the treatment of unstable angina and non-Q-wave myocardial infarction. This analysis compared a cost estimation in U.S. dollars based on hospital billing data in 599 patients with a regression model that imput costs for the total U.S. cohort (n=916). Professional charges were estimated from the Medicare Fee Schedule. Based on findings of the overall ESSENCE Study, including a significant decrease in the requirement for cardiac catheterization, revascularization (angioplasty or bypass surgery), and trends towards decreased hospital stay and rehospitalization, there was a net savings with the use of enoxaparin compared to standard heparin of approximately $U.S. 1,200 per patient. This model assumed that the cost of treatment and monitoring with unfractionated heparin was $0 (a very conservative assumption) and that the cost of enoxaparin was approximately $U.S. 60 per day. When taken in the context of numerous studies of low molecular weight as compared to unfractionated heparin in the treatment of deep venous thrombosis or pulmonary embolism, enoxaparin is not only more cost-effective but also more cost-effective than standard heparin in the treatment of unstable angina and non-Q-wave MI.

Conclusion

The ESSENCE Study presented at the American Heart Association meeting and published in final form in the *New England Journal of Medicine* on August 14, 1997, is an example of promising antithrombotic therapy in the treatment of vascular disease. The ESSENCE study suggests a significant benefit of subcutaneous enoxaparin over standard unfractionated heparin in the treatment of unstable angina and non-Q-wave infarction. In addition to clinical efficacy, there is preliminary data from the ESSENCE Study and established data from the venous thromboembolism trials confirming the cost-effectiveness of this therapy.

While some physicians may choose to await confirmatory results of the TIMI 11b study, the U.S. Food and Drug Administration (FDA) has already approved the use of enoxaparin for unstable coronary syndromes based on its superiority over unfractionated heparin. Therefore, I believe there is adequate data to support the use of enoxaparin presently and I anticipate that Canada's Health Protection Branch (HPB) will follow a similar route and approve enoxaparin use in unstable coronary syndromes.

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