SMH ST. MICHAEL'S HOSPITAL Cardiology
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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

# Scientific Update™

## Low molecular weight heparin in acute coronary syndromes: Preliminary results from the TIMI 11B Study

*Originally presented by:* Elliott Antman, MD

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Reported and discussed by:
SHAUN GOODMAN, MD

**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 PTT monitoring. The role of low molecular weight heparin in the treatment of unstable coronary syndromes is further solidified by impressive efficacy data from large scale clinical trials utilizing enoxaparin.**

### TIMI 11B

The Thrombolysis in Myocardial Infarction (TIMI) 11B study compares the efficacy and safety of unfractionated heparin with the low molecular weight heparin, enoxaparin, in patients with nonpersistent ST segment elevation ischemic syndromes (unstable angina and non-Q-wave myocardial infarction). The preliminary results were presented at the XX$^{th}$ Congress of the European Society of Cardiology by Dr. E. Antman, Associate Professor of Medicine, Harvard Medical School.

### TIMI 11B: The acute phase

As seen in Figure 1, in the acute phase of TIMI 11B, patients with unstable angina or non-Q-wave myocardial infarction (MI) were randomized within 24 hours of chest pain onset to either standard unfractionated intravenous (IV) heparin (70 U/kg bolus followed by 15 U/kg continuous infusion to maintain a partial thromboplastin time [PTT] between 1.5-2.5) for at least 72 hours, or to the low molecular weight heparin enoxaparin (initial IV 30 mg bolus followed by 1 mg/kg twice daily subcutaneous injections).[1] This was a double-blind, double-dummy study in which all patients received IV and subcutaneous administration. After IV therapy was stopped, patients who initially received unfractionated heparin continued to receive placebo subcutaneous injections; those assigned to enoxaparin continued to receive subcutaneous treatment up to 43 days (the chronic phase).

The primary efficacy endpoint of death, MI, or severe recurrent ischemia requiring revascularization was assessed on completion of treatment at 43 days; the primary safety end point was the occurrence of major bleeding or serious adverse event(s) related to study drug. From August 1996 to March 1998, 3,910 patients from 8 countries (including 742



**St. Michael's Hospital, 30 Bond St., Suite 9-004, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5330**

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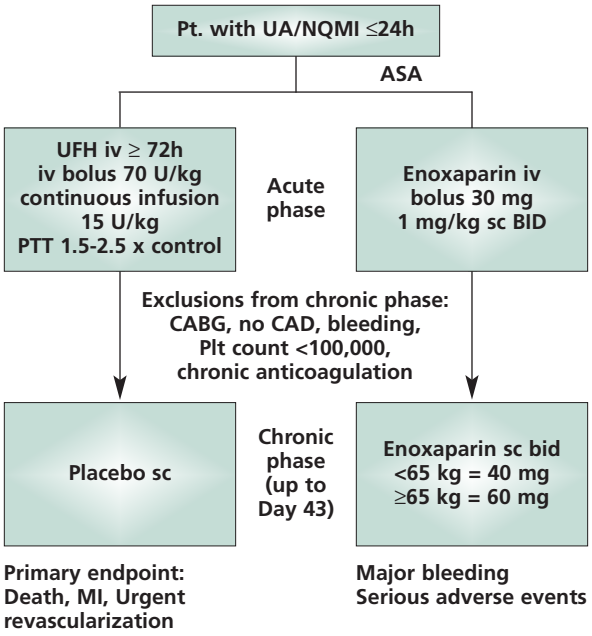
**Figure 1: TIMI 11B: Protocol design**




**Legend**

UA = unstable angina
NQMI = non-Q-wave myocardial infarction
UFH = unfractionated heparin
IV = intravenous
CABG = coronary artery bypass grafting
CAD = coronary artery disease

*Adapted from* Antman EM[1]

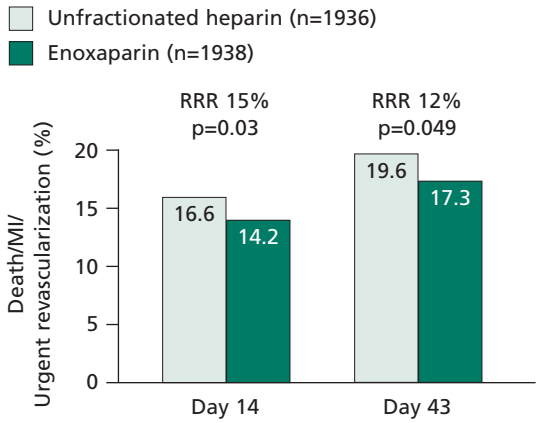
[18.5%] patients from Canadian centres) were enrolled into the trial. Specific inclusion criteria included ischemic discomfort occurring at rest and lasting at least 5 minutes within the past 24 hours. In addition, patients had to have new ST segment changes or evidence of myocardial necrosis to qualify.

Baseline characteristics were similar between the two treatment groups with an overall median age of 65 years. Approximately 20% of the patients had diabetes, one-third a history of prior MI, 20% prior revascularization, and >80% had been receiving ASA in the week prior to study enrollment.

### *The results*

As seen in Figure 2, the 14-day composite endpoint of death, MI, and urgent revascularization, was significantly

**Figure 2: Composite endpoints in TIMI IIB at days 14 and 43**

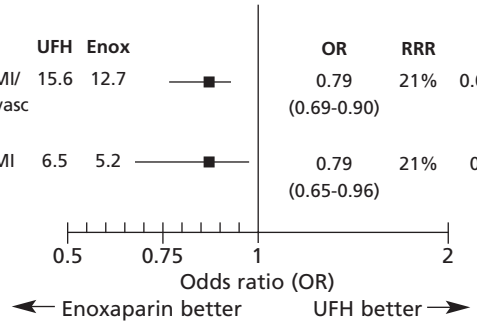



lower among patients treated with enoxaparin as compared to those treated with unfractionated heparin (14.2% versus 16.6%, relative risk reduction [RRR] 15%, p=0.03). Although none of the individual components of the composite endpoint were by themselves statistically significant — the study was not powered to evaluate these endpoints individually — the event rate was consistently lower among patients receiving enoxaparin compared to unfractionated heparin (death: 2.2% versus 2.8%, MI: 4.2% versus 5.3%, and urgent revascularization: 9.6% versus 11.1%, respectively).

Thus, 41 patients need to be treated with enoxaparin (compared with unfractionated heparin) in order to prevent the primary endpoint from occurring. This translates into 24 additional events avoided per 1,000 patients treated with enoxaparin instead of unfractionated heparin.

Prespecified subgroup analyses indicated that the enoxaparin effect was consistent and in keeping with the overall trial results. For example, the absolute benefit was greater among patients with ST segment depression (n=2,150) who received enoxaparin compared to unfractionated heparin (15.3% versus 19.2%, p<0.05), than in patients who did not present with ST segment depression (n=1,760; 12.8% versus 13.4%). As seen in the ESSENCE study, patients who had received ASA in the 24 hours prior

**Figure 3: Enoxaparin for unstable angina/Non-Q-wave MI; TIMI 11B and ESSENCE meta-analysis at Day 14 (n=7081)**




UFH = Unfractionated heparin
RRR = Relative risk reduction

to study enrolment (n=3,152) experienced a significant benefit of enoxaparin over unfractionated heparin (15.1% versus 18.2%, p<0.05).

There were no significant differences with respect to the occurrence of major hemorrhage during the initial 72 hours (enoxaparin 0.8% versus unfractionated heparin 0.7%) or hospital phase (1.5% versus 1.0%, p=ns).

## TIMI 11B: The chronic phase

In the chronic phase of the protocol, patients were eligible to remain in the study and receive blinded subcutaneous BID therapy (placebo versus enoxaparin [40 mg for body weight <65 kg or 60 mg for ≥65 kg]) as long as they did not require bypass surgery, experience any bleeding, have a platelet count <100,000, or require chronic anticoagulation.

### *The results*

By day 43 (Figure 2), the composite endpoint of death, MI, or urgent revascularization remained lower in enoxaparin-treated patients (17.3% versus 19.6%, RRR 12%, p=0.049). Thus, there was no further relative decrease in events with enoxaparin over placebo after the acute phase. However, the chronic phase may have been underpowered to detect a difference between treatments since only 60% of those enrolled in the acute phase continued on to the chronic phase. In addition, "lower risk" patients entered the chronic phase (ie, patients with a complicated acute course or those requiring bypass surgery, etc, did not go on to the outpatient phase), making it more difficult to detect an incremental benefit of enoxaparin beyond the acute phase.

There was a greater number of major hemorrhagic events in the outpatient phase in enoxaparin-treated patients compared to those treated with placebo (2.9% versus 1.5%, p=0.02).

### *Summary*

The TIMI 11B investigators concluded that in the acute phase, enoxaparin is clearly superior to unfractionated heparin in the management of unstable angina/non-Q-wave MI patients for reducing death and serious cardiac ischemic events. This superiority was achieved without an increase in the rate of either spontaneous or instrumented major hemorrhage. During the chronic phase, the initial benefit observed with enoxaparin was sustained through to day 43; however, no further relative decrease in events was observed.. There was a small increase in the rate of major hemorrhage with chronic enoxaparin therapy as compared to placebo treatment.

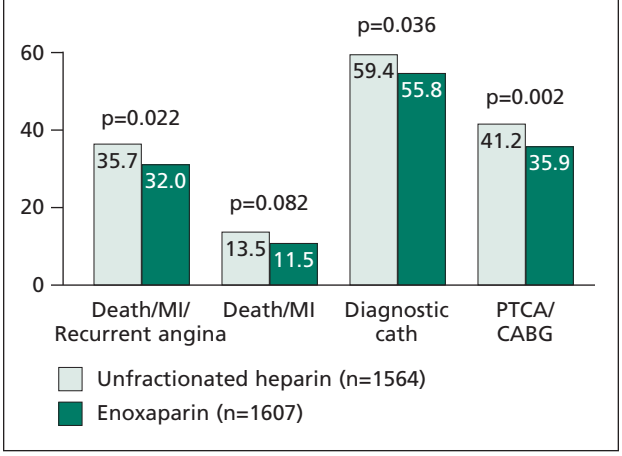
## Meta-analysis of TIMI IIB and ESSENCE

In a preliminary meta-analysis combining the ESSENCE[2] and TIMI 11B study results at days 8, 14, and 43, there was evidence of a consistent, approximate 20% relative risk reduction in the occurrence of death, MI, or urgent revascularization and in death or MI alone (Figure 3).

## ESSENCE: 1-year follow-up results

The initial significant benefit of the low molecular weight heparin enoxaparin as compared to unfractionated heparin in unstable angina/non-Q-wave MI patients was reported in

**Figure 4: ESSENCE 1-year follow-up**




the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study.[2] In order to determine if the observed benefits of enoxaparin plus aspirin — compared to unfractionated heparin plus aspirin — were maintained beyond the early (14- to 30-day) phase, a one-year follow-up survey was undertaken for all patients enrolled in the ESSENCE study (Figure 4).[3]

The incidence of the composite triple end-point (death, MI, or recurrent angina) at one year was lower among enoxaparin-treated patients compared to unfractionated heparin-treated patients, (32% versus 35.7%, p=0.022). As well, there was a trend towards a lower incidence of the secondary composite end-point of death or nonfatal MI (11.5% versus 13.5%, p=0.082). At one year, the need for diagnostic catheterization and coronary revascularization was lower among the enoxaparin group (55.8% versus 59.4%, p=0.036; and 35.9% versus 41.2%, p=0.002, respectively).

Thus, ESSENCE is the first large scale trial (n=3171) showing one year benefit of antithrombotic therapy administered for a relatively brief (median) duration of 2.6 days to patients with unstable angina/non-Q wave MI. The benefit with enoxaparin as compared to unfractionated heparin was established early and maintained without clinical evidence of greater late reactivation of disease.

## Conclusion

Based on the ESSENCE (short and long-term follow-up) and TIMI 11B studies, treatment with subcutaneous enoxaparin (1 mg/kg twice daily), in addition to aspirin, should be considered for at least 48 to 72 hours in patients with unstable angina or non-Q-wave MI to reduce important ischemic events. A simple mode of administration without need for anticoagulation monitoring, low requirement for invasive diagnostic and therapeutic procedures, cost savings and superior short-term and sustained long-term efficacy make enoxaparin an extremely attractive option in the treatment of patients with acute ischemic coronary syndromes presenting without persistent ST segment elevation.

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