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# Assessment of the Treatment Effect of Enoxaparin for Unstable Angina/Non-Q-Wave Myocardial Infarction

## TIMI 11B-ESSENCE Meta-Analysis

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**Background**—Two phase III trials of enoxaparin for unstable angina/non-Q-wave myocardial infarction have shown it to be superior to unfractionated heparin for preventing a composite of death and cardiac ischemic events. A prospectively planned meta-analysis was performed to provide a more precise estimate of the effects of enoxaparin on multiple end points.

**Methods and Results**—Event rates for death, the composite end points of death/nonfatal myocardial infarction and death/nonfatal myocardial infarction/urgent revascularization, and major hemorrhage were extracted from the TIMI 11B and ESSENCE databases. Treatment effects at days 2, 8, 14, and 43 were expressed as the OR (and 95% CI) for enoxaparin versus unfractionated heparin. All heterogeneity tests for efficacy end points were negative, which suggests comparability of the findings in TIMI 11B and ESSENCE. Enoxaparin was associated with a 20% reduction in death and serious cardiac ischemic events that appeared within the first few days of treatment, and this benefit was sustained through 43 days. Enoxaparin's treatment benefit was not associated with an increase in major hemorrhage during the acute phase of therapy, but there was an increase in the rate of minor hemorrhage.

**Conclusions**—The accumulated evidence, coupled with the simplicity of subcutaneous administration and elimination of the need for anticoagulation monitoring, indicates that enoxaparin should be considered as a replacement for unfractionated heparin as the antithrombin for the acute phase of management of patients with high-risk unstable angina/non-Q-wave myocardial infarction. (*Circulation*. 1999;100:1602-1608.)

**Key Words:** enoxaparin ■ heparin ■ meta-analysis ■ anticoagulants

In 1982, Telford and Wilson<sup>1</sup> introduced the idea of the administration of intravenous heparin for the treatment of the acute phase of unstable angina. This was followed by several important clinical trials evaluating the effect of heparin alone and in combination with aspirin.<sup>2-4</sup> The benefits of intravenous heparin from such trials was judged to be sufficiently compelling that authoritative bodies recommended its use in the routine management of patients with unstable angina/non-Q-wave myocardial infarction.<sup>5-7</sup> This recommendation has been embraced widely by clinicians, making it difficult to conduct trials of new antithrombin therapies in which patients might be randomized to treatment with placebo.<sup>8</sup>

It has an unpredictable anticoagulant effect, necessitating frequent testing to adjust the dose being administered to the patient.<sup>9</sup> Although it can be administered subcutaneously, this is of limited effectiveness because of its low and variable bioavailability, and it usually must be delivered by a continuous intravenous infusion. Additional drawbacks include a tendency to a rebound increase in thrombotic events after cessation of its use, sensitivity to the inhibitory effects of platelet factor 4, and the risk of heparin-associated thrombocytopenia and thrombosis.<sup>10</sup> Low-molecular-weight heparins offer the advantages of a stable and predictable anticoagulant response to a given dose, eliminating the need for hematologic monitoring, and much simpler administration via the subcutaneous route.<sup>11-13</sup> These features alone might convince some clinicians to substitute a low-molecular-weight heparin in situations in which they would prescribe unfractionated

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See p 1586

Despite its extensive penetration into clinical practice, unfractionated heparin suffers from several important disad-

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TABLE 1. Comparison of TIMI 11B and ESSENCE Trials

	TIMI 11B	ESSENCE
Inclusion criteria		
Rest angina within 24 h	Required	Required
Additional supportive criteria (at least 1 of the following required):		
ST deviation criteria	$\geq 0.05$ mV	$\geq 0.1$ mV
History of CAD	Acceptable initially, but later dropped as sole supportive criterion	Acceptable for enrollment
Elevated serum cardiac markers	Acceptable for enrollment	Acceptable for enrollment
Major exclusion criteria		
Planned revascularization $\leq 24$ h	Yes	Yes
Correctable cause of angina	Yes	Yes
Contraindications to anticoagulation	Yes	Yes
Dose of study drug in acute phase		
Intravenous unfractionated heparin	Bolus 70 U/kg Infusion $15 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ adjusted to $1.5\text{--}2.5 \times$ control; median duration of Rx 3.0 d	Bolus 5000 U Infusion 1000 U/h adjusted to $1.5\text{--}2.5 \times$ control; median duration of Rx 2.6 d
Enoxaparin	Initial bolus 30 mg IV followed by 1.0 mg/kg SC every 12 hours; median duration of Rx 4.6 d	No initial IV bolus; 1.0 mg/kg SC every 12 h; median duration of Rx 2.6 d
Dose of study drug in outpatient phase		
Placebo	Matched volume of injections to active Rx	None
Enoxaparin	40 mg SC every 12 h if $< 65$ kg; 60 mg SC every 12 h if $\geq 65$ kg	None

CAD indicates coronary artery disease; Rx, treatment.

heparin even if the 2 treatments were of equal efficacy. The decision to use a low-molecular-weight heparin would be even more attractive if it were also more efficacious than intravenous unfractionated heparin, especially in a serious condition such as unstable angina/non-Q-wave myocardial infarction.<sup>14</sup> TIMI 11B and ESSENCE, 2 phase III randomized trials, have independently demonstrated superiority of enoxaparin over unfractionated heparin in reducing a composite of death and serious cardiac ischemic events in patients with unstable angina/non-Q-wave myocardial infarction.<sup>15,16</sup> Neither TIMI 11B nor ESSENCE was designed with sufficient power to detect statistically significant treatment effects of enoxaparin on end points other than the composite ones used in the individual trials. Therefore, the objective of this prospectively planned meta-analysis was to provide more statistically robust estimates of the treatment effects of enoxaparin on death and serious cardiac ischemic events individually and in various combinations, particularly death and nonfatal myocardial infarction, as well as major hemorrhage in patients with unstable angina/non-Q-wave myocardial infarction.<sup>15,16</sup>

## Methods

### Data Acquisition

The details of TIMI 11B and ESSENCE have been reported previously.<sup>15,16</sup> Important aspects of the enrollment criteria and doses of study drug are summarized in Table 1. Prespecified end points of interest include all-cause mortality, recurrent myocardial infarction (defined by ECG and serum marker criteria),<sup>15,16</sup> urgent revascularization,<sup>15</sup> and major hemorrhage.<sup>15,16</sup>

### Statistical Analysis

For each individual trial and for the combination of the 2 trials, the OR for enoxaparin versus unfractionated heparin was estimated along with its 95% CI for each end point of interest at days 2 (period of direct comparison of unfractionated heparin versus enoxaparin), 8 (end of acute phase of management), 14 (time of ascertainment of primary end point in ESSENCE), and 43 (end of outpatient phase in TIMI 11B). For assessment of internal consistency of the observations on the treatment effect of enoxaparin, 3 separate methods of pooling the trial results were used: (1) Peto method comparing observed minus expected events,<sup>17</sup> (2) Mantel-Haenszel method for combining information from a series of  $2 \times 2$  tables,<sup>18,19</sup> and (3) the random-effects model of DerSimonian and Laird.<sup>20,21</sup> The Peto and Mantel-Haenszel methods differ in the method of calculation of variances of the summary OR and may on occasion yield different results, as pointed out by Greenland et al.<sup>22</sup> The random-effects model includes between-study differences in treatment effects in the calculation of the variances and may lead to wider CIs when heterogeneity among trials is observed.<sup>20,21</sup> For each of the 3 methods of evaluating the treatment effect of enoxaparin, heterogeneity testing was performed to screen for any important differences ( $P \leq 0.05$ ) between TIMI 11B and ESSENCE.<sup>23</sup>

## Results

The TIMI 11B and ESSENCE trials were similar in that both trials enrolled patients with unstable angina/non-Q-wave myocardial infarction and excluded patients who presented with ST-segment-elevation myocardial infarction (Table 1). The control group in both trials received intravenous unfractionated heparin adjusted to a similar target activated partial thromboplastin time range via nomograms at each enrolling hospital; a double-blind design was used. The subcutaneous dose of enoxaparin for the acute phase of management was 1.0 mg/kg every 12 hours in both trials; in TIMI 11B, the first

subcutaneous dose was preceded by an intravenous bolus of 30 mg of enoxaparin. The median duration of therapy with unfractionated heparin was similar in the 2 trials (3.0 days in TIMI 11B and 2.6 days in ESSENCE). By protocol design, the median duration of acute-phase treatment with enoxaparin was longer in TIMI 11B at 4.6 days compared with 2.6 days in ESSENCE. Also, by protocol design, a reduced dose of enoxaparin was administered in the outpatient phase in TIMI 11B but not in ESSENCE (Table 1). Long term follow-up was performed in ESSENCE at 3 months and 1 year after randomization; this provided the database for extraction of events in ESSENCE through 43 days and permitted pooling of the findings with TIMI 11B.<sup>24</sup>

### Meta-Analysis Findings

Meta-analyses of each of the end points of interest revealed similar estimates of the ORs and CIs for the treatment effect of enoxaparin for each of the 3 pooling methods. There was no statistically significant evidence of heterogeneity between TIMI 11B and ESSENCE with respect to the efficacy end points. The findings shown in Tables 2 and 3 and Figures 1 and 2 were calculated by the Peto method.

The composite end point of death/nonfatal myocardial infarction was consistently  $\approx 20\%$  lower at all time points in the group that received enoxaparin (Table 2; Figure 1). Statistical significance for the reduction in this end point was observed at day 8 (OR 0.77; 95% CI 0.62 to 0.95;  $P=0.02$ ) and persisted through follow-up at 14 days (OR 0.79; 95% CI 0.65 to 0.96;  $P=0.02$ ) and 43 days (OR 0.82; 95% CI 0.69 to 0.97;  $P=0.02$ ). The absolute difference in event rates for death/nonfatal myocardial infarction between the pooled unfractionated heparin group and the enoxaparin group increased from 1.2% at day 8 to 1.5% at day 43.

A significant treatment benefit of enoxaparin on the composite end point of death/nonfatal myocardial infarction/urgent revascularization was observed at day 2 (OR 0.77;

95% CI 0.63 to 0.94;  $P=0.012$ ). As shown in Table 2 and Figure 2, a highly significant treatment benefit continued to be observed through 43 days (OR 0.80; 95% CI 0.71 to 0.91;  $P=0.0005$ ). The absolute difference in pooled event rates widened from 1.4% at day 2 to 3.2% at day 43. Based on the absolute event rates in Table 2 for the pooled treatment groups, 31 patients would need to be treated to prevent 1 event by day 43.

Beginning at day 8, a trend toward a lower mortality rate was observed in the pooled enoxaparin group (OR 0.80; 95% CI 0.56 to 1.16) that continued to be observed through day 43 (OR 0.84; 95% CI 0.66 to 1.08) (Table 2).

During acute-phase treatment, the pooled rate of major hemorrhage was 1.3% in the enoxaparin group and 1.1% in the unfractionated heparin group (OR 1.23; 95% CI 0.80 to 1.89;  $P=0.35$ ) (Table 3). During the same acute-phase treatment period, the pooled rate of minor hemorrhage was 10.0% in the enoxaparin group and 4.3% in the unfractionated heparin group (OR 2.38; 95% CI 1.98 to 2.85;  $P<0.0001$ ) (Table 3).

### Discussion

Compared with unfractionated heparin, the traditional anti-thrombin, enoxaparin treatment is associated with a 20% reduction in clinical events in patients with unstable angina/non-Q-wave myocardial infarction. The treatment benefit of enoxaparin occurs within 48 hours and is persistent, with a quantitatively similar relative treatment effect observed at day 2 and day 43 (Figures 1 and 2). The reduction in events with enoxaparin is achieved without a significant increase in the rate of major hemorrhage during the acute phase of therapy, although the rate of minor hemorrhages was significantly increased. In the face of increasing event rates between day 2 and day 43 in the unfractionated heparin group, the stable relative treatment effect of enoxaparin occurs by a commensurate increase in the absolute difference

**TABLE 2. Efficacy End Points**

	TIMI 11B			ESSENCE		
	UFH (%) (n=1957)	ENOX (%) (n=1953)	OR (95% CI)	UFH (%) (n=1564)	ENOX (%) (n=1607)	OR (95% CI)
<b>Death/MI</b>						
Day 2	42 (2.1)	33 (1.7)	0.78 (0.50–1.24)	20 (1.3)	17 (1.1)	0.83 (0.43–1.58)
Day 8	115 (5.9)	90 (4.6)	0.77 (0.58–1.03)	73 (4.7)	57 (3.5)	0.75 (0.53–1.07)
Day 14	135 (6.9)	111 (5.7)	0.81 (0.63–1.05)	95 (6.1)	74 (4.6)	0.75 (0.55–1.02)
Day 43	174 (8.9)	155 (7.9)	0.88 (0.70–1.11)	129 (8.2)	99 (6.2)	0.73 (0.56–0.96)
<b>Death/MI/Urgent revascularization</b>						
Day 2	142 (7.3)	108 (5.5)	0.75 (0.58–0.97)	81 (5.2)	68 (4.2)	0.81 (0.58–1.12)
Day 8	284 (14.5)	242 (12.4)	0.83 (0.69–1.00)	190 (12.1)	148 (9.2)	0.73 (0.58–0.92)
Day 14	326 (16.7)	277 (14.2)	0.83 (0.69–0.98)	226 (14.5)	177 (11.0)	0.73 (0.59–0.90)
Day 43	385 (19.7)	337 (17.3)	0.85 (0.72–1.00)	276 (17.6)	220 (13.7)	0.74 (0.61–0.90)
<b>Death</b>						
Day 2	6 (0.3)	11 (0.6)	1.81 (0.70–4.69)	6 (0.4)	6 (0.4)	0.97 (0.31–3.02)
Day 8	41 (2.1)	34 (1.7)	0.83 (0.52–1.31)	23 (1.5)	18 (1.1)	0.76 (0.41–1.41)
Day 14	55 (2.8)	43 (2.2)	0.78 (0.52–1.16)	31 (2.0)	28 (1.7)	0.88 (0.52–1.47)
Day 43	78 (4.0)	75 (3.8)	0.96 (0.70–1.33)	59 (3.8)	42 (2.6)	0.69 (0.46–1.02)

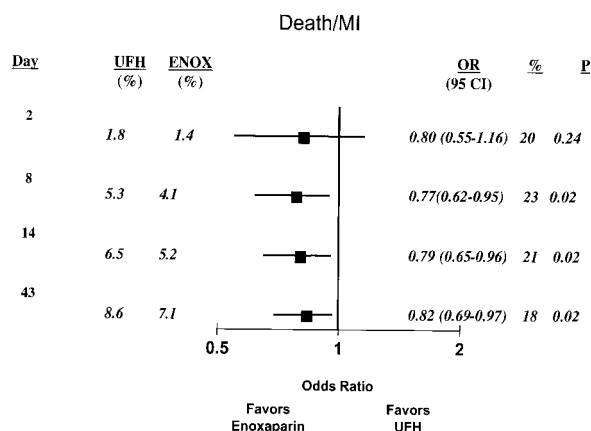
UFH indicates unfractionated heparin; ENOX, enoxaparin.

in event rates over the same time period (Table 2). The findings favoring enoxaparin are statistically robust given (1) the lack of heterogeneity for efficacy end points between TIMI 11B and ESSENCE; (2) consistency of the treatment effect examined across multiple efficacy end points (Table 2), which suggests that the observations were not driven predominantly by any single element in the composite end points examined; and (3) the level of statistical significance observed (Table 2).

### Potential Mechanisms of Superiority Over Unfractionated Heparin

The incomplete and variable inhibition of thrombin by intravenous unfractionated heparin stems in part from a relatively low bioavailability due to extensive nonspecific binding to serum proteins, macrophages, and endothelial cells.<sup>13,25,26</sup> The catalytic activity of heparin preparations that inhibit factor IIa and factor Xa resides in those glycosaminoglycan chains that contain a pentasaccharide sequence required for high-affinity binding to antithrombin.<sup>13</sup> High-affinity material is further subdivided into chains that are >18 saccharides and therefore above the critical length mass (ACLM), which can inhibit both factor IIa and factor Xa, and those that are below the critical length mass (BCLM), which are capable only of inhibiting factor Xa.<sup>13</sup> The BCLM:ACLM ratio of unfractionated heparin is 1:1, whereas low-molecular-weight heparins have ratios >1, leading to a higher anti-factor Xa:anti-factor IIa ratio. This provides a distinct kinetic advantage by inhibiting early steps in the coagulation cascade and inhibiting thrombin generation. Maintenance of a sufficient concentration of anti-factor IIa activity in low-molecular-weight heparin preparations is necessary to simultaneously inhibit thrombin activity.<sup>11,27</sup>

Features of enoxaparin that may permit a greater degree of suppression of thrombin generation than with unfractionated heparin include a higher anti-factor Xa:anti-factor IIa ratio



**Figure 1.** Meta-analysis of the treatment effect of enoxaparin (ENOX) vs unfractionated heparin (UFH) on death and nonfatal myocardial infarction at time points shown. Point estimates of OR for treatment effect are shown as squares, and 95% CIs are depicted by width of horizontal lines.

(3.8:1) and a prolonged duration of anti-factor Xa activity. Brieger and Dawes<sup>28</sup> reported that the anti-factor Xa activity of enoxaparin was detectable up to a week after administration, probably as a result of sequestration in tissue stores. Several investigators<sup>27,29</sup> have noted that the greater bioavailability of enoxaparin (91%) produces a higher level of anti-factor IIa activity than with unfractionated heparin, potentially producing a greater degree of inhibition of thrombin activity. Additional pharmacological advantages of enoxaparin that may be operative in its superiority over unfractionated heparin include less sensitivity to the inhibitory effects of platelet factor 4, a greater capacity to release tissue-factor–pathway inhibitor, a lower propensity to promote activation and aggregation of platelets, and potential antiplatelet effects via higher degrees of suppression of von Willebrand factor.<sup>30–35</sup>

**TABLE 2. Continued**

Pooled		Heterogeneity Test			
UFH (%) (n=3521)	ENOX (%) (n=3560)	OR (95% CI)	P	$\chi^2$	P
62 (1.8)	50 (1.4)	0.80 (0.55–1.16)	0.24	0.02	0.89
188 (5.3)	147 (4.1)	0.77 (0.62–0.95)	0.02	0.02	0.89
230 (6.5)	185 (5.2)	0.79 (0.65–0.96)	0.02	0.17	0.68
303 (8.6)	254 (7.1)	0.82 (0.69–0.97)	0.02	1.11	0.29
223 (6.3)	176 (4.9)	0.77 (0.63–0.94)	0.012	0.13	0.72
474 (13.5)	390 (11.0)	0.79 (0.69–0.91)	0.001	0.73	0.39
552 (15.7)	454 (12.8)	0.79 (0.69–0.90)	0.0005	0.75	0.39
661 (18.8)	557 (15.6)	0.80 (0.71–0.91)	0.0005	1.19	0.28
12 (0.3)	17 (0.5)	1.40 (0.68–2.90)	0.37	0.67	0.41
64 (1.8)	52 (1.5)	0.80 (0.56–1.16)	0.24	0.05	0.82
86 (2.4)	71 (2.0)	0.81 (0.59–1.12)	0.21	0.13	0.72
137 (3.9)	117 (3.3)	0.84 (0.66–1.08)	0.18	1.67	0.20

TABLE 3. Hemorrhages on Weight-Adjusted Treatment

	TIMI 11B			ESSENCE		
	UFH (%) (n=1936)	ENOX (%) (n=1938)	OR (95% CI)	UFH (%) (n=1529)	ENOX (%) (n=1578)	OR (95% CI)
Major hemorrhage	19 (1.0)	29 (1.5)	1.52 (0.86–2.69)	18 (1.2)	17 (1.1)	0.91 (0.47–1.78)
Minor hemorrhage	67 (3.5)	205 (10.6)	2.97 (2.3–3.81)	81 (5.3)	148 (9.4)	1.82 (1.39–2.38)

### Comparison With Other Low-Molecular-Weight Heparins

The low-molecular-weight heparins vary in their average molecular weight, anti-factor Xa:anti-factor IIa ratio, relative patterns of distribution of ACLM and BCLM chains, ionic nature (sodium or calcium salt), release profile of tissue-factor–pathway inhibitor, and potential to cause bleeding in experimental preparations.<sup>36</sup> Enoxaparin is distinguished from both dalteparin and nadroparin by a higher anti-factor Xa:anti-factor IIa ratio, a lower average molecular weight, a higher proportion of glycosaminoglycan species <2000 Da, and a greater ability to inhibit thrombin generation.<sup>37,38</sup> Given considerations such as those noted above, it has been emphasized that it is an oversimplification to consider low-molecular-weight preparations to have a class effect, and it therefore seems inappropriate to conduct meta-analyses of clinical trials that use different low-molecular-weight heparins.<sup>12,36,39,40</sup> Accordingly, we restricted our meta-analysis to trials of enoxaparin.

In addition to distinctions in pharmacological properties, differences in trial design must be considered when studies of low-molecular-weight heparins for unstable angina/non-Q-wave myocardial infarction are compared. Phase III trials with dalteparin and nadroparin failed to show superiority of those agents compared with unfractionated heparin.<sup>41,42</sup> Of note, the times from the qualifying episode of ischemic discomfort to enrollment in the FRIC (FRagmin during Instability in Coronary artery disease) and FRAXIS (FRAXiparine in Ischemic Syndromes) studies were up to 72 and 48 hours, respectively.<sup>41,42</sup> In addition, both of those trials included patients with exacerbations of effort angina, and

only 16% of patients in FRIC and FRAXIS had a non-Q-wave myocardial infarction at enrollment. In contrast, TIMI 11B and ESSENCE restricted enrollment to patients with rest angina within the prior 24 hours, and higher proportions of patients had a non-Q-wave myocardial infarction at enrollment (35% in TIMI 11B and 21% in ESSENCE). The lower risk profile of patients in FRIC and FRAXIS, use of low-molecular-weight heparins with lower anti-factor Xa:anti-factor IIa ratios, and different distribution of ACLM and BCLM chains may have combined to bias those trials to a null effect. In the case of dalteparin, it is unlikely that a higher dose would have permitted superiority to emerge, because a dose of 150 IU/kg every 12 hours was previously found to be associated with unacceptable levels of bleeding, necessitating a reduction to 120 IU/kg every 12 hours.<sup>43</sup>

### Comparison With Direct Antithrombins

Clinical trials with direct antithrombins were designed around the hypothesis that they would be more effective than unfractionated heparin owing to inhibition of both fluid-phase and clot-bound thrombin. However, experience with direct antithrombins has been disappointing to date.<sup>44–48</sup> Initial phase III trials of hirudin were stopped prematurely owing to excessive bleeding, which indicates a safety limitation on the dose that can be administered clinically.<sup>44–46</sup> Subsequent trials with reduced doses of hirudin showed mixed results, with some studies showing no benefit over unfractionated heparin and others showing a small reduction in events, primarily nonfatal myocardial infarction.<sup>49–51</sup> Meta-analysis of the hirudin trials in nonthrombolytic-treated patients showed an initial reduction in death/nonfatal myocardial infarction at 3 days (OR 0.72;  $P=0.0002$ ) but a decrease in the magnitude of the treatment effect, which was no longer significant by 35 days (OR 0.90;  $P=0.057$ ), possibly owing to rebound activation of the coagulation cascade after cessation of treatment.<sup>51,52</sup>

### Clinical Implications

The 20% reduction in clinical events with enoxaparin is of a magnitude that most clinicians would consider sufficient to change their practice pattern. Health economic analysis of the benefits of enoxaparin in the ESSENCE trial show it to be a dominant strategy that simultaneously lowers total costs of care and reduces the rates of important clinical events.<sup>53</sup> The durable treatment effect of enoxaparin also compares quite favorably with the more transitory benefits of intravenously administered direct antithrombins. The accumulated evidence, coupled with the simplicity of subcutaneous administration and elimination of the need for anticoagulation monitoring, indicates that enoxaparin should now be considered

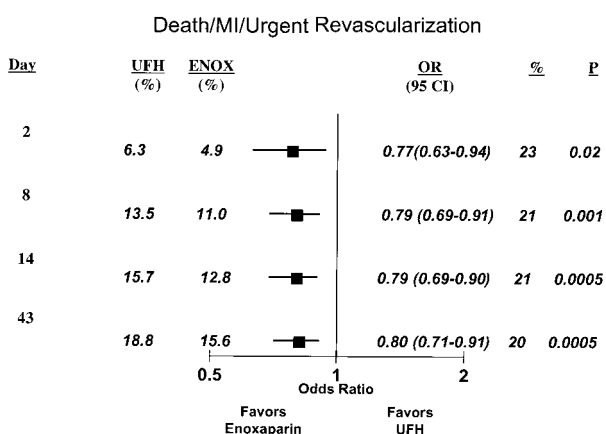


Figure 2. Meta-analysis of treatment effect of enoxaparin (ENOX) vs unfractionated heparin (UFH) on composite end point of death/myocardial infarction/urgent revascularization at time points shown. Arrangement of data as in Figure 1.

TABLE 3. Continued

Pooled		Heterogeneity Test			
UFH (%) (n=3465)	ENOX (%) (n=3516)	OR (95% CI)	P	$\chi^2$	P
37 (1.1)	46 (1.3)	1.23 (0.80–1.89)	0.35	1.30	0.25
148 (4.3)	353 (10.0)	2.38 (1.98–2.85)	<0.0001	6.99	0.008

as a replacement for unfractionated heparin as the antithrombin for the acute phase of management of patients with high-risk unstable angina/non-Q-wave myocardial infarction.

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### References

- Telford AM, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. *Lancet*. 1981; 1:1225–1228.
- Theroux P, Ouimet H, McCans J, Latour J-G, Joly G, Levy G, Pelletier E, Juneau M, Stasiak J, deGuise P, Pelletier GB, Rinzler D, Waters DD. Aspirin, heparin or both to treat unstable angina. *N Engl J Med*. 1988; 319:1105–1111.
- The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet*. 1990;336:827–830.
- Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wiczorek I, Fox KAA, Chesebro JH, Strain J, Keller C, Kelly A, Lancaster G, Ali J, Kronmal R, Fuster V, and the Antithrombotic Therapy in Acute Coronary Syndromes Research Group. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users: primary end points analysis from the ATACS trial. *Circulation*. 1994;89: 81–88.
- Braunwald E, Mark DB, Jones RH, Cheitlin MD, Fuster V, McCauley KM, Edwards C, Green LA, Mushlin AI, Swain JA, Smith EE III, Cowan M, Rose GC, Concannon CA, Grines CL, Brown L, Lytle BW, Goldman L, Topol EJ, Willerson JT, Brown J, Archibald N. *Unstable Angina: Diagnosis and Management*. Rockville, Md: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, Public Health Service, US Dept of Health and Human Services; 1994. Clinical Practice Guideline Number 10.
- Cairns J, Lewis HD Jr, Meade TW, Sutton GC, Theroux P. Anti-thrombotic agents in coronary artery disease. *Chest*. 1995;108: 380S–400S.
- Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. *JAMA*. 1996;276:811–815.
- Ridker PM, O'Donnell CJ, Hennekens CH. Direct comparison of aspirin plus hirudin, aspirin plus heparin, and aspirin alone among 12,000 patients with acute myocardial infarction not receiving thrombolysis: rationale and design of the first American Study of Infarct Survival (ASIS-1). *J Thromb Thrombolysis*. 1995;1:119–124.
- Hirsh J, Fuster V. Guide to anticoagulant therapy, part I: heparin. *Circulation*. 1994;89:1449–1468.
- Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med*. 1992;327:141–145.
- Barrowcliffe T, Johnson E, Thomas D. *Low Molecular Weight Heparin*. Chichester, UK: John Wiley & Sons; 1992.
- Bounameaux H. *Low-Molecular-Weight Heparins in Prophylaxis and Therapy of Thromboembolic Disease*. New York, NY: Marcel Dekker Inc; 1994.
- Weitz JI. Low-molecular-weight heparins. *N Engl J Med*. 1997;337: 688–698.
- Gurfinkel E, Fareed J, Antman E, Cohen M, Mautner B. Rationale for the management of coronary syndromes with low-molecular-weight heparins. *Am J Cardiol*. 1998;82:15L–18L.
- Antman EM, McCabe CH, Gurfinkel EP, Turpie AGG, Bennink PJLM, Salein D, Bayes de Luna A, Fox K, Lablanche JM, Radley D,

- Premmureur J, Braunwald E, for the TIMI (Thrombolysis In Myocardial Infarction) 11B Investigators. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B Trial. *Circulation*. 1999;100:1593–1601.
- Cohen M, Demers C, Gurfinkel EP, Turpie AGG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KAA, Premmureur J, Bigonzi F, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med*. 1997;337:447–452.
- Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J*. 1994;308:81–106.
- Kelsey J, Thompson W, Evans A. Prospective cohort studies, II: further design considerations and analysis. In: *Methods in Observational Epidemiology*. Oxford, UK: Oxford University Press; 1986:105–127.
- Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics*. 1986;42:311–323.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
- Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med*. 1992;327:248–254.
- Greenland S, Salvan A. Bias in the one-step (Peto) method for pooling study results. *Stat Med*. 1990;9:247–252.
- Berlin J, Laird N, Sacks H, Chalmers T. A comparison of statistical methods for combining event rates from clinical trials. *Stat Med*. 1989; 8:141–151.
- Cohen M, Bigonzi F, Lelouer V, Gosset F, Fromell GJ, Goodman S. One year follow-up of the ESSENCE trial (Enoxaparin versus Heparin in Unstable Angina and Non-Q-Wave Myocardial Infarction). *J Am Coll Cardiol*. 1998;31:79A. Abstract.
- Young E, Cosmi B, Hirsh J. Comparison of the non-specific binding of unfractionated heparin and low molecular weight heparin (enoxaparin) to plasma proteins. *Thromb Haemost*. 1993;70:625–630.
- Mombelli G, Marchetti O, Haerberli A, Straub P. Effect of intravenous heparin infusion on thrombin-antithrombin complex and fibrinopeptide A in unstable angina. *Am Heart J*. 1998;136:1106–1113.
- Agnelli G. Pharmacological activities of heparin chains: should our past knowledge be revised? *Haemostasis*. 1996;26:2–9.
- Brieger D, Dawes J. Long-term persistence of biological activity following administration of enoxaparin sodium (clexane) is due to sequestration of antithrombin-binding low molecular weight fragments: comparison with unfractionated heparin. *Thromb Haemost*. 1996;75: 740–746.
- Lindhout T, Hemker H. Anticoagulant mechanism of action of low molecular weight heparins. In: Doutremepuich C, ed. *Low Molecular Weight Heparins in Clinical Practice*. New York, NY: Marcel Dekker Inc; 1992:23–50.
- Lane DA, Denton J, Flynn AM, Thunberg L, Lindahl U. Anticoagulant activities of heparin oligosaccharides and their neutralization by platelet factor 4. *Biochem J*. 1984;218:725–732.
- Abildgaard U, Lindahl AK, Sandset PM. Heparin requires both antithrombin and extrinsic pathway inhibitor for its anticoagulant effect in human blood. *Haemostasis*. 1991;21:254–257.
- Hoppensteadt DA, Jeske W, Fareed J, Bermes EW Jr. The role of tissue factor pathway inhibitor in the mediation of the antithrombotic actions of heparin and low-molecular-weight heparin. *Blood Coagul Fibrinolysis*. 1995;6(suppl 1):S57–S64.
- Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation*. 1998;97: 251–256.
- Montalescot G, Philippe F, Ankri A, Vicaut E, Bearez E, Poulard JE, Carrie D, Flammang D, Dutoit A, Carayon A, Jardel C, Chevrot M, Bastard JP, Bigonzi F, Thomas D. Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: beneficial effects of enoxaparin: French Investigators of the ESSENCE Trial. *Circulation*. 1998;98:294–299.
- Antman EM, Handin R. Low-molecular-weight heparins: an intriguing new twist with profound implications. *Circulation*. 1998;98:287–289.

36. Fareed J, Jeske W, Hoppensteadt D, Clarizio R, Walenga JM. Low-molecular-weight heparins: pharmacologic profile and product differentiation. *Am J Cardiol*. 1998;82:3L-10L.
37. Beguin S, Lindhout T, Hemker HC. The mode of action of heparin in plasma. *Thromb Haemost*. 1988;60:457-462.
38. Beguin S, Mardiguian J, Lindhout T, Hemker HC. The mode of action of low molecular weight heparin preparation (PK10169) and two of its major components on thrombin generation in plasma. *Thromb Haemost*. 1989;61:30-34.
39. Mardiguian J. Methods of preparation of low molecular weight heparins. In: Doutremepuich C, ed. *Low Molecular Weight Heparins in Clinical Practice*. New York, NY: Marcel Dekker Inc; 1992:7-12.
40. Nightingale SL. Appropriate use of low-molecular weight heparins (LMWHs). *JAMA*. 1993;270:1672.
41. Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AGG, van der Meer J, Olaisson E, Undeland S, Ludwig K, for the FRIC Investigators. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease: Fragmin in Unstable Coronary Artery Disease Study (FRIC). *Circulation*. 1997;96:61-68.
42. Verheugt FWA. Hotline sessions at the 20th European Congress of Cardiology. *Eur Heart J*. 1999;20:7-10.
43. FRISC Study Group. Low molecular weight heparin (Fragmin) during instability in coronary artery disease (FRISC). *Lancet*. 1996;347:561-568.
44. Antman EM, for the TIMI 9A Investigators. Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. *Circulation*. 1994;90:1624-1630.
45. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. A randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation*. 1994;90:1631-1637.
46. Neuhaus KL, von Essen R, Tebbe U, Jessel A, Heinrichs H, Mäurer W, Döring W, Harmjanz D, Kötter V, Kalhammer E, Simon E, Horacek T. Safety observations from the pilot phase of the randomized r-hirudin for improvement of thrombolysis (HIT-III) study: a study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte (ALK). *Circulation*. 1994;90:1638-1642.
47. Thrombin Inhibition in Myocardial Ischaemia (TRIM) study group. A low molecular weight, selective thrombin inhibitor, inogatran, vs heparin, in unstable coronary artery disease in 1209 patients: a double-blind, randomized, dose-finding study. *Eur Heart J*. 1997;18:1416-1425.
48. Wallentin L. New antithrombotic treatment in unstable coronary syndrome—for whom? *Lancet*. 1999;353:423-424.
49. Antman EM, for the TIMI 9B Investigators. Hirudin in acute myocardial infarction: thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. *Circulation*. 1996;94:911-921.
50. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med*. 1996;335:775-782.
51. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularization procedures in patients with acute myocardial ischemia without ST elevation: a randomised trial. *Lancet*. 1999;353:429-438.
52. Rao AK, Sun L, Chesebro JH, Fuster V, Harrington RA, Schwartz D, Gallo P, Matos D, Topol EJ, for the Hirudin in Unstable Angina Trial. Distinct effects of recombinant desulfatohirudin (Revasc) and heparin on plasma levels of fibrinopeptide A and prothrombin fragment F1.2 in unstable angina: a multicenter trial. *Circulation*. 1996;94:2389-2395.
53. Mark DB, Cowper PA, Berkowitz SD, Davidson-Ray L, DeLong ER, Turpie AGG, Califf RM, Weatherley B, Cohen M. Economic assessment of low-molecular-weight heparin (enoxaparin) versus unfractionated heparin in acute coronary syndrome patients: results from the ESSENCE randomized trial. *Circulation*. 1998;97:1702-1707.