CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-138

20-164 S-075

DIVISION DIRECTOR MEMO

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 22-138 (enoxaparin in TIMI-28)

Sponsor: Sanofi-Aventis

Review date: 30 May 2007

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-138
DCaRP/Pease-Fye/U
OB/Lawrence
OCP/Hinderling/Zhu/Wang

Enoxaparin is a low-molecular-weight heparin with factor Xa inhibitory activity approved for use to prevent thromboembolic disease in patients with DVT or undergoing limb surgery and for use in acute coronary syndrome. The supplement described below was administratively considered a separate NDA since it was reviewed in a different division than the earlier indications.

The description here is based upon a CMC review by Dr. Srinivasachar (11 May 2007), a clinical pharmacology review by Drs. Hinderling and Zhu (11 April 2007), an amended pharmacometrics review by Drs. Zhu and Wang (16 May 2007), a clinical review by Dr. U (28 March 2007) and a statistical review by Dr. Lawrence (15 March 2007). This supplement is intended to support an indication for use of enoxaparin in the immediate period following myocardial infarction. Although there have been 7 studies in this setting, 4 were open-label (ASSENT 3, ASSENT 3+, TIMI-23, HART II), one had an angiographic end point (AMI-SK), and one was conducted among patients not receiving thrombolysis (TETAMI); none of these 6 showed a reduction in death or recurrent MI. Thus, for the most part, the supplement is supported by the seventh study, ExTRACT or TIMI-25.

There is no new formulation, and no issue with the proposed new IV route of administration. There are no pre-clinical issues and no pre-clinical reviews. There are no issues with manufacturing. Pediatric studies under PREA were waived, because the condition is rare in children. Financial disclosure was adequate.

In TIMI-25, subjects presenting within 6 hours of onset of symptoms and who were eligible for thrombolysis (streptokinase, alteplase, reteplase, or tenecteplase—all approved for use in the US) were randomized evenly to enoxaparin 30 mg bolus then 1 mg/kg BID SC for 8 days or hospital discharge[1] or to heparin 60 U/kg bolus and 12 U/kg/h IV for 2 days (considered to be standard of care) in a randomized, double-blind, double-dummy design, on a background including low-dose aspirin, beta-blockers, and ACE inhibitors.

The primary end point was all-cause death or recurrent MI at 30 days; total follow-up was 1 year. Diagnosis of MI followed ACC guidelines (see page 104 of the medical review), and, although it contains provisions to reduce sensitivity near the index MI, PCI, or CABG, it picks up events with relatively small clinical significance (biomarker elevation above ULN with chest pain or ECG changes, if the index event did not exceed ULN). The study was designed as a superiority trial.

---

[1] *Subjects over age 75 received no bolus and only 0.75 mg/kg BID.*

TIMI-25 was conducted in 47 countries between 2002 and 2005. Overall enrollment (mITT) was 10,256 to enoxaparin and 10,223 to heparin. There are no concerns regarding study conduct. Overall, the event rates at 30 days were 9.9% on enoxaparin and 12% on heparin, a 17% risk reduction ($p<0.000003$ by proportions, $p<0.001$ by time to event). Most first events were deaths, 665 on enoxaparin and 715 on heparin, a favorable trend, but not statistically significant ($p=0.15$ at 30 days). Although there were fewer nonfatal recurrent infarctions as first events, 352 on enoxaparin and 508 on heparin, the difference was highly statistically significant ($p<0.001$) and is mostly responsible for the statistical significance of the composite result. Corresponding numbers for total deaths within 30 days were 708 vs. 765 ($p=0.11$).

The main secondary end point was time to death, MI, or urgent revascularization, for which there was a 19% risk reduction on enoxaparin ($p<0.0001$).

The sponsor's time-to-event analysis for the primary end point is shown in Figure 1.

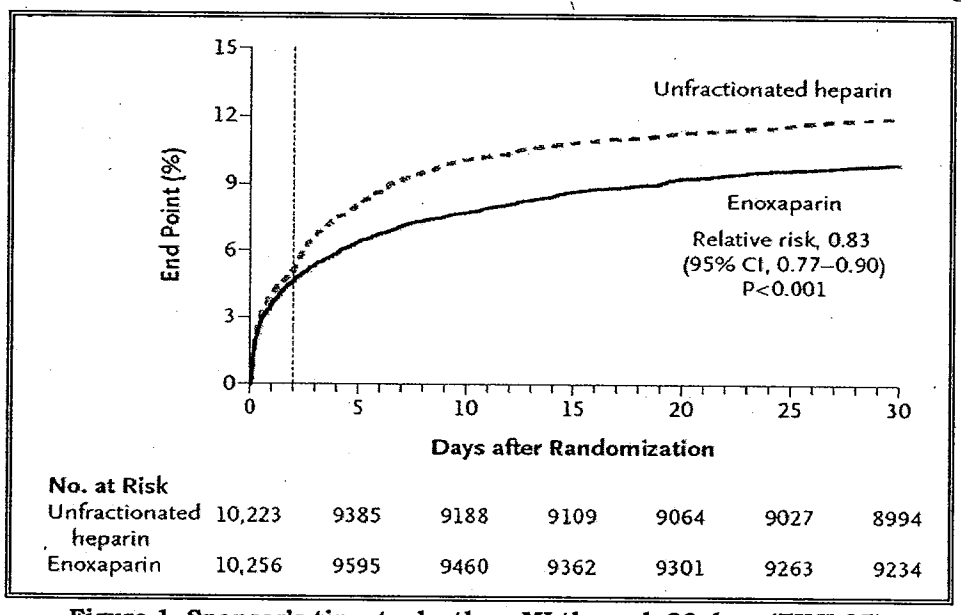

Figure 1. Sponsor's time to death or MI through 30 days (TIMI-25).
The dashed line marks the nominal time of withdrawal of heparin.

The first 4 days are shown in greater detail in Figure 2[2].

[2] *All of the analyses I performed look slightly different from those of the sponsor and the statisitical reviewer. According to the DEMO dataset, there were 20583 subjects enrolled and 20523 subjects randomized. Dataset USMA also has records for 20583 subjects, but assigns randomization to enoxaparin or heparin to 20506 subjects, although 20523 subjects received treatment with enoxaparin or heparin. I do not know how either of these numbers get reduced to the sponsor's mITT count of 20479. However, as will be seen, my interest in duration of treatment led me to exclude subjects for whom a duration of treatment was incalculable—there is no start date for 264 subjects on heparin and for 265 subjects on enoxaparin.*

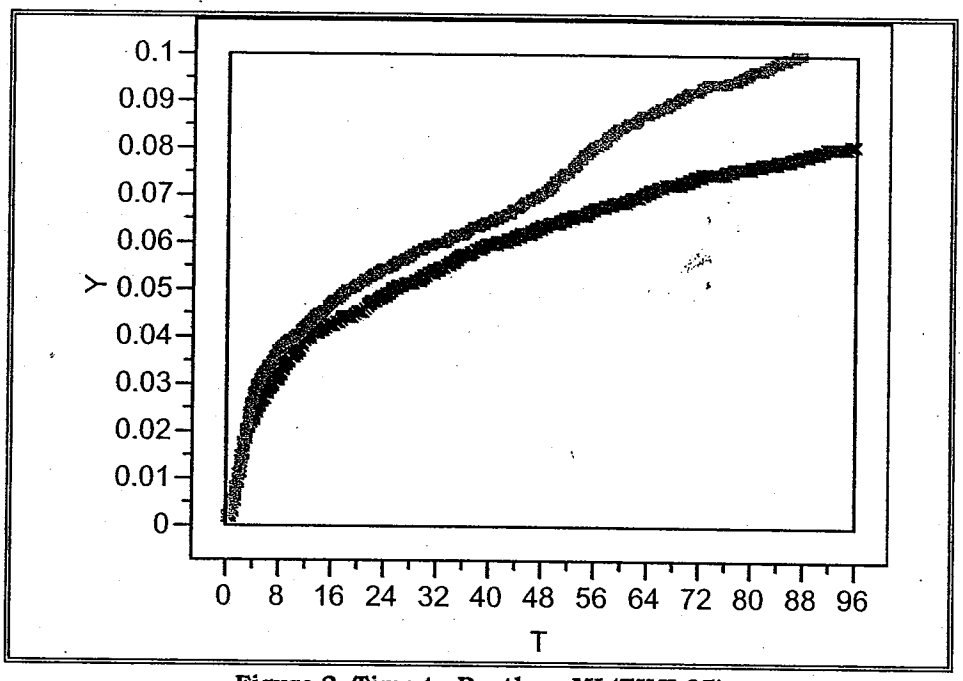

Figure 2. Time to Death or MI (TIMI-25)

The figure shows time to death or MI during the first 96 hours for heparin (green) and enoxaparin (red) groups (this reviewer's analysis).

As part of this review, the data from enoxparin were fit with a two-exponential model (Figure 3 top). Data for heparin had to be fit piecewise to two exponentials, for hours 0-48 (Figure 3 middle) and hours 48-96 (Figure 3 bottom). Fitted parameters are shown in the table that follows the figure.

APPEARS THIS WAY ON ORIGINAL

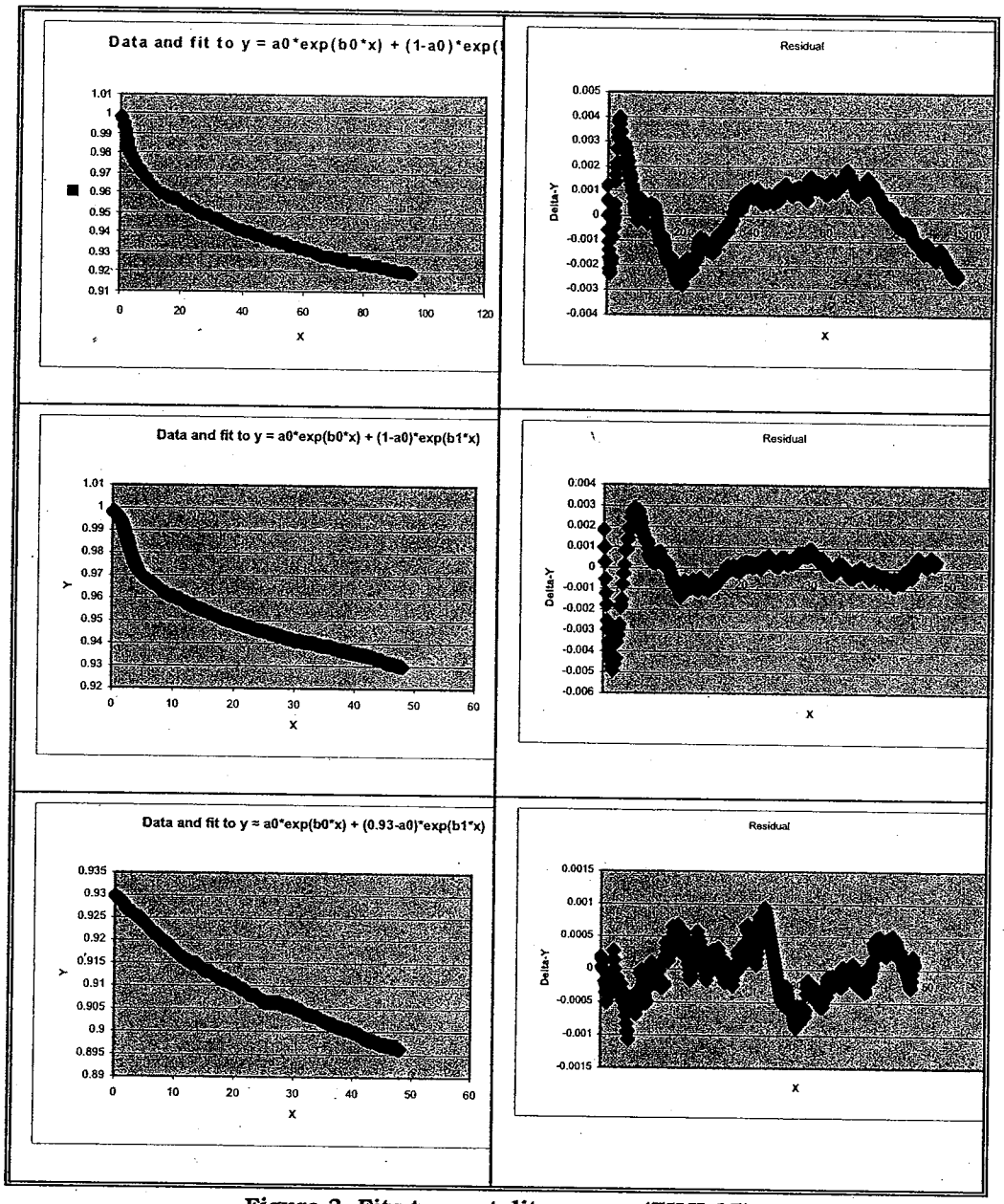

Figure 3. Fits to mortality curves (TIMI-25)

Figure shows fits (left) and residuals (right) for enoxaparin (top), the first 48 hours in the heparin group (middle) and hours 48-96 in the heparin group (bottom; this reviewer's analysis). The fitted curves in the left panel are in red and are generally not visible with the data points overlaid. The equations fit were $y = Ae^{-k_1 t} + (1 - A)e^{-k_2 t}$ **for the enoxaparin and first 48 hours of heparin and** $y = Ae^{-k_1 (t-48)} + (0.93 - A)e^{-k_2 (t-48)}$ **for hours 48-96 of heparin. The fitted parameters (unweighted least squares by SSQMIN) and their SDs are shown in the table below:**

	A	k_1	k_2
Enoxaparin	4.1E-2±1.2E-6	0.14±6.2E-5	4.7E-4±5.2E-10
Heparin 0-48 h	3.8E-2±2.0E-6	0.21±1.2E-4	7.0E-4±3.3E-9
Heparin 48-96 h	1.4E-2±8.8E-7	0.084±2.0E-5	4.6E-4±1.2E-9

The short-term time constants ($1/k_1$) are about 7 hours for enoxaparin and about 5 hours for heparin, indicative of some advantage of enoxaparin over heparin, even during the time they are both being administered. The long time constants ($1/k_2$) are very similar (about 90 days) for enoxaparin and heparin, indicative that there are no long-term effects.

The vast majority of the difference between the two groups develops in the first 24 hours following withdrawal of heparin and is maintained for the entire period of follow-up.

I expect that the main effect of a treatment is to increase the time to the next event (as opposed to reducing the number of people who are at risk for an event). Therefore, if the withdrawal effect seen with heparin were purely reversion to the untreated state, the time constant seen immediately post-withdrawal should be smaller than time constant seen in either treatment group near the initiation of treatment or it could be dominated by the pharmacodynamic time constant for heparin. The observed time constant seen immediately after withdrawing heparin is about 12 hours.

To remove the contribution of differences in time on treatment to the removal time constants, I examined the time to event curves for subjects beginning at the time of withdrawal of the corresponding agent. This also afforded an opportunity to look for a withdrawal effect with enoxaparin; one is not otherwise evident, but the distribution of withdrawal times is wider for enoxaparin than it is for heparin[3].

The results of these analyses are shown in Figure 4.

APPEARS THIS WAY ON ORIGINAL

[3] *See page 78 of the medical review.*

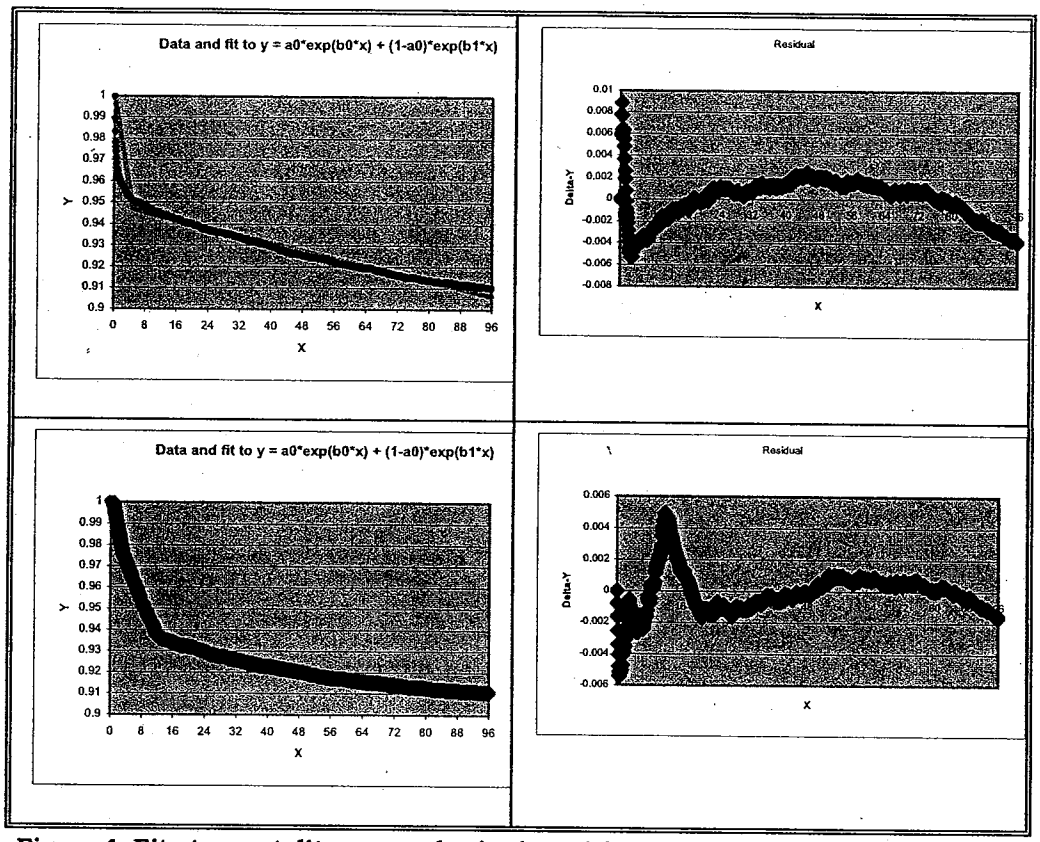

Figure 4. Fits to mortality curves beginning with study drug withdrawal (TIMI-25)

The figure was constructed in a manner similar to that used to generate Figure 3 (this reviewer's analysis). However, in this case, time zero is the point at which the corresponding treatments were discontinued. When that is done for heparin the result is shown in the top row. The fitted short time constant is about 1 h, but the fit is not very good, the actual time constant being somewhat shorter. Enoxaparin (bottom row) does not show the large set of events in the period following withdrawal, and it is relatively well fit by two exponentials. The fitted parameters are shown in the table below.

	A	k_1	k_2
Enoxaparin	6.9E-2±1.1E-6	0.134±3.3E-5	2.5E-4±5.4E-10
Heparin, from withdrawal	5.1E-2±2.0E-6	0.97±3.3E-3	4.8E-4±7.6E-10

The two smaller time constants are about what one might expect, based on the pharmacokinetic and pharmacodynamic properties of the two drugs. Enoxaparin has a pharmacodynamic half-life of 6-8 hours, compared with a time constant here of about 7 hours. Heparin has a half-life on the order of 1 hour, and a time constant here of an hour or less.

Drs. Zhu and Wang in pharmacometrics have reproduced some of these findings using survival analysis with time dependent treatment variable techniques, and it was these analyses that were sent to the sponsor in a Discipline Review Letter on 11 May 2007.

These analyses show the large and highly statistically significant increases in hazard following discontinuation of heparin and enoxaparin[4].

Although there was more bleeding on enoxaparin than on heparin, analyses of death plus MI plus non-fatal stroke or major hemorrhage or intracranial hemorrhage all have $p<0.001$ in favor of enoxaparin. There were only 23 nonfatal intracranial hemorrhages on enoxaparin and 27 on heparin. These results suggest that more aggressive anticoagulation might yield a better net clinical benefit.

I conclude that enoxaparin, as used in TIMI-25, is more effective than the TIMI-25 regimen of heparin in the reduction of death plus recurrent MI in patients receiving thrombolysis and enrolled within 6 hours of the index MI.

However, is heparin effective in this setting? Heparin does not have this indication. ACC guidelines[5] support this use and this regimen, but it has only class C evidentiary support (consensus opinion of experts; no randomized trials).

> *"Over 60 000 patients were enrolled in the randomized ISIS-3 (357) and GISSI-2 (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico)/International (353,354) trials comparing subcutaneous UFH with no routine heparin in conjunction with streptokinase, anistreplase, and alteplase. During the period in which UFH was given, a small reduction in mortality (4 to 5 lives per 1000 treated) was observed in ISIS-3; however, by 30 days, the 2 to 3 lives saved per 1000 treated was no longer statistically significant. A small excess rate of hemorrhagic stroke (1 to 2 per 1000 treated patients) was observed together with a larger excess in systemic bleeding (3 to 5 per 1000 patients), although total stroke rate was not significantly increased. A meta-analysis of these and several smaller studies enrolling a total of 68 000 patients showed that 5 lives were saved per 1000 patients treated with UFH in addition to streptokinase (537). In the GUSTO-I trial (25), more than 20 000 patients treated with streptokinase were randomly assigned to routine intravenous versus routine subcutaneous UFH. No significant differences were observed in death, reinfarction, or non-hemorrhagic stroke rates, whereas excess rates of systemic bleeding and hemorrhagic strokes (trend) were observed in the intravenous UFH group. There was a 36% crossover rate from subcutaneous to intravenous UFH in this trial."*

TIMI-25 provides some further evidence that can be interpreted as a benefit of heparin. Event rates for death plus MI increased just at the nominal time of heparin discontinuation (Figure 1, Figure 2, and the top of Figure 3). The increase is bigger and is more sharply focused around the time of the actual heparin withdrawal in subjects (top of Figure 4). While this might be some adverse response to discontinuation, a rebound phenomenon or some other effect more than unmasking the peri-MI risk, observation of a similar phenomenon upon discontinuation of enoxaparin (bottom of Figure 4), but with a longer time constant consistent with its pharmacodynamics, argues that this is a simple withdrawal phenomenon.

If these data support the use of enoxaparin in this clinical setting, they also support the use of heparin, and that the usual practice of discontinuing it after 2 days is very suboptimal[6].

---

[4] *The resulting hazard ratio is some averaged response over the whole period of observation, so it is not clear how to use it to explore the early vs. late components as I did above. Nevertheless, having the principal findings confirmed by competent modelers is reassuring.*

[5] *http://www.acc.org/qualityandscience/clinical/guidelines/STEMI/Guideline1/InitRecognition.htm*

As noted previously, although there were more deaths than MIs as end point events, the difference in deaths alone was not statistically significantly different between groups, but they did favor randomization to enoxaparin (p=0.11 at 30 days). The review team was concerned that this difference could have been attributable to small differences in the location (and hence clinical implications) of the index MIs. However, 42.8% of index MIs were anterior on enoxaparin and 43.6% were anterior on heparin. The sponsor also produced an analysis of 30-day mortality by treatment and location of index MI that suggests a nominal 4% reduction for enoxaparin in anterior MI and a nominal 12% reduction for enoxaparin in non-anterior MI. On the basis of this result, I concluded that the "lean" in favor of enoxaparin on mortality was a legitimate part of the study's overall findings, and it is included in the Indications.

The basis for diagnosis of recurrent MI in ExTRACT was complicated by proximal index MI and invasive therapy of the index MI. In some cases, the definitions could, and probably did, capture as end-point events some MIs with marginal clinical significance. A little more than half of recurrent MIs were diagnosed on the basis of biomarker elevations when the elevation associated with the index MI was less than the upper limit of normal (ULN). The next most common diagnostic pathway, about 25% of all recurrent MI events and with the largest apparent treatment effect, was a biomarker elevation at >18 hours when the biomarker was greater than ULN from the index MI.

Altogether, about half of the recurrent MIs were diagnosed on the basis of elevations in biomarkers only, but the treatment difference is almost identical for "chemical" MIs and MIs accompanied by ECG changes, as shown in the table below.

	Heparin	**Enoxaparin**	**E/H**
Biomarker only	357	232	0.65
Biomarker+ECG	371	253	0.68

In summary, ExTRACT provides compelling data that both heparin and enoxaparin are effective in reducing the combined end point of death or recurrent MI when used early after an index MI. Most of the observed effect is on MI, although death is the most common subsequent event. It is also quite clear that neither agent should be discontinued as soon as it was in ExTRACT, but how they should be continued is unclear. At some point, as one gets further from the index event, the risk of having a serious (i.e., fatal or intracranial) hemorrhage may exceed the value of remaining on treatment, but how far beyond 2 days this point occurs for heparin or how far beyond 8 days it is for enoxaparin is unknown. Enoxaparin, at least, is amenable to administration at home. The Lovenox supplement should be approved with duration of treatment unspecified.

There should be follow-up on two items. These findings should be published, and the label for heparin should incorporate this indication.

APPEARS THIS WAY ON ORIGINAL

---

[6] *I have not done so, but it should be possible to use the post-withdrawal data to estimate how long patients remain at increased risk for events as a result of an MI. With that information, one could design a rational strategy for how long to treat with heparin or enoxaparin. It would also be of some interest to look for heparin withdrawal effects in ISIS-3 and GISSI-2*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
5/30/2007 03:12:30 PM
MEDICAL OFFICER