

# Urgent AAA Repair Poses Biggest Death Risk

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VIENNA — Patients who underwent urgent or emergency repair of an abdominal aortic aneurysm had the worst survival rate among patients having open vascular surgery in a review of more than 2,700 patients at one center.

The greatest threat to survival for all patients having open vascular surgery were cerebrovascular and cardiovascular events,

which were responsible for 76% of all deaths that occurred immediately following surgery, Dr. Gijs M.J.M. Welten and his associates said in a poster at the annual congress of the European Society of Cardiology. In addition, patients with cardiac complications during or immediately after vascular surgery have an increased risk of long-term death from all causes and chronic complications.

The study included 2,730 vascular surgery patients at Erasmus University in

Rotterdam, the Netherlands, during a 13-year period. There were 1,047 patients having lower-limb reconstructive procedures, 923 undergoing elective infrarenal abdominal aortic aneurysm (AAA) repair, 560 having carotid endarterectomy (CEA), and 200 having urgent/emergency AAA repair. Overall perioperative mortality was 6%.

The perioperative mortality rate was by far the highest in the urgent or emergency AAA repair group, at 29%. Perioperative deaths occurred at a 6% rate in the

elective AAA repair group, 3% in those having lower-limb reconstructions, and 1% in the CEA group, reported Dr. Welten, a researcher in the department of vascular surgery at Erasmus University.

Long-term survival was also the worst for patients with urgent or emergency AAA repair: Their 5-year survival rate was close to 40%, compared with about 60% in both the elective AAA repair and lower-limb surgery groups, and about 80% in the CAE group. ■

## Hemorrhage

The incidence of major hemorrhagic complications during Lovenox treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with Lovenox Injection [see Tables 2 to 7].

Table 6

| Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction | Dosing Regimen                          |  |
|---|---|--|
|   | Lovenox <sup>1</sup><br>1 mg/kg q12h SC | Heparin <sup>1</sup><br>aPTT Adjusted IV Therapy |
| Indication  |   |  |
| Unstable Angina and Non-Q-Wave MI <sup>2,3</sup>                                | n = 1578<br>17 (1%)                     | n = 1529<br>18 (1%)                              |

<sup>1</sup> The rates represent major bleeding on study medication up to 12 hours after dose.

<sup>2</sup> Aspirin therapy was administered concurrently (100 to 325 mg per day).

<sup>3</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by  $\geq 3$  g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Table 7

| Major Bleeding Episodes in acute ST-segment Elevation Myocardial Infarction | Dosing Regimen   |  |
|---|--|--|
|   | Lovenox <sup>1</sup><br>Initial 30-mg IV bolus followed by 1 mg/kg q12h SC | Heparin <sup>1</sup><br>aPTT Adjusted IV Therapy |
| Indication  |  |  |
| acute ST-segment Elevation Myocardial Infarction                            | n = 10176<br>n (%)   | n = 10151<br>n (%)                               |
| - Major bleeding (including ICH) <sup>2</sup>                               | 211 (2.1)  | 138 (1.4)  |
| - Intracranial hemorrhages (ICH)  | 84 (0.8)   | 66 (0.7)   |

<sup>1</sup> The rates represent major bleeding (including ICH) up to 30 days.

<sup>2</sup> Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by  $\geq 5$  g/dL. ICH were always considered major.

## Thrombocytopenia:

[See *Warnings and Precautions* (5.5)]

## Elevations of Serum Aminotransferases

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox should be interpreted with caution.

## Local Reactions

Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox.

## Adverse Events in Lovenox-Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction:

Non-hemorrhagic clinical events reported to be related to Lovenox therapy occurred at an incidence of  $\leq 1\%$ .

Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox than in patients treated with IV heparin.

Serious adverse events with Lovenox or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox group are provided below (irrespective of relationship to drug therapy) [see Table 12].

Table 12

| Serious Adverse Events Occurring at $\geq 0.5\%$ Incidence in Lovenox-Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction | Dosing Regimen             |                                     |
|---|----------------------------|-------------------------------------|
|   | Lovenox<br>1 mg/kg q12h SC | Heparin<br>aPTT Adjusted IV Therapy |
| Adverse Event   | n = 1578<br>n (%)          | n = 1529<br>n (%)                   |
| Atrial fibrillation   | 11 (0.70)                  | 3 (0.20)                            |
| Heart failure   | 15 (0.95)                  | 11 (0.72)                           |
| Lung edema  | 11 (0.70)                  | 11 (0.72)                           |
| Pneumonia   | 13 (0.82)                  | 9 (0.59)                            |

## LOVENOX®

(enoxaparin sodium injection)

## Adverse Reactions in Lovenox-Treated Patients With acute ST-segment Elevation Myocardial Infarction:

In a clinical trial in patients with acute ST-segment elevation myocardial infarction, the only additional possibly related adverse reaction that occurred at a rate of at least 0.5% in the Lovenox group was thrombocytopenia (1.5%).

## Post-Marketing Experience

There have been reports of epidural or spinal hematoma formation with concurrent use of Lovenox and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis.

Local reactions at the injection site (e.g., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (e.g., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytosis, and thrombocytopenia with thrombosis [see *Warnings and Precautions* (5.5)] have been reported. Very rare cases of hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate reliably their frequency or to establish a causal relationship to drug exposure.

## DRUG INTERACTIONS

Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring [see *Warnings and Precautions* (5.9)].

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Pregnancy Category B

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes the potential of Lovenox to increase the risk of developmental abnormalities above background risk.

#### Fetal Risk Summary

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox contains 15 mg benzyl alcohol per 1 mL as a preservative [see *Warnings and Precautions* (5.8)].

#### Clinical Considerations

It is not known if either dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see *Warnings and Precautions* (5.7) and *Use in Specific Populations* (8.6)]. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches [see *Boxed Warning*]. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

#### Data

•*Human Data* - There are no adequate and well-controlled studies in pregnant women.

A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.