

# Predictors of Postsurgery Renal Failure Identified

BY DAMIAN McNAMARA  
Miami Bureau

ORLANDO — Independent risk predictors have been identified that help to target the 1% of patients who develop acute renal failure following general surgery.

Eleven independent risk factors predicted acute renal failure in a logistic regression model performed by Dr. Sachin Kheterpal and his colleagues at the University of Michigan, Ann Arbor.

The researchers reviewed 150,490 operations in the American College of Surgeons' National Surgical Quality Improvement Program data set performed over a 1-year period (2005-2006) and calculated hazard ratios to compare the likelihood of acute renal failure between patients with and without each risk factor.

Preoperative renal insufficiency was associated with the greatest hazard ratio, 8.5. Other risk factors were heart failure (HR 7.6), ascites (HR 6.4), myocardial infarction

within 6 months (HR 5.7), high-risk surgery (HR 3.8), aged 58 years or older (HR 3.2), hypertension requiring chronic medication (HR 3.1), male sex (HR 1.9), diabetes mellitus (HR 2.6), previous cardiac procedure (HR 2.2), and emergency surgery (HR 2.7), Dr. Kheterpal said during a poster discussion session at the annual meeting of the American Society of Anesthesiologists.

Dr. Kheterpal and his associates then took the list one step further.

They developed a "robust" risk-prediction model—an index based on the number of preoperative risk factors. The association between these risk factors and ARF incidence was as follows: one to two risk factors, 0.2% ARF incidence; three risk factors, 1% incidence; four factors, 2% incidence; five factors, 3.3% incidence; and six factors, 9% incidence.

"This is really surprising when you look at how many older patients we have, who are also men, and have hypertension and



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Brief Summary of full prescribing information

## WARNING: SPINAL / EPIDURAL HEMATOMAS

**When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.**

**The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.**

**Monitor patients for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.**

**Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [see Warnings and Precautions (5.1) and Drug Interactions (7)].**

## 1 INDICATIONS AND USAGE

### 1.1 Prophylaxis of Deep Vein Thrombosis

Lovenox is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- in patients undergoing abdominal surgery who are at risk for thromboembolic complications [see *Clinical Studies* (14.1)].
- in patients undergoing hip replacement surgery, during and following hospitalization.
- in patients undergoing knee replacement surgery.
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

### 1.2 Treatment of Acute Deep Vein Thrombosis

Lovenox is indicated for:

- the **inpatient treatment** of acute deep vein thrombosis **with or without pulmonary embolism**, when administered in conjunction with warfarin sodium;
- the **outpatient treatment** of acute deep vein thrombosis **without pulmonary embolism** when administered in conjunction with warfarin sodium.

### 1.3 Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial Infarction

Lovenox is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

### 1.4 Treatment of acute ST- segment Elevation Myocardial Infarction (STEMI)

Lovenox has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute STEMI receiving thrombolysis and being managed medically or with Percutaneous Coronary Intervention (PCI).

## 4 CONTRAINDICATIONS

- Active major bleeding.
- Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium.
- Known hypersensitivity to enoxaparin sodium (*e.g.*, pruritus, urticaria, anaphylactic/anaphylactoid reactions) [see *Adverse Reactions* (6.2)].
- Known hypersensitivity to heparin or pork products.
- Known hypersensitivity to benzyl alcohol (which is in only the multi-dose formulation of Lovenox).

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Increased Risk of Hemorrhage

Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs [see *boxed Warning, Adverse Reactions* (6.2) and *Drug Interactions* (7)].

Lovenox should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

Bleeding can occur at any site during therapy with Lovenox. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

### 5.2 Percutaneous Coronary Revascularization Procedures

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between Lovenox doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC Lovenox. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation [see *Dosage and Administration* (2.1)].

### 5.3 Use of Lovenox with Concomitant Medical Conditions

Lovenox should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction and hemorrhage.

### 5.4 History of Heparin-induced Thrombocytopenia

Lovenox should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

### 5.5 Thrombocytopenia

Thrombocytopenia can occur with the administration of Lovenox.

Moderate thrombocytopenia (platelet counts between 100,000/mm<sup>3</sup> and 50,000/mm<sup>3</sup>) occurred at a rate of 1.3% in patients given Lovenox, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials.

Platelet counts less than 50,000/mm<sup>3</sup> occurred at a rate of 0.1% in patients given Lovenox, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm<sup>3</sup>, Lovenox should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death [see *Warnings and Precautions* (5.4)].

### 5.6 Interchangeability with Other Heparins

Lovenox cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

### 5.7 Pregnant Women with Mechanical Prosthetic Heart Valves

The use of Lovenox for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg twice daily) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed [see *Use in Specific Populations* (8.6)].

### 5.8 Benzyl Alcohol

Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed [see *Use in Specific Populations* (8.1)].

### 5.9 Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox in patients with significant renal impairment. If during Lovenox therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox [see *Clinical Pharmacology* (12.3)].

diabetes—[they] have a fairly good chance of acute renal failure,” Dr. Kheterpal said. The prediction index could be the foundation for informed consent in these patients, he added.

The investigators based their conclusions on information prospectively gathered by trained nurse data collectors from 121 centers, including community and academic centers.

“The data collection system is very detailed. It includes 30-day outcomes, even if the patient leaves and dies at another hospital,” said Dr. Kheterpal of the department of anesthesiology at the university.

Excluded from the study were patients

with preexisting acute renal failure or those requiring dialysis; patients undergoing any nongeneral surgery procedures, including cases performed by vascular, cardiac, urology, ophthalmology, podiatry, or obstetric services; outpatients; and general surgery patients on whom concurrent urology procedures were performed.

Data for 68,147 operations were assessed further. Of these, 712 patients (1%) experienced acute renal failure (ARF) postoperatively. ARF was defined as progressive renal insufficiency—an increase in serum creatinine of 2 mg/dL or more above baseline—or a requirement for postoperative dialysis.

This 1% incidence of acute kidney injury is very close to a previously reported incidence of 0.8% (Anesthesiology 2007; 107:892-902). The use of vasopressors and diuretics was among the factors associated with ARF in this single-center study of more than 65,000 noncardiac procedures. In addition, patients who experienced ARF had increased 30-day, 60-day, and 1-year all-cause mortality.

A meeting attendee asked Dr. Kheterpal if he and other physicians at the University of Michigan are doing anything different based on the study findings. “Yes, we are very aggressive now about hydration. And we’re very aggressive now about not

using diuretics intraoperatively. I’ve gotten into fights about that,” he said.

Having a study with nearly 70,000 general surgery cases allowed Dr. Kheterpal and his associates to do an internal validation study.

He acknowledged that there are also many limitations because the study is based on a national data set. For example, intraoperative data beyond length of each procedure were “very limited,” and there was no information on the use of preoperative medications.

“Next at our institution we will be looking at alternative serum and urinary biomarkers of ARF,” Dr. Kheterpal said. ■

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

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 2**  
**Major Bleeding Episodes Following Abdominal and Colorectal Surgery<sup>1</sup>**

Indications	Dosing Regimen	
	Lovenox 40 mg q.d. SC	Heparin 5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

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

**Table 3**  
**Major Bleeding Episodes Following Hip or Knee Replacement Surgery<sup>1</sup>**

Indications	Dosing Regimen		
	Lovenox 40 mg q.d. SC	Lovenox 30 mg q12h SC	Heparin 15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis <sup>2</sup>		n = 786 31 (4%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis Peri-operative Period <sup>3</sup>	n = 288 4 (2%)		
Extended Prophylaxis Period <sup>4</sup>	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis <sup>2</sup>		n = 294 3 (1%)	n = 225 3 (1%)

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

<sup>2</sup> Lovenox 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

<sup>3</sup> Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

<sup>4</sup> Lovenox 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox patients versus 1.8% of the placebo patients.

**Table 4**  
**Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness<sup>1</sup>**

Indications	Dosing Regimen		
	Lovenox <sup>2</sup> 20 mg q.d. SC	Lovenox <sup>2</sup> 40 mg q.d. SC	Placebo <sup>2</sup>
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of  $\geq$  2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

<sup>2</sup> The rates represent major bleeding on study medication up to 24 hours after last dose.

**Table 5**  
**Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment<sup>1</sup>**

Indication	Dosing Regimen <sup>2</sup>		
	Lovenox 1.5 mg/kg q.d. SC	Lovenox 1 mg/kg q12h SC	Heparin aPTT Adjusted IV Therapy
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

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

<sup>2</sup> All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox or standard heparin therapy and continuing for up to 90 days.

**Table 6**  
**Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction**

Indication	Dosing Regimen	
	Lovenox <sup>1</sup> 1 mg/kg q12h SC	Heparin <sup>1</sup> aPTT Adjusted IV Therapy
Unstable Angina and Non-Q-Wave MI <sup>2,3</sup>	n = 1578 17 (1%)	n = 1529 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**

Indication	Dosing Regimen	
	Lovenox <sup>1</sup> Initial 30-mg IV bolus followed by 1 mg/kg q12h SC	Heparin <sup>1</sup> aPTT Adjusted IV Therapy
acute ST-segment Elevation Myocardial Infarction	n = 10176 n (%)	n = 10151 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.

Other

Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox group, are provided below [see Tables 8 to 11].