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

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[1]

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 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[1]

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 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.

[2] Lovenox 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

[3] Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

[4] 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[1]

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥ 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.

[2] 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[1]

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

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

[2] 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

	Dosing Regimen	
	Lovenox[1]	Heparin[1]
Indication	1 mg/kg q12h SC	aPTT Adjusted IV Therapy
Unstable Angina and Non-Q-Wave MI[2,3]	n = 1578 17 (1%)	n = 1529 18 (1%)

[1] The rates represent major bleeding on study medication up to 12 hours after dose.

[2] Aspirin therapy was administered concurrently (100 to 325 mg per day).

[3] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥ 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[1]	Heparin[1]
Indication	Initial 30-mg IV bolus followed by 1 mg/kg q12h SC	aPTT Adjusted IV Therapy
acute ST-segment Elevation Myocardial Infarction	n = 10176 n (%)	n = 10151 n (%)
- Major bleeding (including ICH)[2]	211 (2.1)	138 (1.4)
- Intracranial hemorrhages (ICH)	84 (0.8)	66 (0.7)

[1] The rates represent major bleeding (including ICH) up to 30 days

[2] Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by ≥ 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].