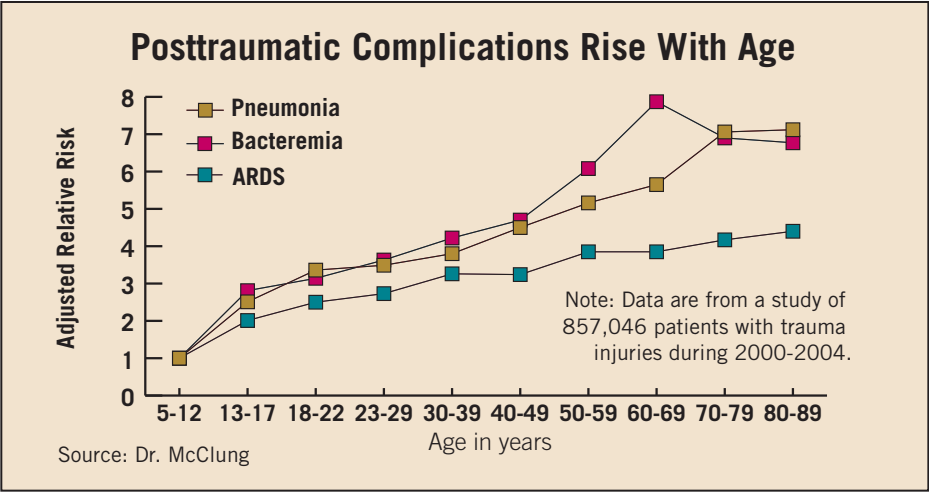




Complications Resulting From Trauma Increase With Age

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — The risks of pneumonia and other serious infectious and septic complications of traumatic injury climb steadily in age-dependent fashion. This finding from an analysis of data from the world’s largest trauma registry suggests that the immune response to trauma varies with age and that the neu-

roendocrine axis is involved in this immunoactivation, Dr. Christian D. McClung observed at the annual scientific sessions of the American Heart Association. He reported on 857,046 patients aged 5-89 years included in the American College of Surgeons National Trauma Data Bank for 2000-2004. The patients were hospitalized at more than 600 participating trauma centers, with a median 3-day length of stay. The mean age of the study popula-

Table 8
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients¹ Undergoing Abdominal or Colorectal Surgery

Adverse Event	Dosing Regimen			
	Lovenox 40 mg q.d. SC n = 1228 %		Heparin 5000 U q8h SC n = 1234 %	
	Severe	Total	Severe	Total
Hemorrhage	<1	7	<1	6
Anemia	<1	3	<1	3
Ecchymosis	0	3	0	3

¹ Excluding unrelated adverse events.

Table 9
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients¹ Undergoing Hip or Knee Replacement Surgery

Adverse Event	Dosing Regimen				
	Lovenox 40 mg q.d. SC		Lovenox 30 mg q12h SC	Heparin 15,000 U/24h SC	Placebo q12h SC
	Peri-operative Period n = 288 ² %	Extended Prophylaxis Period n = 131 ³ %	n = 1080 %	n = 766 %	n = 115 %
	Severe Total	Severe Total	Severe Total	Severe Total	Severe Total
Fever	0 8	0 0	<1 5	<1 4	0 3
Hemorrhage	<1 13	0 5	<1 4	1 4	0 3
Nausea			<1 3	<1 2	0 2
Anemia	0 16	0 <2	<1 2	2 5	<1 7
Edema			<1 2	<1 2	0 2
Peripheral edema	0 6	0 0	<1 3	<1 4	0 3

¹ Excluding unrelated adverse events.
² Data represents Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox peri-operatively in an unblinded fashion in one clinical trial.
³ Data represents Lovenox 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Table 10
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Medical Patients¹ With Severely Restricted Mobility During Acute Illness

Adverse Event	Dosing Regimen	
	Lovenox 40 mg q.d. SC n = 360 %	Placebo q.d. SC n = 362 %
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

¹ Excluding unrelated and unlikely adverse events.

Table 11
Adverse Events Occurring at ≥2% Incidence in Lovenox-Treated Patients¹ Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

Adverse Event	Dosing Regimen					
	Lovenox 1.5 mg/kg q.d. SC n = 298 %		Lovenox 1 mg/kg q12h SC n = 559 %		Heparin aPTT Adjusted I.V. Therapy n = 544 %	
	Severe	Total	Severe	Total	Severe	Total
Injection Site Hemorrhage	0	5	0	3	<1	<1
Injection Site Pain	0	2	0	2	0	0
Hematuria	0	2	0	<1	<1	2

¹ Excluding unrelated adverse events.

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 ≤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 ≥0.5% Incidence in Lovenox-Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction

Adverse Event	Dosing Regimen	
	Lovenox 1 mg/kg q12h SC n = 1578 n (%)	Heparin aPTT Adjusted IV Therapy n = 1529 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)

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%)

6.2 Postmarketing 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 postoperative 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. nodules, inflammation, oozing), systemic allergic reactions (e.g. pruritus, urticaria, anaphylactic/anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thrombocytopenia with thrombosis [see *Warnings and Precautions* (5.5)] have been reported. Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues). 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.

7 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)].

8 USE IN SPECIFIC POPULATIONS
8.1 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

tion was 40 years. Two-thirds were male. The mortality rate was 4.4%.

Pneumonia was a complication of trauma in 1.6% of cases, acute respiratory distress syndrome (ARDS) in 0.5%, and bacteremia in 0.13%, said Dr. McClung, an emergency physician at Los Angeles County-USC Medical Center, Los Angeles.

The risks of pneumonia, bacteremia, and ARDS rose with each decade of age in a multivariate logistic regression analysis adjusted for potential confounders including age, sex, injury severity score, trauma mechanism, and days on a ventilator. The 56,680 children aged 5-12 years served as the comparison group. (See box, page 14). ■

Panel Votes in Favor of MRSA Antimicrobial

BY ELIZABETH MECHCATIE
Senior Writer

COLLEGE PARK, MD. — Clinical trial data show that the antibiotic telavancin is safe and effective for treating complicated skin and skin-structure infections, including those caused by methicillin-resistant *Staphylococcus aureus*, the majority of a federal advisory panel agreed.

The Food and Drug Administration's anti-infective drugs advisory committee voted 21-5 regarding the safety and effi-

cacy of telavancin, with those voting in favor saying that despite their concerns about nephrotoxicity, QT prolongation, and possible teratogenic effects associated with the drug, they believed these risks were manageable.

The panel voted 18-5, with 3 abstentions, that there could be clinical situations in which the benefits of telavancin in pregnant women would outweigh its risks. All but one panelist agreed that a risk management strategy was needed to prevent unintended use in pregnant

women or in women of childbearing potential.

Theravance Inc., the drug's manufacturer, has developed a risk management plan designed to minimize pregnancy exposures, the risk of nephrotoxicity, and the risk related to QT prolongation, and has proposed that the drug not be used during pregnancy, unless the benefit to the patient outweighs the potential risks to the fetus. The plan also includes recommendations to adjust the dose based on creatinine clearance and to avoid the drug in patients with conditions such as congenital long QT syndrome and uncompensated heart failure.

"I voted 'yes,' because I think vancomycin is a dying drug, and I see vancomycin resistance all the time," said panelist Dr. W. Kemper Alston, who is at the University of Vermont, Burlington. Those voting "no" on the safety and efficacy question cited concerns about the association of the drug with more than one toxicity.

"Safety concerns in multiple systems, not just one, complicate risk management," said the acting panel chair, Dr. L. Barth Reller, professor of medicine and pathology, Duke University, Durham, N.C. The mechanism of action was not that different from vancomycin, he added, so it is unclear how much its use would affect the problem of increasing resistance.

The FDA usually follows the advice of its advisory panels, which is not binding. The proposed indication for telavancin is for the treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis*.

Telavancin, a bactericidal lipoglycopeptide antibiotic that has bactericidal activity against most gram-positive bacteria, is administered intravenously once daily. It has a dual mechanism of action: It inhibits cell wall synthesis, like vancomycin, but also disrupts the function of the bacterial membrane, according to Theravance.

For approval, the company submitted the results of two double-blind, randomized phase III noninferiority studies of almost 1,800 adults with cSSSI caused by gram-positive bacteria, enrolled in 2005-2006. (Half of the 1,320 patients with microbiological confirmation of pathogens at baseline had MRSA.) The patients were treated with telavancin or vancomycin. The FDA and company analyses indicated that in both studies, treatment with telavancin for 7-14 days was as effective as with vancomycin—the current standard of care.

Adverse events with telavancin were mostly mild or moderate. The rate of renal adverse events among those on telavancin was 3.4%, compared with 1.2% among those on vancomycin; the rate of severe renal adverse events was also higher among those on telavancin (1.2% vs. 0.4%).

Cardiac-related severe adverse events were similar among those on telavancin and vancomycin (11% in both groups). Four patients on telavancin and six on vancomycin had a fatal cardiac event; two deaths in the telavancin group were possibly related to the drug, according to the FDA. ■

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.

A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been conducted [see *Warnings and Precautions* (5.7)].

• **Animal Data** - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m²/day and 410 mg/m²/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness of Lovenox in pediatric patients have not been established.

8.5 Geriatric Use

Prevention of DVT in hip, knee and abdominal surgery; Treatment of DVT; Prevention of ischemic complications of unstable angina and non-Q-Wave myocardial infarction

Over 2800 patients, 65 years and older, have received Lovenox in pivotal clinical trials. The efficacy of Lovenox in the geriatric (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between geriatric and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox were employed. The incidence of bleeding complications was higher in geriatric patients as compared to younger patients when Lovenox was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox between geriatric and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Lovenox should be used with care in geriatric patients who may show delayed elimination of enoxaparin. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered [see *Warnings and Precautions* (5.9) and *Clinical Pharmacology* (12.3)].

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

In the clinical study for treatment of acute STEMI, there was no evidence of difference in efficacy between patients ≥75 years of age (n = 1241) and patients less than 75 years of age (n=9015). Patients ≥75 years of age did not receive a 30-mg IV bolus prior to the normal dosage regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours [see *Dosage and Administration* (2.3)]. The incidence of bleeding complications was higher in patients ≥65 years of age as compared to younger patients (<65 years).

8.6 Patients with Mechanical Prosthetic Heart Valves

The use of Lovenox has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism [see *Warnings and Precautions* (5.7)].

8.7 Renal Impairment

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)]. In patients with renal failure, treatment with enoxaparin has been associated with the development of hyperkalemia [see *Adverse Reactions* (6.2)].

8.8 Hepatic Impairment

The impact of hepatic impairment on enoxaparin's exposure and antithrombotic effect has not been investigated. Caution should be exercised when administering enoxaparin to patients with hepatic impairment.

8.9 Low-Weight Patients

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Accidental overdosage following administration of Lovenox may lead to hemorrhagic complications. Injected Lovenox may be largely neutralized by the slow IV injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of Lovenox may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

If at least 12 hours have elapsed since the last enoxaparin sodium injection, protamine administration may not be required; however, even with higher doses of protamine, the aPTT may remain more prolonged than following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of protamine sulfate injection products.

17 PATIENT COUNSELING INFORMATION

Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they are treated with Lovenox, and that they should report any unusual bleeding or bruising to their physician [see *Warnings and Precautions* (5.1, 5.5)].

Patients should inform physicians and dentists that they are taking Lovenox and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken [see *Warnings and Precautions* (5.3)].

Patients should inform their physicians and dentists of all medications they are taking, including those obtained without a prescription [see *Drug Interactions* (7)].

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