

POLICY & PRACTICE

Practice Revenues Down, Costs Up

In 2006, the total revenue per full-time equivalent physician declined by 0.72% for cardiologists, while operating costs per FTE increased by 3% to \$538,135, according to the recently published Medical Group Management Association cost survey. Operating costs are increasing largely because of a rise in practice overhead. The median total operating cost as a percentage of revenue has increased 12% since 2000, said MGMA. Sixty-nine percent of practices had total revenues of \$10 million or above; the biggest slice,

21% of practices, had revenues of \$10-\$15 million. Sixty percent operated at a profit and 35% operated at a loss; 4% broke even. According to the survey, to which 94 cardiology and thoracic surgery practices responded, 51% of cardiovascular practices still keep paper medical records; 39% have electronic health records, 9% use a document-imaging management system, and 1% employ another method. A large majority of practices offered ultrasound in the office, but most did not offer in-office cardiac MRI, computed tomography, or peripheral vascular CT.

America's Cholesterol on Target

Americans have met the Healthy People 2010 goal of a serum total cholesterol level of 200 mg/dL or less, according to the Centers for Disease Control and Prevention's National Center for Health Statistics. Using data from the National Health and Nutrition Examination Survey (NHANES), CDC determined that the age-adjusted mean total cholesterol level for adults over age 20 years was 199 mg/dL in 2005-2006, which is a drop from 204 mg/dL in 1999-2000. The decline was primarily in men over age 40 years and women over age 60 years; there wasn't much change for other age and sex groups during that time peri-

od, according to the CDC. However, women over age 60 years had higher cholesterol levels than men their age, and higher than any other group.

FDA Can't Fulfill Mission

Three members of the Food and Drug Administration's Science Board issued a damning report on the state of the agency, saying that "the agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities." The authors wrote that the FDA has become weak and unable to fulfill its mission because of the increasing number of demands put upon it and an inability to respond because of a lack of resources. "FDA's inability to keep up with scientific advances means that American lives are at risk," wrote the panelists, adding that the agency can't fulfill its mission "without substantial and sustained additional appropriations." The report was written by Gail Cassell, Ph.D., vice president of scientific affairs at Eli Lilly & Co.; Dr. Allen D. Roses, Jefferson-Pilot Corp. Professor of Neurobiology and Genetics at Duke University; and Dr. Barbara J. McNeil, head of the health care policy department at Harvard Medical School. Members of the Coalition for a Stronger FDA and the FDA Alliance urged Congress to heed the report's warnings. "FDA can't improve its science, prepare for the future, or protect American consumers without significant additional resources," said coalition member Don Kennedy, Ph.D., a former FDA commissioner and editor-in-chief of the journal *Science*, in a statement.

FDA Sets User Fees for DTC Ads

The FDA is charging drug companies about \$40,000 to review each of their direct-to-consumer television advertisements, according to a notice issued by the agency in December. Last September, Congress authorized FDA to create a user-fee program for the advisory review of DTC prescription-drug television advertisements. The program is voluntary; drug sponsors can choose whether to seek FDA advisory review of their ads before broadcast. However, if they seek review by the agency, they must pay the fee. The \$41,390 fee established for fiscal year 2008 is based on the number of ads slated for review and is expected to generate \$6.25 million in total revenues during the first year of the program.

Agency's Approval Plan Flawed

The Food and Drug Administration is considering new guidance that would allow drug companies to use journal articles to promote "potentially dangerous uses" of drugs and medical devices without prior FDA review and approval, according to a top lawmaker. Rep. Henry Waxman (D-Calif.), who chairs the House Committee on Oversight and Government Reform, urged the agency in a Nov. 30 letter to reconsider its draft guidance. "[It] would, in effect, allow drug and device companies to short-circuit FDA review and approval by sponsoring drug trials that are carefully constructed to deliver positive results and then using the results to influence prescribing patterns," he said. He asked the FDA for detailed information on development of the new policy.

—Alicia Ault

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.

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.

Pediatric Use

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

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).

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)].

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)].

LOVENOX®

(enoxaparin sodium injection)

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.

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)].

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.

CLINICAL PHARMACOLOGY

Mechanism of Action

Enoxaparin is a low molecular weight heparin which has antithrombotic properties.

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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Multiple-dose vials are also manufactured by DSM Pharmaceuticals, Inc.
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