



Critically ill patients who received epoetin alfa were no less likely to receive a red cell transfusion, said Dr. Howard Corwin, FCCP.

Results Mixed for Epoetin in Critically Ill

BY ELIZABETH MEHCATIE

Elsevier Global Medical News

Treatment with epoetin alfa reduced mortality in trauma patients but did not decrease the need for red cell transfusions and was associated with an increased risk of thrombotic vascular events in a prospective, randomized study of 1,460 critically ill surgical, medical, or trauma patients admitted to intensive care units.

Patients who received weekly injections of epoetin alfa for up to 3 weeks were no less likely to receive a red cell transfusion than those who received placebo, but they were at an increased risk of thrombotic events. Treatment was associated with lower

mortality, however, particularly among trauma patients, reported Dr. Howard Corwin, FCCP, of the Dartmouth-Hitchcock Medical Center, Lebanon, N.H., and his associates (*N. Engl. J. Med.* 2007;357:965-76).

The patients in the study were treated at 115 U.S. medical centers between December 2003 and June 2006. They received weekly subcutaneous injections of epoetin alfa (40,000 U) or placebo, weekly, for a maximum of 3 weeks. The injections started within 48 and 96 hours of admission to the intensive care unit, and the patients were followed for 140 days. All patients were age 18 years or older; the mean age was 50 years.

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COPD's Global Toll Is Far Greater Than Commonly Assumed

Study uncovers unexpected prevalence.

BY JONATHAN GARDNER

Elsevier Global Medical News

The burden of chronic obstructive pulmonary disease is underestimated worldwide, and there are higher levels and more advanced forms of the disease than have been reported, according to an international study documenting prevalence.

Researchers found that smoking and advanced age increased the likelihood of developing chronic obstructive pulmonary disease (COPD), but reported that the prevalence of COPD in people who have never smoked, as well as in younger patients, suggests that other factors—such as tuberculosis and exposure to particulates and fumes through occupation or the use of biomass fuels—may also play a role (*Lancet* 2007;370:741-50).

The study, from sites in 12 countries involving 9,425 subjects aged 40 years or older who were tested by spirometry,

found an overall prevalence of 10% for stage II or higher COPD (12% for men, and 9% for women), wrote Dr. A. Sonia Buist of Oregon Health and Science University, Portland, and her colleagues.

The sites were Adana, Turkey; Bergen, Norway; Cape Town, South Africa; Guangzhou, China; Hannover, Germany; Krakow, Poland; Lexington, Ky.; Manila, Philippines; Reykjavik, Iceland; Salzburg, Austria; Sydney, Australia; and Vancouver, B.C., Canada.

Across the sites, the likelihood of developing stage II COPD increased for smokers, with an odds ratio of 1.2 for each additional 10 pack-years (defined as the number of packs per day over the course of a year) the study found. For each additional 10 years of age, the odds ratio of developing stage II COPD was 1.94, the researchers wrote.

Past reviews of COPD data worldwide have found lower

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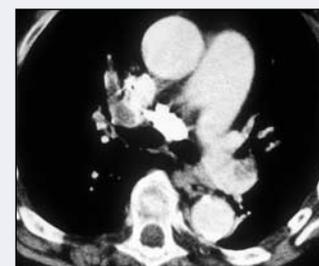
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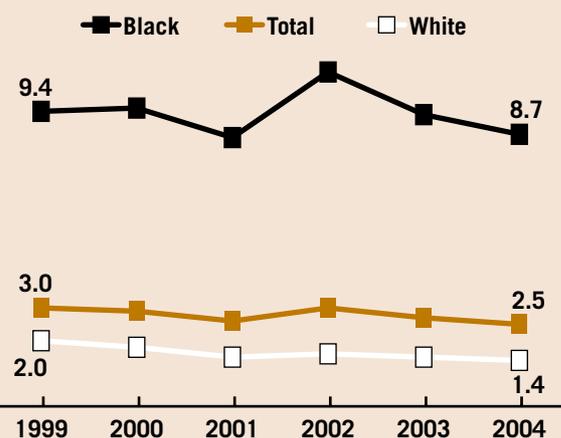
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VITAL SIGNS

Disparities in Asthma Deaths in Children

(mean mortality rate per 1,000,000 children aged 0-17 years)



Source: Centers for Disease Control and Prevention

Sleep Duration Linked to Mortality Risk

BY TIMOTHY F. KIRN

Elsevier Global Medical News

Both too much sleep and not enough sleep appear to be associated with increased mortality, according to a new longitudinal study.

Sleeping less than 6 hours per night or more than 9 hours per night was associated with almost twice the mortality risk of sleeping 6-8 hours per night, according to an analysis of sleep data from a prospective cohort study of more than 10,000 British civil servants.

The findings were recently presented at a meeting of the British Sleep Society, and the research article has been accepted for publication in the journal *Sleep* (www.journalsleep.org/Accepted.aspx).

The investigators found that a

decrease in the amount of time slept was associated with increased mortality from cardiovascular causes. Furthermore, an increase in sleep time was associated with an excess of mortality from all other causes, according to Jane Ferrie, Ph.D., of University College London, and her colleagues.

Previous studies have reported a U-shaped relationship between time sleeping and mortality, the

investigators said. What has not been looked at by a sleep study before is the effect a change in sleep patterns might have.

The researchers examined sleep data collected from British civil service employees aged 35-55 years who were enrolled beginning in 1985 in a long-term study known as Whitehall II. Baseline sleep duration data were

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COPD Burden Assessed

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prevalence rates, ranging between 0.6% and 4% in men and 0.2% and 3.2% in women, although “the general perception is that these estimates are not accurate,” according to Dr. E.F.M. Wouters, FCCP, of University Hospital Maastricht (the Netherlands) in an accompanying commentary. “Further quantification of the burden of COPD is, therefore, crucial” for public health planning, Dr. Wouters added.

The researchers wrote that their findings suggest that international public health officials need to prepare for a higher disease burden in the future. “Our estimates of the overall prevalence and staging of COPD are consistently higher than these figures, which accord with claims that COPD has generally been underestimated in the past,” they said.

The authors found that the prevalence of stage II or higher

COPD was greatest Cape Town (22% among men and 17% among women). Men in Cape Town also had the highest proportion of subjects who had smoked 20 or more pack-years (34%), but Cape Town women were only third in that ranking.

Researchers cautioned that the small number of subjects at each test site (minimum 300 men and 300 women) prevented within-site analysis because of the low absolute number of COPD patients at each site. In addition, they noted that Lexington, Ky., and Vancouver, B.C., had low

response rates because they recruited patients through random-digit dialing, a weakness that could have introduced some bias.

A second Lancet study on the risk of COPD from passive smoking in China found that adults at the highest exposure levels have increased odds of developing COPD, according to Peng Yin of the University of Birmingham (England) and colleagues (Lancet 2007;370:751-7).

The survey of 6,497 members of a Guangzhou, China, community social and welfare association for people older than age

50 years found significantly elevated odds of COPD among subjects who never smoked if they were exposed to more than 40 hours a week of passive smoke for more than 5 years at home (adjusted odds ratio 1.6), work (OR 1.5), or combined work and home (OR 1.48).

“This study adds fuel to the controversy, showing that passive smoking might also have a role,” wrote Dr. Ana B. Menezes and Dr. Pedro C. Hallal of the Universidade Federal de Pelotas (Brazil) in an accompanying commentary. ■

Routine ICU Epo Use Not Supported

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The proportion of patients who received a red cell transfusion between days 1 and 29, the primary end point, was 46% among those who received epoetin and 48% among those who received placebo. The mean number of red cell units transfused per patient between days 1 and 42, a secondary end point, also was similar among those on epoetin (4.5 U) and those on placebo (4.3 U).

The change in hemoglobin concentration from baseline, another secondary end point, increased significantly more among those on epoetin at day 29, when it was 1.6 g/dL higher, compared with 1.2 g/dL higher among those on placebo, a significant difference. The absolute hemoglobin value at day 29—11.2 g/dL versus 10.8 g/dL—was also significantly higher among those on epoetin. But at day 42, the differences in hemoglobin concentrations between the two groups were no longer significantly different.

At day 29, mortality in the overall population was significantly lower among those on epoetin (8.5%) than among those on placebo (11.4%). Among the trauma patients, mortality was 3.5% among those treated with epoetin and 6.6% among those on placebo, also a significant difference. Mortality followed a similar pattern at 140 days. The mortality difference was the most important finding of the study, the authors said.

Among those on epoetin alfa, the incidence of thrombotic vascular events through 140 days was significantly higher among those who received three doses of epoetin (23%, compared with 16% for those who received three

placebo doses). A greater proportion of patients who received one and two doses of epoetin had thrombotic events, compared with those who received one and two doses of placebo, but those differences were not significant.

The study hypothesis was that the use of epoetin alfa would improve clinical outcomes by preventing adverse events with red blood cell transfusions, but “this was clearly not the case,” the authors said, and pointed out that mortality was reduced, despite the lack of an effect on transfusions.

On the basis of available data, “we believe that epoetin alfa could benefit trauma patients remaining in an ICU for more than 48 hours,” who have hemoglobin concentrations under 12 g/dL and no history of thrombotic disease, and who meet other inclusion criteria of their study.

Until more studies are done, the data suggest that epoetin alfa should not be used in a patient who has not spent at least 48 hours in the ICU, they added.

In an editorial, Dr. Deborah Cook and Dr. Mark Crowther, of the department of medicine at St. Joseph’s Healthcare, McMaster University, Hamilton, Ont., said that it was “tantalizing but premature” to suggest that treatment with epoetin alfa could save the lives of trauma patients who have hemoglobin concentrations below 12 g/dL, have been in the ICU for at least 48

hours, and have no renal insufficiency or history of venous thromboembolism.

The absolute difference in the number of trauma patients who had died at day 29 and 140 was small, “and is insufficient to provide support for the routine use of erythropoietin in practice,” they wrote (N. Engl. J. Med. 2007;357:1037-9).

The Procrit brand of epoetin alfa was used in the study. Four of the study authors were from Johnson & Johnson Pharmaceutical Research and Development, which sponsored the study. Several of the authors disclosed that they received consulting and/or lecture fees from Ortho Biotech and/or Johnson & Johnson Pharmaceutical Research and Development. Drs. Cook and Crowther reported no ties to the manufacturer. ■

Dr. Stephen Pastores, FCCP, comments: Given that epoetin alfa did not reduce the incidence of red cell transfusion (in the context of a restrictive transfusion strategy) and its association with an increased risk of thrombotic events, the routine use of epoetin alfa cannot be recommended in the critically ill. Furthermore, the finding of a decreased mortality among trauma patients treated with epoetin alfa must be interpreted cautiously, because of the small absolute difference in the number of deaths between the placebo group and the epoetin alfa group.

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Predictive Markers Useful in Scleroderma Lung Disease

BY NANCY WALSH
Elsevier Global Medical News

BARCELONA — Following three serum markers of disease activity could provide a simple, noninvasive means of monitoring the efficacy of cyclophosphamide in patients with systemic sclerosis who develop interstitial pneumonia, according to the results of a new study.

Interstitial pneumonia develops in more than 50% of patients with systemic sclerosis and is the major cause of death in this condition. Findings from a double-blind trial of cyclophosphamide plus corticosteroids demonstrated significant benefits in improving scleroderma lung disease (N. Engl. J. Med. 2006;354:2655-66).

However, thus far no means of monitoring treatment response have been established, according to Dr. Chihiro Tanaka of Kanazawa (Japan) University.

Serum levels of surfactant protein-A (SP-A) and SP-D have been reported to reflect disease activity in interstitial lung diseases such as idiopathic pulmonary fibrosis and pulmonary proteinosis, Dr. Tanaka wrote in a poster session at the annual European College of Rheumatology.

Surfactants are proteins secreted by type II alveolar cells that help maintain the elasticity of pulmonary tissue. SP-D also plays an important role in the innate immune system in the lungs (J. Rheumatol. 2004;31:1112-20).

The third marker, KL-6, is a glycoprotein antigen expressed primarily on type II pneumocytes in the alveoli and on respiratory bronchiolar epithelial cells. Elevations of this antigen have been observed in multiple types of interstitial lung diseases, including idiopathic interstitial pneumonia, hypersensitivity pneumonia, and sarcoidosis.

Concentrations of KL-6 also have been shown to be higher among patients with systemic sclerosis who have pulmonary fibrosis, compared with scleroderma patients without lung involvement (J. Rheumatol. 2000;27:930-4).

In Dr. Tanaka's study, 16 adult patients with systemic sclerosis and interstitial pneumonia each underwent six monthly cycles of cyclophosphamide pulses in doses of 15 mg/kg, plus oral prednisolone, 10-30 mg/day.

They were classified as having active interstitial pneumonia based on analysis of bronchoalveolar lavage fluid and high-resolution

computed tomography (HRCT). Response to treatment also was evaluated by HRCT, and the findings correlated with serum levels of SP-A, SP-D, and KL-6.

The 10 patients who showed improvements on HRCT after six cycles of cyclophosphamide also showed decreases in KL-6 and SP-A, Dr. Tanaka noted.

Among the four patients whose HRCT findings did not change following treatment, serum levels of KL-6, SP-D, and SP-A also did not change.

In the two patients whose HRCT findings worsened, serum levels of KL-6 and SP-D increased rapidly until the third cycle, while SP-A levels did not change.

Taken together, these three markers could provide a way of evaluating re-

sponse to cyclophosphamide treatment that is less expensive and noninvasive, compared with HRCT and bronchoalveolar lavage, he concluded. SP-D may prove to be the most sensitive, he added.

Possible mechanisms for the elevation of these markers in patients with scleroderma-associated lung disease include increases in total numbers of type II cells and increased secretion by each type II cell, as well as increased leak from the airspace into the interstitium and decreased clearance from the vascular compartment (Eur. Respir. J. 2002;19:439-46).

Dr. Susan Harding, FCCP, comments: *These preliminary data need to be supported with a large cohort. The Scleroderma Lung Study examined the effect of 1 year of oral cyclophosphamide on scleroderma lung disease, showing a limited beneficial effect (N. Engl. J. Med. 2006;354:2655-66). Tashkin and colleagues recently reported their outcomes at 2 years, showing continued beneficial effects on pulmonary function through 18 months, which then dissipated (Am. J. Respir. Crit. Care Med. 2007; Aug 23, ePub ahead of publication). Maybe the investigators of the Scleroderma Lung Study could carefully examine these biomarkers' ability to predict improved pulmonary function in these patients with cytoxan. Meanwhile, polymorphisms impacting the transcription of connective tissue growth factor (CTGF) was a risk factor for fibrosing alveolitis in scleroderma patients (N. Engl. J. Med. 2007;257:1215-20), giving us new insight into the pathogenesis and potential new targets for treatment of this life-threatening disease.*

Idraparinux Was Effective For DVT, but Not for PE

BY MARY ANN MOON
Elsevier Global Medical News

The synthetic pentasaccharide idraparinux was as effective as standard anticoagulant treatment in preventing short-term recurrences of deep vein thrombosis but not short-term recurrences of pulmonary embolism in a worldwide clinical trial comparing the two approaches.

When idraparinux therapy was extended for a further 6 months, it prevented long-term recurrences of both types of thromboembolism, but raised the risk of hemorrhage to such a degree that the net clinical benefit was deemed "marginal," researchers said.

Idraparinux is a long-acting inhibitor of activated factor X with a substantially longer half-life than the related anticoagulant fondaparinux. Its advantage over standard anticoagulation therapy in venous thromboembolism (VTE) is that it is administered in once-weekly subcutaneous injections at a fixed dose that doesn't require any adjustment or laboratory monitoring.

Dr. Harry R. Buller of the University of Amsterdam and his associates in the van Gogh studies, evaluated idraparinux for VTE at 145 medical centers in 25 countries. The studies were funded by the drug's manufacturer, Sanofi-Aventis.

The first report involved two parallel randomized open-label trials comparing the efficacy and safety of idraparinux with those of standard anticoagulant therapy in patients with deep vein thrombosis (2,904 subjects) or pulmonary embolism (2,215 subjects). The patients were treated for 3-6 months.

For the DVT patients, the incidence of recurrent thromboembolism was similar with idraparinux as with standard therapy. However, the drug's efficacy was inferior to that of standard therapy for PE. "This difference in efficacy was due to an excess of early fatal

and nonfatal recurrences of PE and was associated with an increase in total mortality," Dr. Buller and his associates said (N. Engl. J. Med. 2007;357:1094-104).

"A plausible explanation for the observed differences is lacking, especially since many patients with DVT probably had concurrent asymptomatic PE," they noted.

Adverse bleeding event rates with idraparinux were similar to or lower than those with standard therapy.

"Another factor that was not specifically addressed in these two trials, but which should be considered in evaluating the risks and benefits of idraparinux, is the absence of a specific antidote for this anticoagulant that could be administered during bleeding. ... [This] is a particular liability for an agent with such a long duration of action," the van Gogh investigators pointed out.

In the second report, Dr. Buller and his associates evaluated an additional 6 months of prophylaxis using idraparinux compared with placebo. The 1,215 subjects were followed for a further 3-6 months after discontinuing the drug.

Idraparinux reduced the frequency of recurrent thromboembolism to 1%, compared with nearly 4% for placebo, for a relative risk reduction of 73%. However, there was an excess of major bleeding episodes, including fatal hemorrhages, with the drug—an overall rate of nearly 3%, compared with no such episodes in the placebo group.

"These observations suggest a prolonged risk of hemorrhage in patients treated with idraparinux for more than 6 months," the investigators said (N. Engl. J. Med. 2007;357:1105-12).

This trial "showed the efficacy of idraparinux during a 6-month extended treatment period, at the expense of an increased risk of bleeding. We conclude that the net clinical benefit of such treatment is marginal," they noted. ■

PAH Drug Sitaxsentan Faces Uncertain Approval Future in United States

The manufacturer of sitaxsentan continues to pursue U.S. approval of the endothelin receptor antagonist for treating pulmonary arterial hypertension, after receiving its third notice from the Food and Drug Administration that the supporting application lacked evidence of effectiveness.

The FDA has been reviewing sitaxsentan for treating pulmonary arterial hypertension

(PAH). But in June, manufacturer Encysive announced that it had received a third "approvable" letter for the drug from the FDA, stating that the drug's effectiveness had not been demonstrated, but that there was some evidence of improved exercise tolerance and that the company should conduct another trial.

In response to the company's subsequent request for a formal dispute resolution on the new

drug application (NDA), the FDA reviewer "agreed with the decision of the Division of Cardiovascular and Renal Products that, while the data provided in the NDA are suggestive of the effectiveness of [sitaxsentan], it did not provide the substantial evidence of effectiveness needed for approval," the company announced in September. The reviewer encouraged the company to conduct another study to

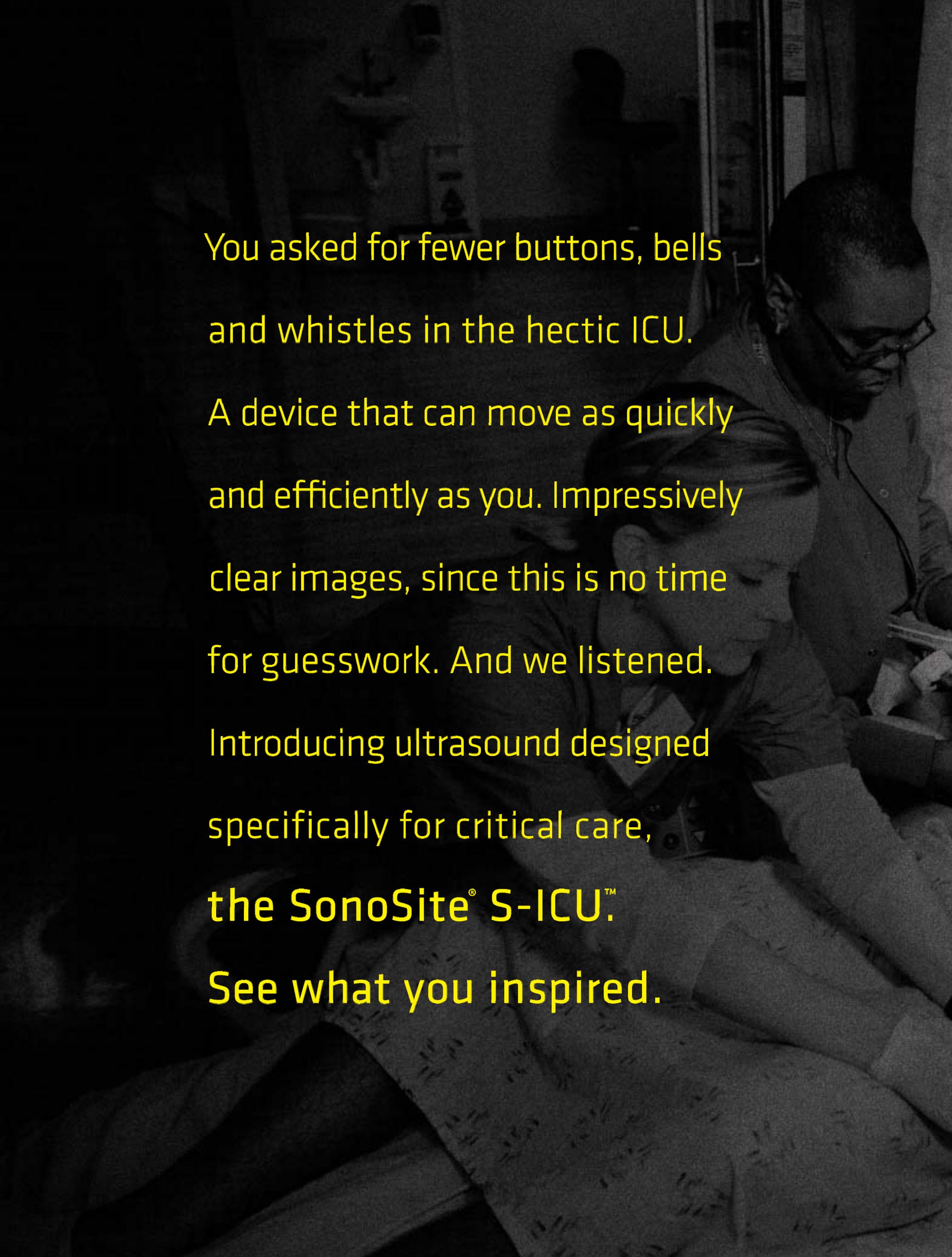
show the drug's effectiveness in exercise capacity, as measured by the change in 6-minute walk distance.

The company is working with outside clinical and statistical experts to develop another phase III study protocol, "so we can move ahead quickly with a new trial if it is ultimately required for approval in the United States," George Cole, president and chief executive officer of Encysive, said

in a statement. "We continue to believe that the issue raised by the FDA was sufficiently addressed in the NDA." Sitaxsentan is approved for treating PAH in Europe, Canada, and Australia.

If approved, sitaxsentan would be the seventh drug approved by the FDA for treating PAH; the sixth was the endothelin receptor antagonist ambrisentan (Letairis) approved by the FDA in June.

—Elizabeth Mechatie



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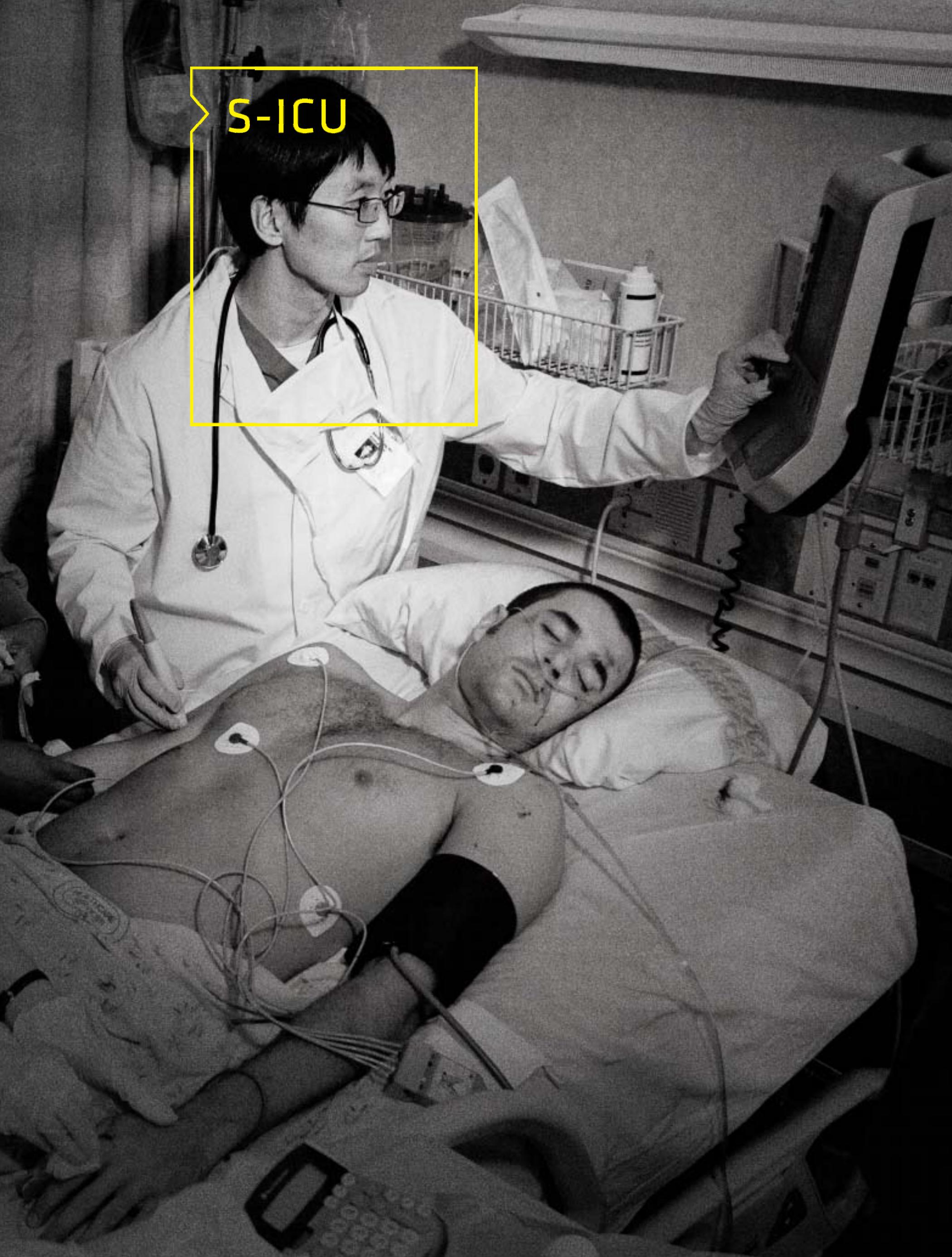
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Pulmonary Perspectives

New Guidelines for the Diagnosis and Management of Asthma—Will They Improve Care of Patients With Asthma?

The Expert Panel recommends the use of multifaceted, clinician education programs that reinforce guideline-based asthma care and are based on interactive learning strategies” (Evidence B). This quote from the section of the full report titled “Education for a Partnership in Asthma Care” highlights a discussion of the evidence supporting improvement and standardization in the quality of care given to people with asthma. An extensive literature search from 1997 through 2006 was undertaken to identify studies that focused on methods of implementing guideline-based practice. The process of implementation is designed to change the behavior of clinicians. Reasons for lack of adherence to guidelines were shown in an observational study (Cabana et al. *Arch Pediatr Adolesc Med* 2001;115:1057) that identified the barriers to pediatricians’ adherence to asthma guidelines. Lack of time, lack of educational resources, lack of support staff, lack of feeling competent in educating patients with asthma, and, what they considered to be a major barrier, lack of reimbursement were all cited as reasons for not adopting guideline-directed care. The review of the literature identified that multifaceted clinician education programs based on interactive learning strategies can improve quality of care and patient outcomes. If the multifaceted, tailored intervention to the audience is not undertaken, the standard “guideline” talk, with or without feedback, is unlikely to promote change in general practice care.

Interactive learning strategies present a promising venue for moving forward to both improve and standardize care for all patients with asthma but require clinicians to participate in programs designed to enhance their skills in communicating with patients with asthma. In addition, the report recommends documenting the discussion with the patient, as well as the level of the patient’s asthma control, at every visit. Search of the literature identified a lack of documentation of the content of medical visits for asthma, including a lack of information necessary to assess either asthma severity or asthma control.

The release of the first National Asthma Education and Prevention Program (NAEPP) clinical practice guideline in 1991 opened the door to a focused approach to evaluation and management of patients with asthma. To help health-care professionals bridge the gap between current knowledge and practice, the NAEPP of the National Heart, Lung, and Blood Institute (NHLBI) convened Expert Panels to prepare asthma guidelines. The charge to all three panels has been the same; develop a report that would provide a general approach to

diagnosing and managing asthma based on current science. This third report, Expert Panel Report (EPR) 3, like the preceding two, is organized around four components of effective asthma management:

1. Use of an objective measure of lung function to assess the severity of asthma and to monitor the course of therapy.
2. Environmental control measures to avoid or eliminate factors that precipitate asthma symptoms or exacerbations.
3. Patient education that fosters a partnership among the patients, his or her family, and clinicians.
4. Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent the airway inflammation characteristic of asthma, as well as pharmacologic therapy to manage asthma exacerbations.

An extensive literature review was conducted in three cycles over an 18-month period (September 2004 to March 2006, with additional major articles included until May 2007). The combined number of titles screened from

these three cycles was 15,444, which did not include many titles identified by the panel members. Of these, 1,654 articles serve as a reference resource used to update the guidelines and are available on the NHLBI Web site. Evidence tables were prepared for selected topics to better assess the weight of the evidence. The Expert Panel agreed to specify the level of evidence used to justify the recommendations being made. Panel members only included ranking of evidence for recommendations they made based on the scientific literature reviewed. The system used to describe the level of evidence is as follows (Jadad et al. *BMJ* 2000; 320: 537):

Evidence Category A: Randomized controlled trials (RCTs), rich body of evidence with substantial numbers of studies with large populations participating.

Evidence Category B: RCTs, limited body of data. Evidence is from end points of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs.

Evidence Category C: Nonrandomized trials and observational studies.

Evidence Category D: Panel consensus judgment. Clinical literature addressing the subject was insufficient to justify placement in one of the other categories but provision of some guidance was deemed valuable.

In addition to specifying the level of evidence to support any recommendation, the Expert Panel agreed to indicate the strength of the recommendation by using the term “is recommended.” When the phrase “should,

or may be considered,” is used, this indicates the recommendation for application to clinical practice is less strong. This distinction was the panel’s effort to address nuances of using the evidence ranking system. The process behind the development of EPR 3: Full Report 2007 included interpretation of the evidence, drafting of summary statements of the literature reviewed, reviewing comments from various external reviewers, and responding to queries raised during public review of a draft version from February through March 2007.

In summary, the process behind the NAEPP “Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report 2007” represents the commitment and efforts of the NHLBI/NAEPP

to produce evidence-based guidelines that are practical for clinicians to incorporate into their practices.

Given the 3-year process for development of the new document and the difficulties of implementing asthma guidelines into practice, what is it that forms the foundation of the new document and can these

concepts be incorporated into practice? This asthma guideline is founded on the concepts of severity and control, with the two domains of impairment and risk acting as “bridges” to improved care. The functions of assessing and monitoring patients with asthma are closely linked to these concepts of severity, control, and responsiveness to treatment:

Severity: the intrinsic intensity of the disease process. Severity is most easily and directly measured in a patient who is not currently receiving long-term control treatment.

Control: the degree to which the manifestations of asthma (symptoms, functional impairments, and risk of untoward events) are minimized and the goals of therapy are met.

Responsiveness: the ease with which control is achieved by therapy.

It is important to recognize that asthma severity, control, and responsiveness are linked together such that the goals of asthma therapy are identical for all levels of baseline asthma severity: to assist the patient in becoming well-controlled, which will minimize both the patient’s impairment in the present and risk in the future.

Both asthma severity and asthma control are bridged by two domains: impairment and risk. Impairment is an assessment of the frequency and intensity of symptoms in the present, as well as the functional limitations that a patient is experiencing now or has recently experienced. Risk is an estimate of the likelihood in the future of either an asthma exacerbation defined as the need for a course of oral systemic corticosteroids, progressive

irreversible loss of pulmonary function over time, or adverse response to medications.

The Expert Panel recommends that clinicians classify asthma severity using the domains of current impairment and future risk. Initial assessment of patients who have confirmed asthma begins with the severity classification, because the selection of type, amount, and scheduling of therapy should correspond to their asthma severity classification. This initial assessment of asthma severity should take place once the diagnosis has been confirmed. Assessment of the disease is made on the basis of the patient’s recall of symptoms, as well as current spirometry results. No longer is peak flow monitoring encouraged for assisting in the diagnosis of the disease, given the enormous variability of its results. Peak flow may serve as a useful tool for monitoring trends in asthma control over time, especially in patients with moderate to severe asthma that is not well-controlled, patients with a history of severe exacerbations, or in patients who are poor perceivers of their airflow obstruction and worsening asthma symptoms.

Pre- and postbronchodilator spirometry is encouraged when considering the diagnosis; repeated once the patient’s condition has stabilized while receiving therapy, which is usually at 3 to 4 months into therapy; during periods of progressive or prolonged loss of asthma control; and, at a minimum, every 1 to 2 years, depending on the patient’s asthma control.

The components of current impairment include the following symptoms: daytime symptoms, nighttime awakenings, need for rescue inhalers (short-acting bronchodilators), interference with normal activities (work, school, recreational/athletic endeavors), and quality-of-life assessments. Quality of life assessments include any work or school missed because of asthma, any disturbance in sleep due to asthma, any change in caregivers’ activities due to a child’s asthma, and any reduction in usual activities. Evaluation of clinical trial data and observational studies has confirmed that the parameters for the impairment domain (symptoms, activity levels, and pulmonary function) reflect increasing gradients of severity, especially in studies of adults.

A closely related and second dimension of severity is the concept of future risk of adverse events, including exacerbations, irreversible loss of pulmonary function, risk of death, and risk of potential adverse response to medications. The assessment of risk in the future requires a careful medical history, observation, and clinician judgment. Although the classification of severity in EPR 3 focuses on the frequency of exacerbations, it is important to note that the severity of disease does not always correlate with intensity of exacerbations, which may vary from mild to life-threatening. Any patient with

Continued on following page

DR. GENE L. COLICE, FCCP

Editor,

Pulmonary Perspectives

**THIS ASTHMA GUIDELINE IS
FOUNDED ON THE CONCEPTS
OF SEVERITY AND CONTROL,
WITH THE TWO DOMAINS OF
IMPAIRMENT AND RISK
ACTING AS ‘BRIDGES’ TO
IMPROVED CARE.**

PRESIDENT'S REPORT
The President Says 'Farewell'

This is my final column as President of the ACCP, which calls for retrospection, analysis, a look ahead, and some reflection on what it has meant to me personally. One of the things I was told as "President Designate" was, "Mark, you have to have a theme for the year as President. My first reaction can be summarized delicately here as, "Don't Make the ACCP Worse." The members will have to judge if the College is better, worse, or the same as last year. My "official" and loftier theme was about building teams to improve the College, our profession, and most of all, the care we give to our patients. I believe that we can look back and agree that we moved ahead in many areas, with some extraordinary successes and few backward steps. We also did it with team efforts and despite increasing government and regulatory scrutiny of professional organizations, contracting budgets, and increasing competition from other organizations.

To me, the primary goal of the College is to offer the best education in the world in chest diseases, critical care, and sleep medicine. Here, we accomplished much in the last 2 years. The journal *CHEST* has a new look and new standards about what gets published. As a result, the journal is better than it ever was, and I believe that most of our clinician colleagues would agree that *CHEST* is the most important, relevant, and therefore valuable, peer-reviewed journal in our field. The Health and Science Policy Committee designed and implemented processes for developing evidence-based clinical practice guidelines that are recognized increasingly as the profession's standard. Our board review courses for pulmonary medicine and critical care medicine are already the best anywhere, and this year, the College offered our second Sleep Medicine Board Review Course. Surpassing all expectations, this "sold out" course had an even higher attendance than the other two board reviews, and the evaluations were consistently outstanding, confirming the College's importance in sleep medicine and education.

The ACCP is on the verge of implementing some bold and innovative strategies to bring us to a different level as

an educational organization. At CHEST 2007, we are introducing a new concept that clearly identifies each session's format, where it fits into our overall curriculum, and classifies it by the type of instruction and methodology used. You ask, "So what? I just come to hear good speakers on good topics." So you should, but our new approach will offer a variety of educational methods that provide interactive experiences and simulated clinical environments that are proven to be more effective than

standard lectures. Starting with CHEST 2007, all ACCP CME certificates will be issued electronically after the attendee provides the feedback that we need to make these meetings even better. This is not a traditional CME certificate that only reflects the total hours attended. Rather, it also categorizes the hours by instructional methodology and specifies the hours linked to common areas required by state medical licensing requirements.

This year saw major progress in the College's use of simulation technology and instructional methods in our educational

programs, and we will soon have a permanent simulation center at ACCP headquarters in Northbrook, IL. There, we will offer programs that will probably provide the most effective educational experiences anywhere. The ACCP embraced the use of ultrasonography in pulmonary and critical care medicine, and we ran our first large, hands-on course this year. It was so well received, that we will conduct similar courses regularly. We will work this year with our expert colleagues from France to develop standards for training in this important field.

Another major component of the College's work is to advocate for our patients and our profession. It was a good year here, too. The Patient-Focused Critical Care Enhancement Act was introduced into the Senate largely as a result of our efforts in collaboration with ATS, SCCM, and AACN. The Capitol Hill Caucus was well-attended and inspiring, as always, and we learned from political insiders more about the enormity of the problems with our "system" of health care and the importance of these issues in the upcoming presidential election. We also emerged with new knowledge that we

need to focus our advocacy activities on issues that distinguish our members and our patients from others in medicine. Yes, we need to advocate forcefully to change the Medicare Sustainable Growth Rate formula that is driving physicians away from caring for patients, but we also need to advocate for (among other things) our patients' ability to use portable oxygen concentrators on all commercial airlines and for them to be covered under Medicare and Medicaid for pulmonary rehabilitation services. Our advocacy efforts will be planned and executed increasingly by collaboration among the ACCP Governors, Government Relations Committee, and Practice Management Committee.

The College's international efforts are also expanding. We are increasing our collaboration with the major international professional organizations and some national societies to improve education and patient care. Our international Regents and Governors are calling for more programs outside of North America and an increased role in the operations of the College; in response, we constituted a strategic planning group that will meet soon to plan for these efforts.

The ACCP does many great things, and putting it together involves many disciplines working in complex relationships. All of the College's accomplishments are attributable to the forward thinking and intense effort by teams of ACCP staff and our volunteer members. The individuals who comprise these teams are paragons of commitment, ability, and innovation. We also manage somehow to accomplish this as friends. Speaking for myself, I look forward to every project I work on with others at the College. Dr. Alvin Thomas will assume the challenges, responsibilities, and satisfaction that come with being ACCP President, and I wish him the best.

On reviewing this manuscript, it looks more like a "State of the Union" than a "Farewell to the Troops." Rightly so, because I'm not leaving—working with the College is one of the most fulfilling things that any of us can do. I will stay on to work with all of the wonderful staff and members as long as I can. Starting immediately, and for the next few years, I am delighted to have the opportunity to become more active in the efforts of the Education Committee. See you around. ■



BY DR. MARK J.
ROSEN, FCCP

Continued from previous page

asthma, even intermittent asthma, can have a severe exacerbation. This is why the new guideline removed the term "mild" intermittent and replaced it with "intermittent," which should emphasize that patients at any level of severity are at risk for severe, life-threatening exacerbations. The frequency of exacerbations requiring oral systemic corticosteroids has been correlated in observational studies with the designation of persistent, rather than intermittent asthma. Utilizing the frequency and intensity of exacerbations has been incorporated into the classification of severity in this document. For all age groups, the more frequent and intense the exacerbation, the greater the degree of underlying disease severity. All figures on severity in the document include a detailed discussion on this issue in the "note" section of the figure.

Once severity is determined using the domains of impairment and risk during the patient's initial presentation, appropriate medication and other therapeutic interventions are initiated. Classifying severity is

emphasized for initiating therapy. The emphasis thereafter for clinical management is changed to the assessment of asthma control. The level of asthma control will be used to monitor and guide all future decisions to either maintain or adjust therapy. This is in sharp contrast to the previous asthma guidelines that raised questions about applying the severity classifications once treatment was established and resulted in placing more emphasis on severity rather than on the ongoing monitoring of whether the goals of asthma therapy were being met. This new guideline, EPR 3, clarifies this important issue.

The level of asthma control (well-controlled, not well-controlled, or very poorly controlled) is the degree to which both dimensions of the manifestations of asthma impairment and risk are minimized by therapeutic intervention. The level of control should be evaluated at all future visits and will determine therapeutic options, including maintaining or adjusting therapy, *ie*, step-up or step-down. Asthma control is defined by both (1) reducing impairment: preventing chronic and troublesome symptoms, decreased

use of rescue inhalers, normal or (near) normal pulmonary function, maintaining normal activity levels, and meeting patient and family expectations of and satisfaction with care; and (2) reducing risk: prevent recurrent exacerbations of asthma and minimize need for ED visits or hospitalizations and prevent progressive and irreversible loss of lung function; for children, prevent reduced lung growth and provide optimal pharmacotherapy with minimal or no adverse effects.

There is a great deal more in this new guideline that emphasizes the education for a partnership in asthma care between the clinician, the patient, and the family, with multiple points of care defined as opportunities to educate the patient and family. In addition, there is a strong recommendation for all patients with asthma to have a written asthma action plan that includes instructions for daily management, as well as recognizing and handling worsening asthma, including the self-adjustment of medications in response to acute symptoms or changes in peak flow measurements if being performed.

In the section on medications, there is an extensive discussion on the role of long-acting bronchodilators in persistent asthma. "In the opinion of the Expert Panel, the beneficial effects of LABA in combination therapy for the great majority of patients who require more therapy than low-dose ICS alone to control asthma (*i.e.*, require step 3 care or higher) should be weighed against the increased risk of severe exacerbations, although uncommon, associated with the daily use of LABAs (see discussion in text)." ■

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma is available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

Dr. Stuart W. Stoloff
 Clinical Professor of Family &
 Community Medicine
 University of Nevada School of Medicine
 Reno, NV
 Member of Expert Panel Report 3
 NIH/NHLBI/NAEPP Guidelines for the
 Diagnosis and Management of Asthma

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF
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Updated Surgery Report**ACS Issues 2007 Edition of
*Physicians as Assistants at Surgery***

The American College of Surgeons (ACS) has issued the fourth edition of *Physicians as Assistants at Surgery*, a report developed in cooperation with 22 other surgical specialty organizations.

The report reflects the consensus opinion of the surgical specialties about whether a physician, as an assistant, is required "almost always," "some of the time," or "almost never" for each surgical procedure listed in the American Medical Association's *Current Procedural Terminology® (CPT) 2007*.

Surgeons who are appealing claims denials for these procedures often rely on this resource. Health insurance companies also

frequently refer to the report to inform reimbursement policies for assistants at surgery.

As indicated in the report, ACS maintains that health insurers should reimburse all medically necessary services.

An indication that a physician would "almost never" be needed for some procedures does *not* imply that a physician is never needed. ACS acknowledges that it may be necessary to use non-physicians (eg, physician's assistants or surgeon's assistants with additional surgical training, registered nurses with specialized training) to assist in operations, depending on local resources and individual patient needs.

The *Physicians as Assistants at Surgery* report is available on the ACS Web site at www.facs.org/ahp/pubs/2007physasstsurg.pdf. ■

NSF Pickwick Postdoctoral Fellowship Is Now Open

As part of its ongoing commitment to advancing sleep research, the National Sleep Foundation (NSF) is pleased to offer the NSF Pickwick Postdoctoral Fellowship and invite interested candidates to apply!

This fellowship supports researchers pursuing careers in basic, clinical, and applied sleep research.

The application deadline is November 1, 2007. Funding begins July 2008.

Since 1996, the NSF Pickwick Fellowship

program has funded more than 30 young investigators who have gone on to have exemplary and thriving research careers.

We encourage you to share this information with potential candidates, colleagues, and others who may be interested.

For more information about the fellowship, visit www.sleepfoundation.org/pickwick, or contact Jessica Steinitz at jsteinitz@sleepfoundation.org. Thank you for your support! ■



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2007-08

November 15 - 18, 2007
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A joint meeting of the
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Cape Town, South Africa

**November 30 -
December 4, 2007**
12th Congress of the APSR;
2nd Joint Congress of the
APSR/ACCP
Queensland, Australia

December 6 - 9, 2007
Meeting Post-CHEST
SBPT/ACCP
Araxa, Brazil

December 7 - 9, 2007
Ultrasonography:
Fundamentals in
Critical Care
Scottsdale, Arizona

January 10 - 13, 2008
Sleep Medicine 2008
Scottsdale, Arizona

April 4 - 6, 2008
Celebration of Pediatric
Pulmonology 2008
Weston, Florida

April 11 - 13, 2008
Ultrasonography:
Fundamentals in
Critical Care
St. Louis, Missouri

August 22 - 25, 2008
ACCP Sleep Medicine Board
Review Course
Orlando, Florida

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ACCP Releases Lung Cancer Guidelines

The American College of Chest Physicians (ACCP) has released new evidence-based lung cancer guidelines in hopes that an updated series of recommendations will assist physicians in achieving the best possible outcomes for their patients. Published as a supplement to the September issue of *CHEST* (www.chestjournal.org), the guidelines cite that there is little evidence to show lung cancer screening impacts mortality in patients, including those who are considered at high risk for the disease, and recommend against use of low-dose computed tomography (LDCT) for general screening of lung cancer.

“Even in high risk populations, current research does not show that lung cancer screening alters mortality outcomes,” said Dr. W. Michael Alberts, FCCP, co-chair of the ACCP lung cancer guidelines and Chief Medical Officer, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL. “We hope that one day, we can find a useful and accurate tool for general lung cancer screening, but, at this time, the evidence does not support the use of LDCT screening.”

Diagnosis and Management of Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition) provides 260 comprehensive recommendations related to lung cancer prevention, screening, diagnosis, staging, and medical and surgical treatments. The guidelines also include new recommendations related to bronchioloalveolar carcinoma (BAC), often seen in nonsmokers, and updated recommendations related to adjuvant chemotherapy after surgical resection and the diagnosis and treatment of solitary pulmonary nodules. Listed below are a few of the new recommendations.

Screening

Due to the lack of supporting evidence, the guidelines recommend against the use of LDCT, chest radiographs, or single or serial sputum cytologic evaluation for lung cancer screening in the general population, including smokers or others at high risk, except in the context of a well-designed clinical trial.

“Population screening for lung cancer is not recommended and may, ultimately, put the patient at risk for further complications,” said Dr. Gene L. Colice, FCCP, vice chair of the ACCP lung cancer guidelines and Director, Pulmonary, Critical Care, and Respiratory Services, Washington Hospital Center, Washington, DC. “Nodules are commonly found during screening; however, to determine whether they are cancerous requires additional testing, which is fairly

invasive and extensive. This may cause the patient needless risk, both physically and psychologically.”

Bronchioloalveolar Carcinoma

For the first time, the guidelines include recommendations on the diagnosis, prognosis, and treatment of BAC.

Recommendations suggest that although staging, diagnosis, and treatment are the same for BAC as for other histologic subtypes of non-small cell lung cancer (NSCLC), additional treatment options for patients with BAC exist that may prove to be equivalent, if not more effective, including sublobar resection and

the use of epidermal growth factor receptor-targeted agents.

Adjuvant Chemotherapy

Previous recommendations did not support postoperative chemotherapy for Stage I or Stage II NSCLC. However, the new guidelines support the use of platinum-based

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Deep Venous Thrombosis and Pulmonary Embolism in Hospitalized Patients With Acute Respiratory Diseases Including COPD

The importance of appropriate evidence-based pharmacologic prophylaxis

James T. Good Jr, MD

Up to 2 million Americans suffer from deep venous thrombosis (DVT) annually,¹ and approximately 300,000 die from pulmonary embolism (PE),² most cases of which result from DVT.³ Complications from DVT kill more Americans than AIDS and breast cancer combined.¹ DVT/PE risk is increased in patients with comorbid conditions and various risk factors, including acute respiratory diseases.⁴

Eleven million US adults are affected by chronic obstructive pulmonary disease (COPD).⁵ Each year, as many as 3.5 million hospitalizations occur for the management of COPD.⁶

Hospitalized COPD Patients Are at Increased Risk for Developing DVT

Hospitalized patients with acute respiratory disease are at risk for DVT, which may lead to PE, the most common cause of preventable hospital death.⁷ In fact, up to 25% of hospitalized patients with respiratory disease may have DVT.⁸ Conversely, statistics from a registry of consecutive patients with acute PE indicate that 14% of these patients have COPD.⁹ At autopsy, one study found that up to 51% of COPD patients had comorbid PE.¹⁰ The common overlap of these conditions may be partly attributable to the fact that many risk factors for DVT are also often present in patients with COPD (Table 1).⁷

Table 1. Common DVT/PE Risk Factors Present in Patients With COPD

• Reduced mobility	• Smoking
• Polycythemia	• Previous DVT
• Infection	• Mechanical ventilation
• Heart failure	• Obesity

Evidence-based Guidelines Recommend Medical Prophylaxis

The 2004 ACCP Guidelines on the Prevention of Venous Thromboembolism recommend prophylaxis with either low-dose unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for acutely ill medical patients admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors.⁷

The guidelines state explicitly that waiting for symptomatic DVT or PE before taking action may have

fatal consequences.⁷ Nevertheless, national data indicate only 53.9% of medical patients with COPD receive anticoagulants.¹¹ Appropriate prophylaxis takes on an additional urgency in hospitalized patients with COPD because symptoms of acute respiratory disease may mask comorbid PE.¹²

COPD Exacerbation, PE, or Both? The Diagnostic Challenge

COPD exacerbation and PE have similar signs, symptoms, and radiographic findings (Table 2).^{12,13} And the usual diagnostic standbys for identification of PE may have reduced prognostic value in the patient with COPD; it has been noted that in this patient group, V/Q scans yield less information than in patients with no cardiopulmonary disease or cardiopulmonary disease exclusive of COPD.¹³

Table 2. Most Frequent Symptoms, Signs, and Radiographic Findings in Patients With COPD and Suspected Acute PE

• Dyspnea	• Wheezing
• Cough	• Atelectasis
• Pleuritic pain	• Effusion

LOVENOX® (enoxaparin sodium injection) Provided Effective Thromboprophylaxis

In the MEDENOX (Prophylaxis in Medical Patients with Enoxaparin) study, 1102 patients with acute medical illness were enrolled. A majority (53%) had chronic respiratory failure. In a double-blind comparison to placebo, 40 mg once daily LOVENOX® was associated with a significant reduction in DVT or PE after 14 days; 14.9% of patients in the placebo group experienced DVT or PE, while the incidence was 5.5% in the LOVENOX® group ($P<0.001$).¹⁴

During the treatment period of 14 days, a major hemorrhage was suffered by 1.1% of those who received placebo, 0.3% of those receiving 20 mg of enoxaparin daily, and 1.7% of those receiving 40 mg enoxaparin; by the end of the follow-up period (110 days), the percentages were 2.0, 1.2, and 3.4, respectively.¹⁴

In a MEDENOX subanalysis of patients with acute respiratory disease (ie, COPD exacerbation), the incidence of DVT or PE was 13.1% among placebo patients and only 3.3% among patients who received 40 mg once daily LOVENOX®, a statistically significant reduction ($P=0.003$).¹⁵

NEWS FROM THE COLLEGE



adjuvant chemotherapy for patients with completely resected Stage II NSCLC who have good performance status. The change in the recommendation was prompted by new research showing adjuvant therapy significantly reduced the risk of death in patients with Stage II NSCLC.

Solitary Pulmonary Nodules

The new recommendations outline a specific algorithm for the evaluation

and management of solitary pulmonary nodules. They also stress the value of risk factor assessment, the utility of imaging tests, the need to weigh the risks and benefits of different management strategies, and the importance of obtaining patient preferences.

The recommendations were rigorously developed and reviewed by 100 multidisciplinary panel members,

including pulmonologists, medical oncologists, radiation oncologists, thoracic surgeons, integrative medicine specialists, oncology nurses, pathologists, health-care researchers, and epidemiologists.

The guidelines were further reviewed and approved by the ACCP Thoracic Oncology NetWork, the Health and Science Policy Committee, the Board of Regents, and external

reviewers from the journal *CHEST*. The guidelines have been endorsed by the American Association for Bronchology, American Association for Thoracic Surgery, American College of Surgeons Oncology Group, American Society for Therapeutic Radiology and Oncology, Asian Pacific Society of Respiriology, Oncology Nurses Society, The Society of Thoracic Surgeons, and the World Association of Bronchology. ■

LOVENOX® is indicated for the prophylaxis of DVT, which may lead to PE, in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness

Table 3. THE-PRINCE Safety Data

	LOVENOX® n=239*	UFH n=212*	Fisher's Exact Test (2 tailed) P value
Total events (DVT or PE), n (%)	20 (8.4)	22 (10.4)	0.015
Total events among patients with severe respiratory disease	9 (7.1)	7 (5.9)	NS
Bleeding complications	5 (1.5)	12 (3.6)	NS
Hematoma at injection site (>5 cm)	24 (7.2)	42 (12.6)	0.027

NS, not significant. *Evaluable

In a Comparative Trial, LOVENOX® Had Similar Efficacy to UFH

The Thromboembolism-Prevention in Cardiac or Respiratory Disease with Enoxaparin (THE-PRINCE) study was a multicenter, controlled, randomized, open-label study of LOVENOX® against UFH for the prophylaxis of DVT and PE in 2 patient groups: patients with heart failure (333 randomized) and patients with severe respiratory disease (332 randomized).¹⁶

After 10±2 days of prophylaxis, there was an equivalent incidence of DVT/PE in the LOVENOX® group vs UFH (8.4% vs 10.4%, $P=0.015$) (Table 3).¹⁶ Among the patients with severe respiratory disease, the incidence of DVT/PE was 7.1% in the LOVENOX® group and 5.9% in the UFH group, a difference that was not statistically significant. Overall, there were fewer bleeding complications in the LOVENOX® group (1.5% vs 3.6% for UFH), although this difference also was not statistically significant. However, there was a significantly lower incidence of injection-site hemorrhage in the LOVENOX® group (7.2% vs 12.6% for UFH).¹⁶

Appropriate DVT/PE Prophylaxis Benefited Hospitalized Patients With Acute Respiratory Diseases Including COPD Exacerbation

Large, randomized clinical trials demonstrated that appropriate prophylaxis with LOVENOX® reduced the risk of DVT and PE in acutely ill medical patients with severely restricted mobility.^{14,16} LOVENOX® was as effective as UFH in this population and has advantages in safety and convenience.¹⁶

IMPORTANT SAFETY INFORMATION

LOVENOX® (enoxaparin sodium injection) cannot be used interchangeably with other low-molecular-weight heparins or unfractionated heparin, as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. **When epidural/spinal anesthesia or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low-molecular-weight heparins or heparinoids 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 postoperative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis. Patients should be frequently monitored for signs and symptoms of neurological impairment (see boxed WARNING).

As with other anticoagulants, use with extreme caution in patients with conditions that increase the risk of hemorrhage. Dosage adjustment is recommended in patients with severe renal impairment. Unless otherwise indicated, agents that may affect hemostasis should be discontinued prior to LOVENOX® therapy. Bleeding can occur at any site during LOVENOX® therapy. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site (see WARNINGS and PRECAUTIONS).

Thrombocytopenia can occur with LOVENOX®. In patients with a history of heparin-induced thrombocytopenia, LOVENOX® should be used with extreme caution. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, LOVENOX® should be discontinued. Cases of heparin-induced thrombocytopenia have been observed in clinical practice (see WARNINGS).

The use of LOVENOX® has not been adequately studied for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves (see WARNINGS).

LOVENOX® is contraindicated in patients with hypersensitivity to enoxaparin sodium, heparin, or pork products, and in patients with active major bleeding.

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Please see a brief summary of prescribing information including boxed WARNING on the next page.

Be 'Aware' in November of COPD and Lung Cancer

November is designated as both Lung Cancer Awareness Month and COPD Awareness Month, and the ACCP urges you to participate in related activities. These national and international observances offer patients, families, physicians, and health-care advocates a wide range of opportunities to

heighten awareness, stress prevention, and help improve patient care and treatment for these diseases.

World COPD Day is held on Wednesday, November 14. This year's theme is "Breathless, not Helpless."

The 31st Annual Great American Smokeout will be celebrated on the

following day, Thursday, November 15. The daylong event was first held in 1977 and is sponsored by the American Cancer Society. Its goal is to get smokers to quit by challenging them to remain cigarette-free for 24 hours.

While these two events provide a great opportunity to get involved,

remember that the lung cancer and COPD awareness campaigns last all month. The ACCP and The CHEST Foundation have developed a series of products and resources to help you support the fight against lung cancer and COPD. To learn more, visit www.chestnet.org.



Rx only
Brief Summary of Prescribing Information Rev. September 2006

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. Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary. The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also **WARNINGS, Hemorrhage, and PRECAUTIONS, Drug Interactions**).

INDICATIONS AND USAGE

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

See **DOSE AND ADMINISTRATION: Adult Dosage** for appropriate dosage regimens.

CONTRAINDICATIONS

Lovenox Injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection. Patients with known hypersensitivity to benzyl alcohol should not be treated using the multi-dose formulation of Lovenox.

WARNINGS

Lovenox Injection is not intended for intramuscular administration. Lovenox Injection 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.

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

Hemorrhage:

Lovenox Injection, like other anticoagulants, 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.

Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox Injection 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, Ongoing Safety Surveillance, and PRECAUTIONS, Drug Interactions).

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 Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:

Thrombocytopenia can occur with the administration of Lovenox Injection. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given Lovenox Injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mm³ occurred at a rate of 0.1% in patients given Lovenox Injection, 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/mm³, Lovenox Injection 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.

Pregnant Women with Mechanical Prosthetic Heart Valves:

The use of Lovenox Injection 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 bid) 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 (10 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.

Miscellaneous:

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 **PRECAUTIONS, Pregnancy**).

PRECAUTIONS

General:

Lovenox Injection should not be mixed with other injections or infusions. Lovenox Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. Lovenox Injection should be used with care in elderly patients who may show delayed elimination of enoxaparin.

If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.

Mechanical Prosthetic Heart Valves:

The use of Lovenox Injection 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, Pregnant Women with Mechanical Prosthetic Heart Valves**).

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 **DOSE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations**).

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, Pharmacokinetics, Special Populations**).

Laboratory Tests:

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. 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 Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Drug Interactions:

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m²).

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 Lovenox's potential 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.

Clinical Considerations

It is not known if 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, Pregnant Women with Mechanical Prosthetic Heart Valves and PRECAUTIONS, Mechanical Prosthetic Heart Valves**). Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also 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, SPINAL/EPIDURAL HEMATOMAS**). 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.¹

There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. 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.

See **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves** for a clinical study of pregnant women with mechanical prosthetic heart valves.

• **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.

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 solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see **WARNINGS, Miscellaneous**).

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 Injection is administered to nursing women.

Pediatric Use:

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

Geriatric Use:

Over 2800 patients, 65 years and older, have received Lovenox Injection in pivotal clinical trials. The efficacy of Lovenox Injection in the elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox Injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Lovenox Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse events (including with age for patients receiving Lovenox Injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox Injection between elderly and younger

patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered (see **CLINICAL PHARMACOLOGY and General and Laboratory Tests** subsections of **PRECAUTIONS**).

ADVERSE REACTIONS

Hemorrhage:

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

The following rates of major bleeding events have been reported during clinical trials with Lovenox Injection.

Indications	Dosing Regimen	
	Lovenox Inj. 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%)

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.

Major Bleeding Episodes Following Hip or Knee Replacement Surgery¹

Indications	Dosing Regimen	
	Lovenox Inj. 40 mg q.d. SC	Heparin 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 Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

³ Lovenox Injection 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 Injection 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 Injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness¹

Indications	Dosing Regimen		Placebo ²
	Lovenox Inj. ² 20 mg q.d. SC	Lovenox Inj. ² 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.

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

Indication	Dosing Regimen	
	Lovenox Inj. ¹ 1 mg/kg q12h SC	Heparin ¹ aPTT Adjusted i.v. 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 ≥ 3 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment¹

Indication	Dosing Regimen ²	
	Lovenox Inj. 1.5 mg/kg q.d. SC	Lovenox Inj. 1 mg/kg q12h SC Heparin aPTT Adjusted i.v. 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 Injection or standard heparin therapy and continuing for up to 90 days.

Thrombocytopenia:

see WARNINGS: Thrombocytopenia.

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 Injection. 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 Injection should be interpreted with caution.

Local Reactions:

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

NEWS FROM THE COLLEGE



This Month in CHEST: Editor's Picks



BY DR. RICHARD S. IRWIN, FCCP
Editor in Chief, CHEST

► **Association of RBC Transfusion With Mortality in Patients With Acute Lung Injury.** *By Dr. G. Netzer, FCCP, et al*

► **Contralateral Recurrence of Primary Spontaneous Pneumothorax.** *By Dr. T-W. Huang, et al*
 ► **Topics in Practice Management: Interfacility Transport of the Critically Ill Pediatric Patient.** *By Dr. S. J. Ajizian; and Dr. T. A. Nakagawa*

► **No Difference in Risk for Thrombocytopenia During Treatment of Pulmonary Embolism and Deep Venous Thrombosis With Either Low-Molecular-Weight Heparin or Unfractionated Heparin: A Metaanalysis.**

By Dr. T. A. Morris, FCCP, et al
 ► **Assessing Future Need for Acute Care in Adult Asthmatics: The Profile of Asthma Risk Study: A Prospective HMO-Based Study.**
By Dr. M. L. Osbourne, FCCP, et al
www.chestjournal.org

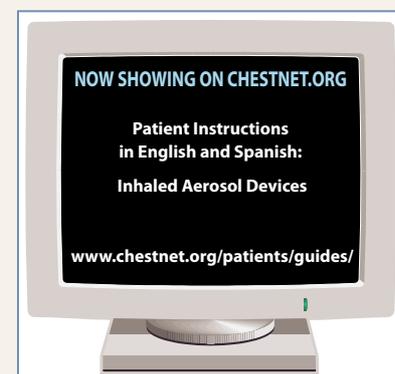
Editor's Note—Watch for It CHEST Participates in an International Collaboration

The Council of Science Editors has organized a Global Theme Issue on Poverty and Human Development to “raise awareness, stimulate interest, and stimulate research into poverty and human development.” CHEST is one of over 220 biomedical journals to agree to participate in this endeavor, with a common publication date on or after Monday, October 22, 2007. CHEST is publishing in its November issue an editorial that highlights the work of the ACCP and The CHEST Foundation in poverty and human development; special features focus on indoor air pollution and child mortality, socioeconomic status and lung function, and technology in developing countries. CHEST also is publishing original research on chronic bronchitis associated with the use of biomass fuel. ■

New ACCP-SEEK Volume XVII Pulmonary Medicine

This invaluable study tool comes directly from the content blueprints for the Pulmonary Disease subspecialty board examination. The book consists of 200 case-based questions written to test your recall, interpretation, and problem-solving skills. Case-based questions feature patient histories, lab workups, and diagnostic images. Both right and wrong answers are discussed in detail.

You can earn up to 50 CME credits. To purchase the new ACCP-SEEK XVII, please visit the ACCP Store online at www.chestnet.org, and click on the ACCP Store icon, located at the top right of the page. ■



Other:
 Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, 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 Injection group, are provided below.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients Undergoing Abdominal or Colorectal Surgery

Adverse Event	Lovenox Inj. 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.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients Undergoing Hip or Knee Replacement Surgery

Adverse Event	Lovenox Inj. 40 mg q.d. SC		Heparin 30 mg q12h SC n = 1080		Placebo q12h SC n = 766		Peri-operative Period n = 288 ²		Extended Prophylaxis Period n = 131 ³	
	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	0%	16%	0%	<2%	<1%	3%	<1%	2%	0%	2%
Anemia	0%	16%	0%	<2%	<1%	2%	2%	5%	<1%	7%
Edema	0%	6%	0%	0%	<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 Injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox Injection peri-operatively in an unblinded fashion in one clinical trial.
³ Data represents Lovenox Injection 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.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Medical Patients With Severely Restricted Mobility During Acute Illness

Adverse Event	Lovenox Inj. 40 mg q.d. SC n = 360		Placebo q.d. SC n = 362	
	Severe	Total	Severe	Total
Dyspnea	0%	3.3%	0%	5.2%
Thrombocytopenia	0%	2.8%	0%	2.8%
Confusion	0%	2.2%	0%	1.1%
Diarrhea	0%	2.2%	0%	1.7%
Nausea	0%	2.5%	0%	1.7%

¹ Excluding unrelated and unlikely adverse events.
Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction:
 Non-hemorrhagic clinical events reported to be related to Lovenox Injection 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 Injection than in patients treated with i.v. heparin.
 Serious adverse events with Lovenox Injection 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 Injection group, are provided below (irrespective of relationship to drug therapy).

Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction

Adverse Event	Lovenox Inj. 40 mg q.d. SC n = 1578		Heparin aPTT Adjusted i.v. Therapy n = 1529	
	n (%)	n (%)	n (%)	n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)	11 (0.72)	11 (0.72)
Heart failure	15 (0.95)	11 (0.72)	11 (0.72)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)	11 (0.72)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)	9 (0.59)	9 (0.59)

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

Adverse Event	Lovenox Inj. 1.5 mg/kg q.d. SC n = 298		Lovenox Inj. 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.
Ongoing Safety Surveillance:
 Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection 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. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Other Ongoing Safety Surveillance Reports:
 Local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytopenia, and thrombocytopenia with thrombosis (see WARNINGS, Thrombocytopenia). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

OVERDOSAGE
Symptoms/Treatment:
 Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox Injection, 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 Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.
 After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found 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, USP, products.
 A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

DOSE AND ADMINISTRATION
 All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Lovenox Injection activity, routine monitoring of coagulation parameters is not required (see PRECAUTIONS, Laboratory Tests).

Note: Lovenox Injection is available in two concentrations:
 1. **100 mg/mL Concentration:** 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes, 300 mg / 3.0 mL multiple-dose vials.
 2. **150 mg/mL Concentration:** 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

Adult Dosage:
Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.
Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day SC**, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.

Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in the controlled clinical trial.

Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is **1 mg/kg administered SC every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. 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. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.
Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC or **1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.

Renal Impairment:
 Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.
 The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in the following table (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and PRECAUTIONS, Renal Impairment).

Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30mL/minute)

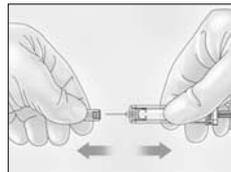
Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily

Administration:
 Lovenox Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.
 The use of a tuberculin syringe or equivalent is recommended when using Lovenox multiple-dose vials to assure withdrawal of the appropriate volume of drug.
 Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.
Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right antero-

LOVENOX® (enoxaparin sodium injection)

lateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.
 Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



- Inject using standard technique, pushing the plunger to the bottom of the syringe.



- Remove the syringe from the injection site keeping your finger on the plunger rod.



- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.



- Immediately dispose of the syringe in the nearest sharps container.



- NOTE:**
- The safety system can only be activated once the syringe has been emptied.
 - Activation of the safety system must be done only after removing the needle from the patient's skin.
 - Do not replace the needle shield after injection.
 - The safety system should not be sterilized.
 - Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep out of the reach of children.

¹ Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *Br J Obstet Gynecol* 2001; 108 (11): 1134-40.

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Dr. Petty Tribute at the Making a Difference Awards Dinner

A special reception and tribute are being held in honor of Thomas L. Petty, MD, Master FCCP, at the ninth annual Making a Difference Awards Dinner on Saturday, October 20, 2007, at the Chicago Cultural Center, in Chicago.

The CHEST Foundation, and Platinum Exclusive Sponsor, Boehringer Ingelheim Pharmaceuticals, Inc., is hosting the Thomas L. Petty, MD, Master FCCP VIP Reception, which precedes the dinner.

The private reception is being attended by physicians who were trained by Dr. Petty, as well as upper level donors to the Thomas L. Petty, MD, Master FCCP Endowment in Lung Research and Making a Difference Awards Dinner sponsors at the Bronze Sponsorship level and above.

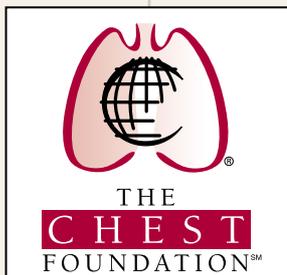
The tribute paid to Dr. Petty during the Making a Difference Awards Dinner

is highlighting Dr. Petty's dedication and accomplishments to further lung health and research and his personal interest in improving patient care.

The Thomas L. Petty, MD, Master FCCP Endowment in Lung Research is The CHEST Foundation's way of continuing to express admiration and appreciation for Dr. Petty's outstanding work.

Your donation to this important endowment fund will support, in perpetuity, lung research and the improvement of care for patients with respiratory diseases.

Visit The Foundation's Web site at www.chestfoundation.org for more information on how to contribute, or contact Teri Ruiz at truiz@chestnet.org or (847) 498-8308. ■



Comings and Goings—CHEST Foundation Board

Six CHEST Foundation board members are rotating off the board this year and are being recognized during The CHEST Foundation's meeting at CHEST 2007 for their exceptional support and service to The Foundation during the past 4 years.

A number of areas within The Foundation have been strengthened by the outstanding work of these Board members, and The Foundation is grateful for their commitment of time and financial resources that will enable The Foundation to build on the momentum they were so much a part of creating.

The Foundation sincerely thanks the following trustees for their service from 2003 to 2007:

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The CHEST Foundation Board of Trustees also welcomes those newly nominated:

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- ▶ Aspen Lung Conference Endowment Fund
- ▶ National Lung Health Education Program

Continuing the Legacy

To honor Dr. Petty's accomplishments, The CHEST Foundation, in partnership with Boehringer Ingelheim, Inc., has established the Thomas L. Petty, MD, Master FCCP Endowment in Lung Research to support research and advances in patient care. Show your appreciation for Dr. Petty's outstanding work and continue his legacy by donating to this important fund.

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CT Reading Tips Sharpen Diagnosis in Potential PE

Multidetector CT imaging is a good second test to provide more information.

BY KERRI WACHTER
Elsevier Global Medical News

WASHINGTON — CT imaging can be a useful tool to distinguish pulmonary embolism from other conditions with similar symptoms, provided you're familiar with some of the common pitfalls, Dr. J. Jeffrey Carr, a professor of radiologic sciences and public health sciences at Wake Forest University, Winston-Salem, N.C., said at the annual meeting of the Society of Cardiovascular Computed Tomography.

The symptoms of pulmonary embolism (PE) are well known: a sudden onset of dyspnea, tachypnea, pleuritic chest pain, and fainting, said Dr. Carr. Unfortunately, these symptoms are often common in patients without PE.

D-dimer assays are usually the first test used to diagnose PE. D-dimer is a degradation product produced by plasmin-mediated proteases of cross-linked fibrin, which increases with thrombosis. It's important to know whether your institution uses the latex agglutination assay or the enzyme-linked immunosorbent assay, Dr. Carr explained, because different cut points are used with each test.

"The key thing to realize with the D-dimer is that it's not useful in the inpatient population or

for individuals that you think have an intermediate or high risk of pulmonary emboli," said Dr. Carr. Even in a population of patients at low risk, a quarter of the tests will be negative, which means that 75% of patients in this population will have indeterminate results.

Multidetector CT imaging is a good second test to provide more information. In an April 27, 2005, meta-analysis of studies that used a CT to rule out pulmonary embolism, researchers looked at the overall clinical validity. They identified 15 studies involving 3,500 patients (JAMA 2005;293:2012-7). They found that the negative predictive value of CT angiography of the pulmonary arteries was 99.4%. The authors concluded that the clinical validity of CT imaging to rule out PE is similar to that of conventional pulmonary angiography. Of note, this meta-analysis primarily included studies using single-slice CT.

"One of the real advantages ... is that CT provides an [alternative diagnosis] in a significant percentage of people who come in to the CT suite," said Dr. Carr. Alternative diagnoses are made using CT in 25%-46% of cases. "That's very valuable, because it allows much more appropriate management."

These diagnoses include pneumonia, malignancies, pleural effusions, esophagitis, pericarditis, aortic dissections, and coronary artery disease. "Even if you don't do cardiac-gated CT in the emergency

department but you are using a 64-slice scanner for the evaluation of pulmonary embolism, you will see a remarkable amount of coronary artery disease ... that was unidentified simply because of the very high temporal resolution of even the ungated CT scan," said Dr. Carr.

In terms of common PE findings, "typically you're going to see more than one vessel involved; on average, you'll see three emboli somewhere in the pulmonary arterial circulation," said Dr. Carr. It's also common to find large thrombi located in the central or lobar branches.

Most emboli are nonocclusive. "So you'll see the clot kind of dangling there in the pulmonary artery with contrast surrounding it," said Dr. Carr. There is a greater prevalence of clots in the lower lobes because of the greater blood flow to the lower lobes. Most (58%) of PEs identified are in the lower lobes. The clots often end up being long and linear, and typically straddle bifurcations.

When viewed on CT cross-section, the intraluminal filling defect sometimes will

have a doughnut-hole appearance. When the vessel in plane is imaged, the railway track appearance is often common. "You'll have a long clot within a vessel. Sometimes these can be completely occluded and

you won't get contrast on either side of it, but typically you're going to see contrast on one side or the other," said Dr. Carr.

When occlusion is complete, it's common to see the vessel cut off. "You'll be following a blood vessel—the pulmonary artery—and you'll see contrast, which will just disappear from an occlusive clot," said Dr. Carr.

"One of the things that many of us have learned is that there are lung findings associated with pulmonary emboli. Unfortunately, these are not terribly helpful in the diagnosis," said Dr. Carr. Both wedge-shaped opacities and linear bands have been shown to be significant findings in studies, but they are also relatively common in patients without PE. Likewise, pleural effusions and perfusion defects are not diagnostic.

When a CT is viewed, it's very important to view the vessels sequentially by following a vessel down. "If you see one suspected pulmonary [embolus], look at the rest of the pulmonary arteries, because you'll often see two, three, or four others involved in the distribution of the clot," said Dr. Carr.

There are numerous pitfalls to imaging the lungs, cautioned Dr. Carr. Motion defects are chief among these. Patients suspected of PE typically are short of breath and have difficulty holding their breath, which can pose a problem for imaging the lungs. However, the advent of multidetector-row CT has decreased the time



A CT of the chest shows contrast in the pulmonary vessels and a clot in the right pulmonary artery.

by tracing the vessels: Lymph nodes will lie adjacent to vessels, not inside them.

Mucus plugs can also be tricky. The key is to follow the bronchi up and down. "Identify that it's really a bronchus that's occluded and not a pulmonary artery," said Dr. Carr.

Extensive mucoid impaction can also occur. "The

necessary for patients to hold their breath.

Another key artifact is incomplete opacification of the pulmonary arteries. "You need to beware that you don't have good opacification of the pulmonary arteries and mistakenly call that a pulmonary [embolus]," said Dr. Carr.

Perhaps the largest imaging pitfall for physicians just starting out is a normal lymph node within the lung, said Dr. Carr. Lymph nodes can very closely simulate clots. Lymph nodes can be distinguished

key thing is to remember that the bronchi and the pulmonary arteries travel together," said Dr. Carr. Trace these together to ensure you've identified them correctly.

It's also common to mistake the pulmonary vein for the pulmonary artery. Again, trace the vessels up and down. The pulmonary vein will tend to run more horizontally, "so you'll tend to have it in plane," said Dr. Carr.

Dr. Carr disclosed that he had no relevant conflicts of interest. ■

'ONE OF THE REAL ADVANTAGES ... IS THAT CT PROVIDES AN [ALTERNATIVE DIAGNOSIS] IN A SIGNIFICANT PERCENTAGE OF PEOPLE WHO COME IN.'

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Sleep Tied to Cardiovascular Risk

Sleep Duration • from page 1

available for 9,781 subjects who were interviewed in 1985-1988, while follow-up data were available for 7,729 who were interviewed again in 1992-1993. Mortality data were available through September 2004.

After adjustment for factors such as age, sex, smoking status, body mass index, and cholesterol, those Whitehall II participants who reported sleeping 5 hours or less a night at the first interview had a death hazard ratio of from all causes of 1.24, relative to those who slept 7 hours per night. Those who slept 9 hours or more had a fully adjusted hazard ratio of 1.54.

The fully adjusted hazard ratios of all-cause mortality were slightly higher for those who reported sleep for 5 hours or less and 9 hours or more at the second interview, 1.78 and 1.95, respectively.

The risk of death due to cardiovascular causes was relatively greater for those who slept less after the baseline period than for those who slept more.

Participants whose sleep decreased from 6-8 hours a night at the first interview to less than 6 hours at the second interview had a fully adjusted hazard ratio of mortality from cardiovascular cause of

2.04, compared with 1.22 for those who slept more. Those whose sleep increased from 7-8 hours at the first interview to more than 8 hours at the second interview had a fully adjusted hazard ratio of mortality from noncardiovascular causes of 2.06, compared with 1.44 for those who slept less.

Investigators found a positive association between marital status and sleep duration. Married women were more likely to sleep longer, while married men were more likely to average 7 to 8 hours of sleep per night.

The connection between sleep duration and body mass index wasn't as clear cut. At the Whitehall II study's baseline, higher BMI was associated both with short and long sleep duration in women, but

only with short sleep duration in men. By 1992-1993, BMI and sleep duration showed no association in women, but both short and long sleep durations were associated with higher BMI in men.

"Our findings suggest that either a decrease in sleep duration from a regular 6, 7, or 8 hours or an increase from a regular 7 or 8 hours predict all-cause mortality," the authors wrote.

"Patients reporting a decrease in sleep should be regarded as higher risk populations for cardiovascular and all-cause mortality," according to the investigators.

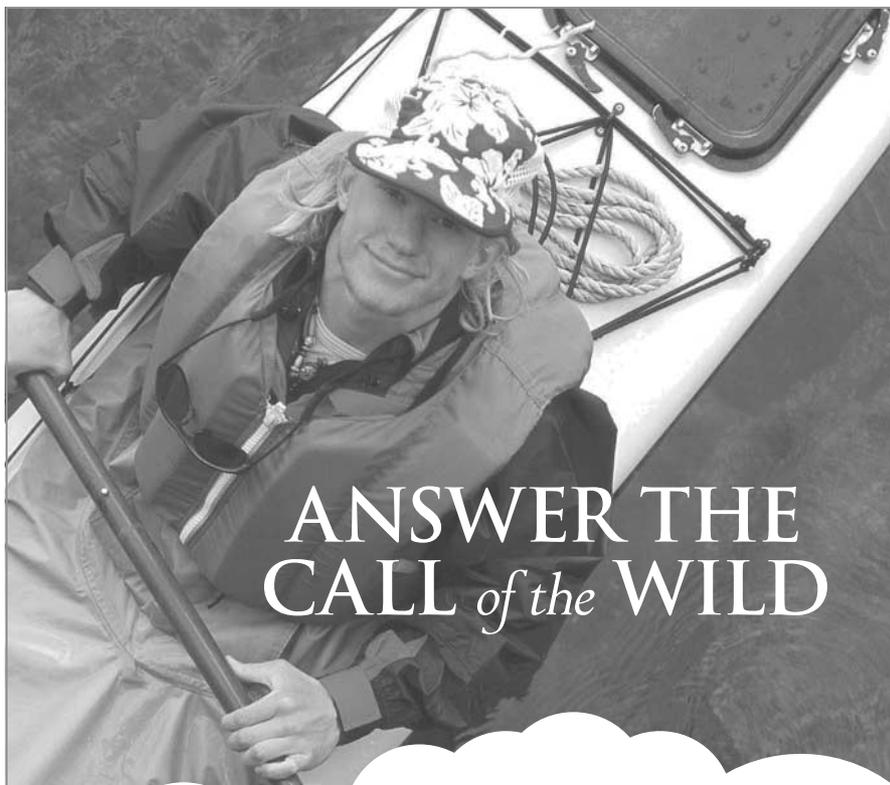
One of the authors holds the Cephalon Chair at Warwick Medical School, Coventry, U.K. None of the other authors had conflicts of interest to declare. ■

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Sleep Labs Help in Pediatric Respiratory Disorders

BY CAROLYN SACHS
Elsevier Global Medical News

MAUI, HAWAII — Sleep is a period of vulnerability for the respiratory system, so sleep labs are extremely helpful for dealing with respiratory disorders, Dr. Sally Ward said at a meeting sponsored by the University Children's Medical Group and the American Academy of Pediatrics.

Dr. Ward, head of the division of pediatric pulmonology at Children's Hospital Los Angeles, discussed ways in which polysomnography can be useful in diagnosing or treating a variety of respiratory disorders:

► **Obstructive sleep apnea syndrome (OSAS).** "Why bother with a polysomnogram [PSG] in a patient with big tonsils?" Dr. Ward asked. She suggested that a common assumption might be, "They're snoring, they probably have OSAS." Why did the American Academy of Pediatrics say in its practice guidelines that children with symptoms suggestive of OSAS should undergo further testing?

"The presence of obstructive sleep apnea, or the severity, cannot be predicted by history or physical alone," she said. Studies have failed to reveal a relationship between the size of the adenoids and tonsils,

and the presence of sleep apnea. And primary snoring, which is more common than is OSAS, is not an indication for surgery, she observed. "It's important that an accurate diagnosis be made in order to prevent unnecessary treatment," and sleep studies help with that process.

Polysomnography also can benefit patients who receive a diagnosis of OSAS and are candidates for surgery. Information about the severity of OSAS affects the pre- and postoperative care and the timing of surgery, Dr. Ward said at the meeting, also sponsored by California Chapter 2 of the AAP. And a PSG provides a basis for comparison in patients who continue to have symptoms after surgery.

Some patients with OSAS who are not amenable to surgery or positive-pressure therapy may be helped by receiving supplemental oxygen during sleep, she said. The procedure can be titrated in a sleep lab to ensure "hitting the target." Patients in this group might include those with craniofacial abnormalities, laryngomalacia, or cerebral palsy.

► **Chronic lung disease.** A sleep study can help determine when a baby with chronic lung disease of infancy—bronchopulmonary dysplasia—is able to graduate from wearing oxygen during sleep.

"Using the PSG allows you to choose the proper oxygen level during REM sleep when hypoxia can worsen because of the skeletal muscle atonia. It guides weaning as the conditions may improve, which is usually the case with chronic lung disease of infancy," Dr. Ward explained.

"Children who are graduates from the nursery who are failing to thrive, or who are doing poorly, may be suffering from unsuspected hypoxemia during sleep," she said. A PSG can be useful in that instance.

In older children with chronic lung disease—such as patients with cystic fibrosis—who may have hypoxemia during sleep, "the use of supplemental oxygen has been shown to increase quality of life," Dr. Ward said. "Titrating oxygen during a sleep study in the patient who may have longstanding hypoxemia will allow you to know that you're not decreasing their hypoxic drive with a resulting increase in carbon dioxide."

► **Ventilatory muscle weakness.** Children with neuromuscular disease can benefit from a sleep investigation to identify hypoventilation.

These are patients with "a whole host of diagnoses that can involve the respiratory muscles," Dr. Ward said, including spinal muscular atrophy, Duchenne muscular

dystrophy, congenital myopathies, myotonic dystrophy, and mitochondrial disorders. They are at risk for chronic respiratory failure, which can be insidious, she said. "It can be just like a slippery slope that can go unnoticed."

► **Chronic respiratory failure.** "Given the opportunity, most families in our experience will opt for assisted ventilation for their child as they enter respiratory failure," Dr. Ward said. "It behooves us to try and recognize this issue prior to a crisis, so that elective institution of ventilation can be offered." Because PSGs are very effective at identifying chronic respiratory failure, they can help in managing this transition.

Polysomnography also makes it possible to assess the adequacy of nocturnal ventilation in children who have already been identified as having chronic respiratory failure, and who are technology dependent.

"Ventilatory needs are different during sleep than they are during wakefulness," she said. Once a child is on a ventilator, "using the sleep laboratory can ensure that we're providing normal oxygenation and ventilation during sleep, which is critical to preventing complications and providing these children with good daytime function." ■

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NIPPV Didn't Cut Mortality In Acute Pulmonary Edema

BY MITCHEL L. ZOLER
Elsevier Global Medical News

VIENNA — Noninvasive ventilation was safe in helping resolve symptoms in patients with acute cardiogenic pulmonary edema, but the treatment was not lifesaving—it had no effect on mortality in a study with more than 1,000 patients.

“Use [noninvasive ventilation] to relieve patient suffering in the early hours of this illness, but it really only helps the patient in crisis. For the longer term, it doesn't cause harm or benefit,” Dr. David Newby said at the annual congress of the European Society of Cardiology.

The study compared both continuous positive airway pressure (CPAP) and noninvasive intermittent positive pressure ventilation (NIPPV) against passive oxygen therapy. Both were equally safe and effective when compared with a standard regimen without high-pressure oxygen.

With 1,069 patients, the 3 Treatments for Cardiogenic Pulmonary Oedema (3CPO) trial is the first large-scale study to test the impact of high-pressure oxygen in this setting, noted Dr. Newby, a professor of cardiology at the University of Edinburgh.

The new study was done at 26 emergency departments in the United Kingdom and was sponsored by England's National Health Service. Patients were enrolled as soon as they arrived at the hospital, and were eligible only if they had acute dyspnea and chest crepitations, were acidotic with an arterial pH of less than 7.35, and were tachypneic with more than 20 breaths per minute. They were randomized to passive oxygen, CPAP administered at an average pressure of 10 cm H₂O, or NIPPV at an average pressure of 14/7 cm H₂O. Therapy was applied for 2 hours. Patients were also treated with nitrates and diuretics.

Treatment with noninvasive ventilation led to small but statistically significant improvements in pulse rate, respiratory rate, and arterial pH, compared with patients in the control group (see table), but the clinical impact of these changes are unclear. In general, however, patients who received either CPAP or NIPPV had more rapid resolution of their dyspnea and other acute symptoms, Dr. Newby said in an interview. Ventilation had no effect on the average length of hospitalization or need for intensive care.

The study's primary end point was the mortality rate at 7 and 30 days after treatment. These rates were very similar for all

three treatment groups. Seven-day mortality was 9.8% in 367 patients on standard oxygen, 9.6% for 346 patients on CPAP, and 9.4% for 356 patients on NIPPV. The 30-day mortality rates were 16.7%, 15.4%, and 15.4%, respectively.

The combined rate of death or need for intubation was 11.7% in the control group and 11.1% among the patients on noninvasive ventilation.

Average Levels 1 Hour After Oxygen Therapy for Pulmonary Edema

	Passive oxygen therapy (n = 367)	Noninvasive ventilation (n = 356)
Pulse rate	102 beats per min	96 beats per min
Respiration rate	26 breaths per min	25 breaths per min
Arterial pH	7.30	7.32
Oxygen saturation	94%	93%
Arterial CO ₂ partial pressure	6.7 kPa	6.2 kPa

Note: All differences between the two treatment groups are statistically significant.
Source: Dr. Newby

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CSL Behring Zemaira® Alpha₁-Proteinase Inhibitor (Human)

Manufactured by:
CSL Behring LLC
Kankakee, IL 60901 USA
US License No. 1767

Rx only

Before prescribing, please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE

Zemaira® is indicated for chronic augmentation and maintenance therapy in individuals with alpha₁-proteinase inhibitor (A₁-PI) deficiency and clinical evidence of emphysema.

Zemaira® increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of A₁-PI. Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira® are not available.

Safety and effectiveness in pediatric patients have not been established.

Zemaira® is not indicated as therapy for lung disease patients in whom severe congenital A₁-PI deficiency has not been established.

CONTRAINDICATIONS

Zemaira® is contraindicated in individuals with a known hypersensitivity to any of its components. Zemaira® is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A₁-PI products.

Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira®, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira®.

WARNINGS

Zemaira® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Zemaira® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture. (See DESCRIPTION section for viral reduction measures.) The manufacturing procedure for Zemaira® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction steps of the Zemaira® manufacturing process are pasteurization (60°C for 10 hours) and two sequential ultrafiltration steps. Additional purification procedures used in the manufacture of Zemaira® also potentially provide viral reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see Information For Patients). During clinical studies, no cases of hepatitis A, B, C, or HIV viral infections were reported with the use of Zemaira®.

PRECAUTIONS

General - Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.

As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira®. Caution should therefore be used in patients at risk for circulatory overload.

Information For Patients - Patients should be informed of the early signs of hypersensitivity reactions

including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

As with all plasma-derived products, some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect pregnant women and immune-compromised individuals. Symptoms of parvovirus B19 include fever, drowsiness, chills, and runny nose followed two weeks later by a rash and joint pain. Patients should be encouraged to consult their physician if such symptoms occur.

Pregnancy Category C - Animal reproduction studies have not been conducted with Zemaira®, Alpha₁-Proteinase Inhibitor (Human). It is also not known whether Zemaira® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zemaira® should be given to a pregnant woman only if clearly needed.

Nursing Mothers - It is not known whether Zemaira® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemaira® is administered to a nursing woman.

Pediatric Use - Safety and effectiveness in the pediatric population have not been established.

Geriatric Use - Clinical studies of Zemaira® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

ADVERSE REACTIONS

Intravenous administration of Zemaira®, 60 mg/kg weekly, has been shown to be generally well tolerated. In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus. Each of these related adverse events was observed in 1 of 89 subjects (1%). The adverse reactions were mild.

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate countermeasures and supportive therapy should be administered.

Table 3 summarizes the adverse event data obtained with single and multiple doses during clinical trials with Zemaira® and Prolastin®. No clinically significant differences were detected between the two treatment groups.

Table 3: Summary of Adverse Events

	Zemaira®	Prolastin®
No. of subjects treated	89	32
No. of subjects with adverse events regardless of causality (%)	69 (78%)	20 (63%)
No. of subjects with related adverse events (%)	5 (6%)	4 (13%)
No. of subjects with related serious adverse events	0	0
No. of infusions	1296	160
No. of adverse events regardless of causality (rates per infusion)	298 (0.230)	83 (0.519)
No. of related adverse events (rates per infusion)	6 (0.005)	5 (0.031)

The frequencies of adverse events per infusion that were ≥0.4% in Zemaira®-treated subjects, regardless of causality, were: headache (33 events per 1296 infusions, 2.5%), upper respiratory infection (1.6%), sinusitis (1.5%), injection site hemorrhage (0.9%), sore throat (0.9%), bronchitis (0.8%), asthenia (0.6%), fever (0.6%), pain (0.5%), rhinitis (0.5%), bronchospasm (0.5%), chest pain (0.5%), increased cough (0.4%), rash (0.4%), and infection (0.4%).

The following adverse events, regardless of causality, occurred at a rate of 0.2% to <0.4% per infusion: abdominal pain, diarrhea, dizziness, ecchymosis, myalgia, pruritus, vasodilation, accidental injury, back pain, dyspepsia, dyspnea, hemorrhage, injection site reaction, lung disorder, migraine, nausea, and paresthesia. Diffuse interstitial lung disease was noted on a routine chest x-ray of one subject at Week 24. Causality could not be determined.

In a retrospective analysis, during the 10-week blinded portion of the 24-week clinical study, 6 subjects (20%) of the 30 treated with Zemaira® had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). Nine subjects (64%) of the 14 treated with Prolastin® had a total of 11 exacerbations of their COPD. The observed difference between groups was 44% (95% confidence interval from 8% to 70%). Over the entire 24-week treatment period, of the 30 subjects in the Zemaira® treatment group, 7 subjects (23%) had a total of 11 exacerbations of their COPD.

HOW SUPPLIED

Zemaira® is supplied in a single use vial containing the labeled amount of functionally active A₁-PI, as stated on the label. Each product package (NDC 0053-7201-02) contains one single use vial of Zemaira®, one 20 mL vial of Sterile Water for Injection, USP (diluent), and one vented transfer device.

STORAGE

When stored up to 25°C (77°F), Zemaira® is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

Prolastin® is a registered trademark of Bayer Corporation.

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Adapted from 19131-05

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- **Pure** — The only Alpha-1 augmentation therapy approved by the FDA as highly purified (lot release specification, $\geq 94\%$ purity)^{*,1-3}
- **Effective** — **Three times fewer** COPD exacerbations than with Prolastin^{®†}
- **Well tolerated** — **Six times fewer** infusion-related adverse events than with Prolastin^{®‡}
- **Fast** — **Half or less** the infusion time of other augmentation therapies^{§,1-3}

Zemaira® is indicated for chronic augmentation and maintenance therapy for adults with alpha₁-proteinase inhibitor (A₁-PI) deficiency and emphysema.

Clinical data demonstrating the long-term effects of chronic augmentation therapy with Zemaira® are not available. As with other Alpha-1 therapies, Zemaira® may not be appropriate for the following adult individuals as they may experience severe reactions, including anaphylaxis: individuals with a known hypersensitivity and/or history of anaphylaxis or severe systemic reaction to A₁-PI products or their components and individuals with selective IgA deficiencies who have known antibodies against IgA.

In clinical studies, the following treatment-related adverse events were reported in 1% of subjects: asthenia, injection-site pain, dizziness, headache, paresthesia, and pruritus.

Zemaira® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

For more information, call **1-866-ZEMAIRA (1-866-936-2472)**, or visit www.Zemaira.com.

References: 1. Prolastin® Alpha₁-Proteinase Inhibitor (Human), Full Prescribing Information, January 2005. 2. Aralast™ Alpha₁-Proteinase Inhibitor (Human), Full Prescribing Information, August 2005. 3. Data on file, CSL Behring LLC.

Zemaira®
alpha₁-proteinase inhibitor (Human)

Unmatched purity. Uncompromised care.

Please see brief summary of full prescribing information on following page.

* Shelf life purity specification is $\geq 90\%$

† In a retrospective analysis in the pivotal clinical trial, Zemaira® patients were three times less likely to experience exacerbations of their COPD than Prolastin® patients

‡ No clinically significant differences were detected between the treatment groups

§ Based on recommended dosage as stated in the product package inserts of 60 mg/kg body weight at the infusion rate of 0.08 mL/kg/min

Prolastin is a registered trademark of Talecris Biotherapeutics, Inc.