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PATRICE WENDLING/ELSEVIER GLOBAL MEDICAL NEWS

"Patients in real-world major orthopedic surgery benefit from VTE prophylaxis with rivaroxaban even more than could be expected from the phase III results of the RECORD trial," Dr. Jan Beyer-Westendorf said.

Rivaroxaban Excels in 'Real-World' Trial

BY PATRICE WENDLING
Elsevier Global Medical News

SAN DIEGO – Prophylaxis with rivaroxaban achieved significant reductions in venous thromboembolism, compared with two commonly used drugs, when put to the test in 5,346 consecutive, unselected patients undergoing major orthopedic surgery.

The incidence of in-hospital symptomatic venous thromboembolism (VTE) was 2.4% with rivaroxaban (Xarelto), compared with 3.9% with low-molecular-weight heparin (LMWH) and 5.5% with fondaparinux (Arixtra). This corresponds to a relative risk reduction of 39% compared with LMWH, and 57% compared with fondaparinux.

Rivaroxaban, an oral factor Xa inhibitor, also has superior safety with regard to major bleeding and surgical complications, according to Dr. Jan Beyer-Westendorf, with the University Clinic at Dresden (Germany) Technical University.

"Patients in real-world major orthopedic surgery benefit from VTE prophylaxis with rivaroxaban even more than could be expected from the phase III results of the RECORD trial," he said at the annual meeting of the American Society of Hematology.

The four phase III RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism) trials compared rivaroxaban with enoxaparin in more than 12,500 patients undergoing knee and hip replacement. The trials did not evaluate fondaparinux or LMWH, despite being the standard of care at many hospitals.

Rivaroxaban was approved in the United States in July 2011 for deep vein thrombosis (DVT) prophylaxis in adults undergoing hip and knee replacement surgery, and gained a second

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Late Stage of Sepsis May Hold Treatment Option

Evidence found for immunosuppression.

BY MARY ANN MOON
Elsevier Global Medical News

During the natural course of sepsis, patients enter an immunosuppressed state after the initial intense inflammatory response well known to clinicians as a "cytokine storm."

Most therapies for sepsis target this initial hyperinflammatory state and are focused on blocking inflammation and immune activation. Such therapies may be successful if used early in the course of sepsis, but harmful if used during the later, underrecognized immunosuppressed phase, said Jonathan S. Boomer, Ph.D., of the department of medicine, Washington University, St. Louis, and his associates.

This latter phase of sepsis only came to light once clinical management improved enough to allow these patients to survive the early hyperinflammatory phase. Then clinicians began noting that patients who survived early sepsis often developed nosocomial infections with organisms that typically do not affect immunocompetent hosts. These patients also frequently experienced reactivation of latent viruses, Dr. Boomer and his colleagues wrote in JAMA.

These observations lead some to hypothesize that hyperinflammation gives way to significant immunosuppression in such patients. The hypothesis has been controversial. Dr. Boomer and his associates explored the issue through rapid postmortem examination of cells from the spleens and lungs of affected patients – "a lymphoid organ and a peripheral organ that [are] frequent site[s] of nosocomial infection."

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INSIDE

Problems Linger for ALI Survivors

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

Survivors of acute lung injury are likely to experience depression and physical impairment for up to 2 years after leaving the intensive care unit.

In a prospective study, 40% of patients had new-onset depression and 66% had new physical impairment after discharge. The findings seem inextricably linked on both psychological and physiological levels, Dr. Oscar J. Bienvenu and his colleagues wrote in the American Journal of Respiratory and Critical Care Medicine.

"Depressive symptoms may decrease motivation for and reward from the physical activities necessary for recovery of maintenance of functioning. … [They] can also amplify symptoms of general medical illnesses, and an increased physical symptom load could negatively affect functioning."

In addition, there may be less-understood links between depression and physical functioning, wrote Dr. Bienvenu of

See **ALI** • *page 18*

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Sleep-Deprived Police Endanger Public Safety

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

Nearly half of North American police officers might be suffering from a sleep disorder that could interfere with the safe execution of their duties.

A survey of nearly 5,000 officers found that 40.4% of them screened positive for a sleep disorder, most of these undiagnosed. Those officers with a sleep disorder were significantly more likely to commit administrative errors, lose their temper with citizens, and even fall asleep while driving, Shantha M.W. Rajaratnam, Ph.D., and colleagues reported.

"Almost half [reported] having fallen asleep while driving," and about a quarter said that this occurs one to two times per month, said Dr. Rajaratnam of Brigham and Women's Hospital, Boston. "This is despite police officers apparently recognizing the dangers associated with drowsy driving." In a different survey of North American police officers, almost 90% regarded drowsy driving to be as dangerous as drunk driving, the investigators noted (JAMA 2011;306:2567-78).

The team conducted an online and in-person survey of 4,957 police officers, 97% of whom were based in the United States and 3% in Canada. The subjects responded to a variety of questionnaires that screen for sleep disorders, including obstructive sleep apnea, insomnia, restless legs syndrome, narcolepsy, and cataplexy. The survey also screened for shift-work disorder. Subjects provided basic health information, as well as information about alcohol intake and feelings of emotional burnout. They then completed monthly surveys for the next 2 years, with an accumulation of 15, 735 surveys.

The mean age of the cohort was 38.5 years; 82.3% were male. More than half (58%) reported their health as very good or excellent. However, 79.3% of the respondents were overweight or obese, and 33.5% were obese.

Most were patrol officers (66.5%), followed by managers (15%), and criminal investigators (8.2%). Only 38% reported never having night-shift work; the rest worked overnight from once per month to nearly every shift.

Of the entire cohort, 2,003 (40.4%) screened positive for at least one sleep disorder. Obstructive sleep apnea was the most commonly identified problem, affecting 1,666 (33.6%) of the participants. The next most commonly identified problem was moderate to severe insomnia, found in 281 (6.5%).

Other findings were shift-work disorder (5.4%), restless legs syndrome (1.4%), and narcolepsy with cataplexy (0.3%).

The group with shift-work disorder represented 14% of those who worked overnight hours, the investigators noted. However, they said, if they applied the International Classification of Sleep Disorders–2 criteria for shift-work disorder (excessive wake-time sleepiness or insomnia), 1,004 (53.9%) of the police officers who worked night shifts screened positive.

The investigators found some significant associations between sleep disorders and health/safety outcomes. Those with a positive screen were almost three times as likely to report depression (odds ratio, 2.75) and job burnout (OR, 2.87), and almost five times as likely to report having fallen asleep while driving after work (OR, 4.64). Of the entire cohort, 2,276 (46%) reported having fallen asleep while driving (56.9% at least once a month, and 13.5% once or twice a week).

At the 2-year follow-up, data were collected on 6,587 person-months for those with positive screens and 9,148 person-months for those with negative screens. Again, the authors found significant correlations between a sleep disorder and a behavioral or safety issue. Compared with those having a negative screen, those with a positive screen were 43% more likely to make an administrative error, 51% more likely to fall asleep while driving, and 63% more likely to make a fatigue-related safety error.

Sleep disorders also significantly correlated with public interaction. Those with positive screens were 25% more likely to experience uncontrolled anger at a citizen or suspect, and 35% more likely to incur a citizen complaint.

Over the follow-up period, those in the cohort experienced 287 motor vehicle accidents, which were 49% more common among those who had reported falling asleep while driving and 68% more common among those who reported falling asleep while stopped in traffic.

Most officers in the study were aware of their personal and performance problems, but they had no idea that a sleep disorder was a key factor.

"This study illustrates that the public at large may also be at risk when police officers are impaired in performing their duties because of sleep deprivation or an untreated sleep disorder," the authors said.

Dr. Rajaratnam reported numerous financial relationships with pharmaceutical and medical device companies. The study was sponsored by the National Institute of Justice and the Centers for Disease Control and Prevention. ■

COMMENTARY

Dr. Paul Selecky, FCCP, comments: Sleep disorders in police officers are similar to sleep disorders in other professionals who must provide services on a 24/7 basis, such as commercial truck drivers, air traffic controllers, firefighters, health care personnel, and others. Maybe this is the time to begin a dialogue with our local police department about sleep disorders. Of interest, note that the study was sponsored in part by the National Institute of Justice.

IN THIS ISSUE

Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of CHEST PHYSICIAN.

CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group, an Elsevier company. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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NEWS FROM THE FDA

Pneumonia Vaccine Approved for Age 50 and Older

A pediatric pneumococcal vaccine has been approved for use in adults aged 50 years and older for preventing pneumonia and invasive disease caused by *Streptococcus pneumoniae*, the Food and Drug Administration announced.

The approval of Prevnar 13, a pneumococcal 13-valent conjugate vaccine, "provides an additional vaccine for preventing pneumococcal pneumonia and invasive disease in this age group," Dr. Karen Midthun, director of the FDA's Center for Biologics Evaluation and Research, said in the statement announcing the approval. Pneumococcal disease is "a substantial cause of illness and death," and about 300,000 adults aged 50 years and older are hospitalized for pneumococcal pneumonia annually in the United States, she added.

Prevnar 13, manufactured by Wyeth Pharmaceuticals, a subsidiary of Pfizer, was approved in 2010 for children aged 6 weeks through 5 years for the prevention of invasive disease caused by 13 serotypes of *S. pneumoniae*, and for the prevention of otitis media caused by seven *S. pneumoniae* serotypes.

The approval in adults is an accelerated approval, which is used to approve products that have meaningful clinical benefit over existing treatments for serious and life-threatening illnesses, based on studies using surrogate effectiveness end points considered reasonably likely to predict clinical benefit. A product can be approved under the accelerated approval regulation if a follow-up clinical study confirming the anticipated clinical benefits is conducted.

The accelerated approval was based on randomized studies comparing immune responses to Prevnar 13 or Pneumovax 23 (a 23-valent pneumococcal vaccine approved in 1983 for children and for adults aged 50 and older) in more than 2,000 patients aged 50 and older in the United States and Europe. "The studies showed that for the 12 common serotypes, Prevnar 13 induced antibody levels that were either comparable to or higher than the levels induced by Pneumovax 23," according to the FDA statement.

To meet postmarketing requirements, the manufacturer is conducting a study of more than 84,000 people aged 65 years and older who have not received Pneumovax 23. The goal is to evaluate whether Prevnar 13 is effective in preventing the first episode of community-acquired pneumonia caused by the 13 serotypes in the vaccine, according to the statement issued by Pfizer announcing the approval. The company is also conducting a study to evaluate the concomitant use of Prevnar 13 and the annual influenza vaccine in adults aged 59 years and older who have previously received the conventional pneumococcal polysaccharide vaccine.

–Elizabeth Mechatie

Low-Dose Zolpidem Approved for Night Awakening

A low-dose sublingual formulation of zolpidem tartrate is the first agent to be approved to treat insomnia characterized by middle-of-the-night waking followed by difficulty returning to sleep, the FDA announced.

Zolpidem tartrate was first approved in the United States in 1992 as the higher-dose formulation known as Ambien.

"For people whose insomnia causes them to wake in the middle of the night with difficulty returning to sleep, this new medication offers a safer choice than taking a higher dose of zolpidem upon waking," said Dr. Robert Temple, deputy center director for clinical science in the FDA's Center for Drug Evaluation and Research, in a statement. "With this lower dose, there is less risk of a person having too much drug in the body upon waking, which can cause dangerous drowsiness and impair driving."

Intermezzo (Transcept Pharmaceuticals) should only be used when a person has at least 4 hours of bedtime remaining. It should not be taken if alcohol has been consumed or with any other sleep aid.

The recommended and maximum dose of Intermezzo is 1.75 mg for women and 3.5 mg for men, taken once per night. The recommended dose for women is lower because women clear zolpidem from the body at a slower rate than men.

Intermezzo was studied in two clinical trials involving more than 370 patients. In the studies, patients taking the drug fell back to sleep faster after awakening, compared with those taking a placebo. The most commonly reported adverse reactions in the clinical trials were headache, nausea, and fatigue.

Potential side effects include getting out of bed while not fully awake and undertaking activities that are not remembered. Reported and not remembered activities have included driving a car, making and eating food, having sex, talking on the phone, and sleepwalking. Risks of such activities increase with use of alcohol or sedating drugs.

Intermezzo is a federally controlled substance.

–Mary Jo Dales

Mortality Increased With Dronedarone and Permanent AF

Dronedarone increases the risk of death and serious cardiovascular events in people with permanent atrial fibrillation, and its use should be limited to the approved indication: the treatment of nonpermanent AF, the FDA has concluded.

In a statement, the FDA announced that its safety review of dronedarone, an antiarrhythmic drug approved in July 2009, has been completed. "The FDA believes that Multaq provides a benefit for patients with nonpermanent AF and recommends that health care professionals who prescribe Multaq follow the recommendations in the revised Multaq drug label," the FDA statement said.

Dronedarone, marketed as Multaq by Sanofi-Aventis, is indicated to "reduce hospitalizations for AF in patients in sinus rhythm with a history of nonpermanent AF."

The FDA's conclusions are based on a review of a large outcomes study that was meant to evaluate the effectiveness of dronedarone in more than 3,000 patients with permanent AF, but was terminated early when it became clear that cardiovascular events were higher among those treated with the drug than in those on placebo. In that study, PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy), the risk of total deaths was increased twofold among those treated with dronedarone compared with those on placebo. Also increased were the risks of death from arrhythmia or sudden death (hazard ratio, 3.26), stroke (HR, 2.32), and hospitalization for heart failure (HR, 1.81) over placebo.

The FDA's reanalysis of the data from ATHENA, the clinical trial that supported the approval of dronedarone in patients with nonpermanent AF, found no increased risk of cardiovascular death, stroke, or heart failure among those on dronedarone compared with those on placebo, and treatment was associated with a reduced the risk of hospitalizations.

The prescribing information for dronedarone has been revised to reflect the results of the safety review, and now advises against prescribing dronedarone to patients with AF "who will not or cannot be converted into normal sinus rhythm," because "it doubles the rate of cardiovascular death, stroke, and heart failure in such patients."

The label also recommends an electrocardiogram to monitor heart rhythm in patients on the drug at least once every 3 months, and if a patient is in AF, treatment should be stopped or, if clinically indicated, the patient should be cardioverted. Patients on dronedarone should also be on "appropriate antithrombotic therapy," the label now states.

From July 2009 through October 2011, about 1.3 million dronedarone prescriptions were dispensed, and about 278,000 patients received prescriptions for the drug from U.S. outpatient retail pharmacies, according to the FDA.

–Elizabeth Mechatie

Atrial Fibrillation Ablation Device Effective; Safety Uncertain

An FDA avisory panel did not support the approval of a catheter-based radiofrequency ablation device for treating persistent atrial fibrillation, citing concerns over safety issues.

At the meeting, the FDA's Circulatory System Devices Panel voted 8 to 2 that the data on the Medtronic cardiac ablation system did not demonstrate that the benefits outweighed the risks of the device for the proposed indication: the treatment of symptomatic, drug refractory, persistent atrial fibrillation or long-standing persistent atrial fibrillation of up to 4 years in duration. Panelists described it as a pioneering and innovative device that was effective in a difficult-to-treat population and unanimously voted that there was "reasonable assurance" that it was effective for the proposed indication.

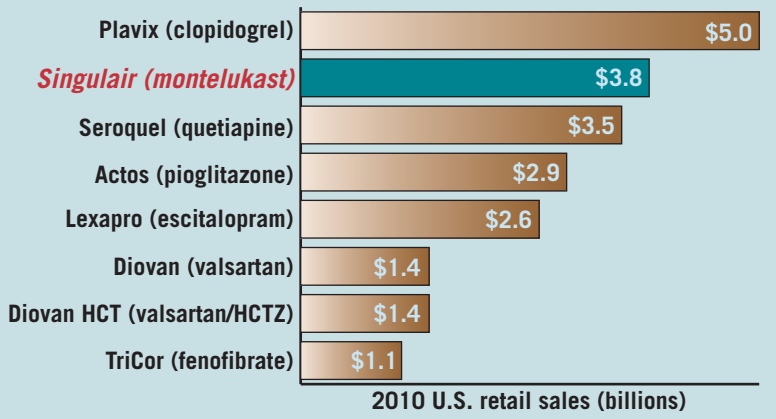
But they voted 9 to 1 that there was not reasonable assurance that it was safe, primarily because of the increased rate of strokes around the time of the procedure (3% of those treated with the device, compared with none among those treated medically) and the 4% rate of pulmonary vein stenosis and symptomatic narrowing of the pulmonary vein seen on CT or MRI 6 months after treatment with the device. Panelists were also concerned about reports in the literature of asymptomatic cerebrovascular emboli in patients treated with the device, which has been available in Europe since 2006, where it is approved for the treatment of paroxysmal atrial fibrillation.

In a prospective multicenter study of 210 patients with a history of symptomatic, refractory atrial fibrillation, patients were randomized to treatment with the device or medical treatment with new antiarrhythmic medications or titration of existing medication, in a 2:1 ratio. The primary end point of the study – acute procedural success and at least a 90% reduction in clinically significant AF/atrial flutter on 48-hour Holter at 6 months – was met by 56% of those treated with the device, compared with 26% of those who were medically managed, a statistically significant difference.

–Elizabeth Mechatie

DATA WATCH

Singulair Among Potential Patent Expirations for 2012



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Source: Medco

Heparin Bridging Linked With Increased Bleeding Risk

Findings suggested 'no risk reduction … with heparin or low-molecular-weight bridging.'

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO – Patients who receive heparin bridging during an interruption of oral anticoagulation appear to be at a 5.4-fold increased risk of overall bleeding and a 3.6-fold increased risk of major bleeding, without a reduction in risk of thromboembolic events.

Those are key findings from a systematic review and meta-analysis of recently published medical literature presented by Dr. Jovana Yudin at the annual meeting of the American Society of Hematology.

Antithrombotic and thrombolytic therapy guidelines published by the American College of Chest Physicians in 2008 recommended bridging according to an individualized approach (Chest 2008;133[suppl. 6]:299S-339S). "They suggested bridging according to patients' bleeding and thromboembolic risk," said Dr. Yudin, a fellow in the hematology residency program at McMaster University, Hamilton, Ont. "Within the last decade, several new studies have been published using periprocedural bridging. In these studies, low-molecular-weight heparin has been used with increased frequency. However, optimal strategies for bridging remain unclear. Our objective was to do a systematic review and meta-analysis of bridging trials published in the last decade to look at thromboembolic risk as well as bleeding risk."

Dr. Yudin and her associates searched the MEDLINE, EMBASE, and Cochrane Collaboration databases for systematic reviews and meta-analyses of studies published between Jan. 1, 2001, and July 31, 2010, that examined bleeding and thromboembolic events in patients receiving bridging therapy during temporary oral anticoagulation interruption for elective surgical or invasive procedures. Studies were excluded if the reporting of thromboembolic or bleeding outcomes was unclear, or if they focused exclusively on patients with renal failure. All studies were reviewed by two independent investigators.

The researchers identified and screened 1,164 studies for review. Of these, 35 studies that included 7,169 bridged patients were selected for the final review. Most of the studies (33) were observational, and only two were randomized. The median follow-up was 30 days.

The most common indication for anticoagulation was atrial fibrillation (44%), followed by mechanical valve (24%), prior venous thromboembolism (22%), and other (10%).

The most common preoperative strategy was to discontinue oral anticoagulation more than 3 days in advance. Low-molecular-weight heparin was most commonly used, both preoperatively and postoperatively.

Dr. Yudin reported that thromboembolic events, which were primarily arterial in nature, occurred in 73 of the 7,169 patients (mean rate, 0.96%). The mean rate of overall bleeding was 13.01%, whereas the mean rate of major bleeding was 4.32%.

Eight of the studies included in the final analysis had control groups from which the researchers were able to pull data to determine an odds ratio for thromboembolism with bridging vs. no bridging. These studies included 1,691 bridged patients and 3,493 nonbridged patients. The odds ratio for thromboembolic events was 0.80, with a 95% confidence interval (CI) of 0.42-1.54, "suggesting no risk reduction for thromboembolic events with heparin or low-molecular-weight bridging," Dr. Yudin said. "There was also no difference between these two groups in the risk for arterial or venous thromboembolism."

To determine the risk of overall bleeding, the researchers pulled data from 13 studies that included control groups. These studies included 1,935 bridged patients and 5,160 nonbridged patients. The odds ratio for overall bleeding with bridging was 5.40 (95% CI, 3.00-9.74). "This suggested an increased risk of overall bleeding with bridging anticoagulation, but there was significant heterogeneity noted across these studies."

For major bleeding, five studies with control groups were assessed. These included 1,397 bridged patients and 2,104 nonbridged patients. The odds ratio for major bleeding was 3.60 (95% CI, 1.52-8.50), "again suggesting an increased risk in major bleeding with bridging," she said. "There was significant heterogeneity noted across studies."

Dr. Yudin acknowledged that the review had certain limitations: Most of the studies included in the analysis were observational, and only about a third had control groups. "Our control groups consisted largely of low-thromboembolic-risk patients, or patients who were not chronically on vitamin K antagonists, suggesting that they had a different risk profile for thromboembolism than many of the bridged patients," she said.

The findings "underline the need for studies of higher [methodological] quality in periprocedural bridging," she concluded. "It also tells us that there is a need for standardized definitions in terms of outcomes. We suspect that much of our heterogeneity had to do with varying definitions for outcomes such as major bleeding." ■

VITALS

Major Finding: Patients who received heparin bridging during interruption of oral anticoagulation had a significantly increased risk of overall bleeding (odds ratio 5.4) and major bleeding (OR 3.6), compared with nonbridged patients.

Data Source: A meta-analysis of 35 studies that examined bleeding and thromboembolic events in patients receiving bridging therapy during temporary interruption of oral anticoagulants for elective procedures.

Disclosures: Dr. Yudin said that she had no relevant financial conflicts to disclose.

COMMENTARY

Dr. Jun Chiong, FCCP, comments: The findings underline the need for further studies, especially in vulnerable populations such as the elderly, in whom the need for anticoagulation is greater due to a higher incidence of atrial fibrillation. With the advent of the three new orally administered anticoagulants (apixaban, dabigatran, and rivaroxaban) that have a shorter time to therapeutic level, the need for bridging heparin may not always be necessary, except in specific cases, such as pulmonary embolism.

Less Bleeding, Shorter Stay

Rivaroxaban • *from page 1*

indication in November 2011 for stroke prophylaxis in patients with nonvalvular atrial fibrillation.

Dr. Beyer-Westendorf and colleagues analyzed 5,346 consecutive patients who underwent major orthopedic surgery at the university clinic during three periods: 2005-2007 when LMWH was the standard prophylaxis; 2008-2009 when fondaparinux was the standard; and finally from 2010 to June 2011 when rivaroxaban became the clinic's standard prophylaxis.

In all, 1,055 patients were treated with rivaroxaban, 1,683 with LMWH, and 2,069 with fondaparinux. Of note, previous VTE was more common at baseline in the rivaroxaban group at 4% vs. 1.4% in the LMWH group and 1.1% in the fondaparinux group, he said.

Rivaroxaban reduced the relative risk of the composite of proximal DVT, pulmonary embolism, and VTE-related death by 29%, compared with LMWH, and 42% compared with fondaparinux, but the difference between the three groups did not achieve statistical significance (1.0% vs. 1.4% vs. 1.7%), Dr. Beyer-Westendorf said.

In a pooled analysis of RECORD 1, 2, and 3, rivaroxaban significantly reduced the composite of symptomatic VTE and all-cause mortality during the 2-week period after surgery, compared with enoxaparin (0.4% vs. 0.8%), according to the Bayer HealthCare website.

In the current analysis, severe bleeding was significantly lower with rivaroxaban at 7.4% vs. 14.9% with LMWH and 11.1% with fondaparinux. Bleeding leading to surgical revisions was also significantly lower at 0.4% vs. 1.7% with LMWH and 1.1% with fondaparinux.

Dr. Beyer-Westendorf pointed out that severe bleeding rates were less than 1% in the RECORD 1-4 trials using a more narrow definition of severe bleeding as overt bleeding outside of the surgical site. Their analysis used the International Society on Thrombosis and Hemostasis criteria for severe bleeding.

Finally, the reduction in VTE events, bleeding, and surgical revisions was correlated with a significantly shorter median hospital stay in patients given rivaroxaban prophylaxis vs. LMWH or fondaparinux (8.3 days vs. 11.6 days vs. 9.3 days).

Dr. Beyer-Westendorf said it was unlikely that changes in anesthesia or surgical practice over the study period could have attenuated the results. In addition, the researchers conducted a matched-pair analysis to evaluate whether the benefits of rivaroxaban were due to selection or detection bias. Outcomes remained superior for rivaroxaban after matching patients according to age, gender, type of surgery, and history of VTE. Complete compression ultrasound testing also remained constant at about 13% from 2005 to 2010 before falling to 8.2% in 2011 due to fewer complete compression ultrasound–positive findings, Dr. Beyer-Westendorf noted.

"These findings in a large real-world surgery cohort are robust and not significantly influenced by a selection or detection bias," he said. ■

COMMENTARY

Dr. Vera DePalo, FCCP, comments: Venous thromboembolism can be a complication of surgery, in particular hip and knee surgeries. Its consequences have a significant impact on postsurgical morbidity and mortality. Thus, VTE prophylaxis is an important part of postsurgical care. An oral factor Xa inhibitor, with good efficacy and safety profiles, offers the clinician additional options for treatment with an easier route of administration and the possibility of better patient compliance.

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

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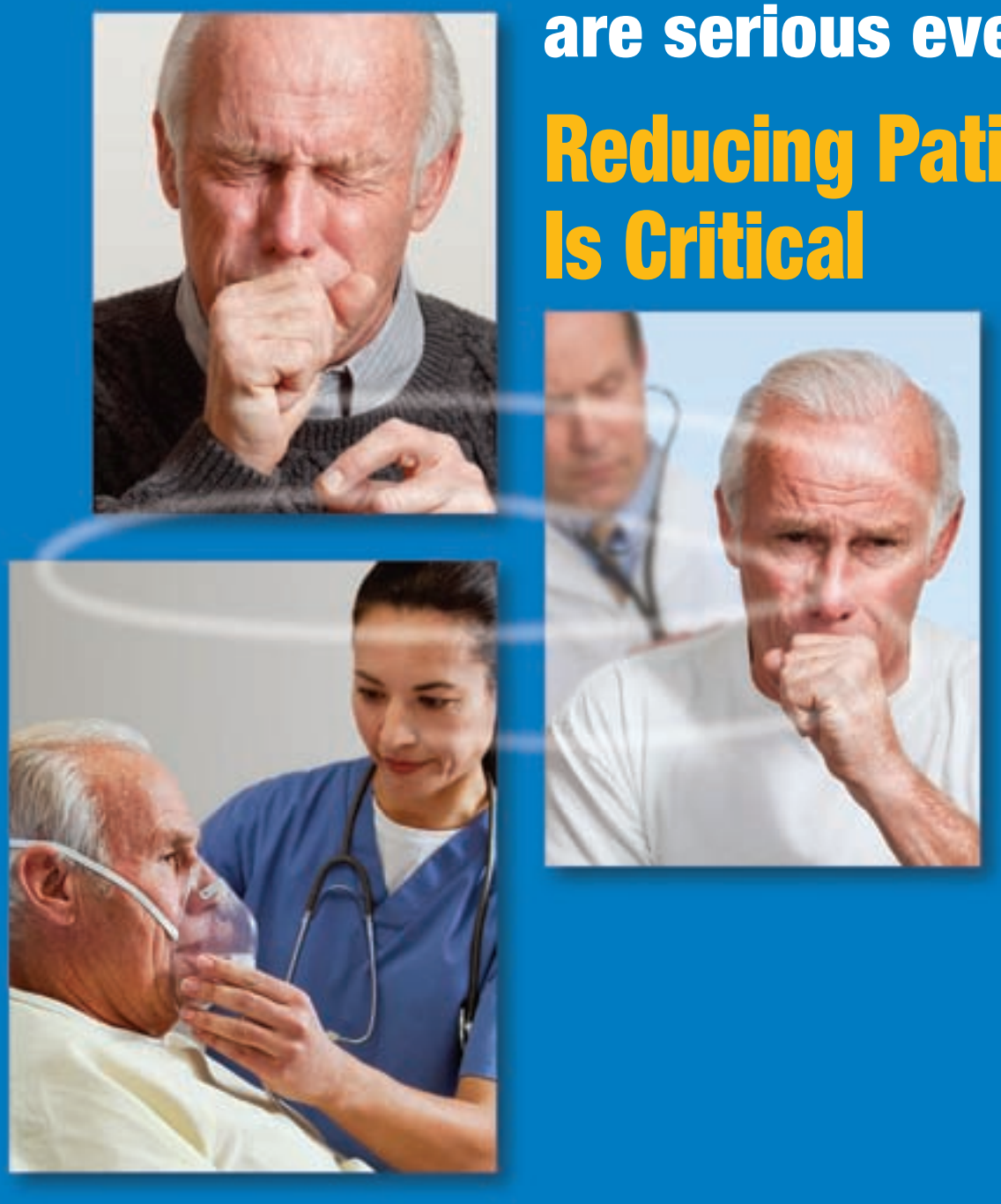

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Tablet shown not actual size.

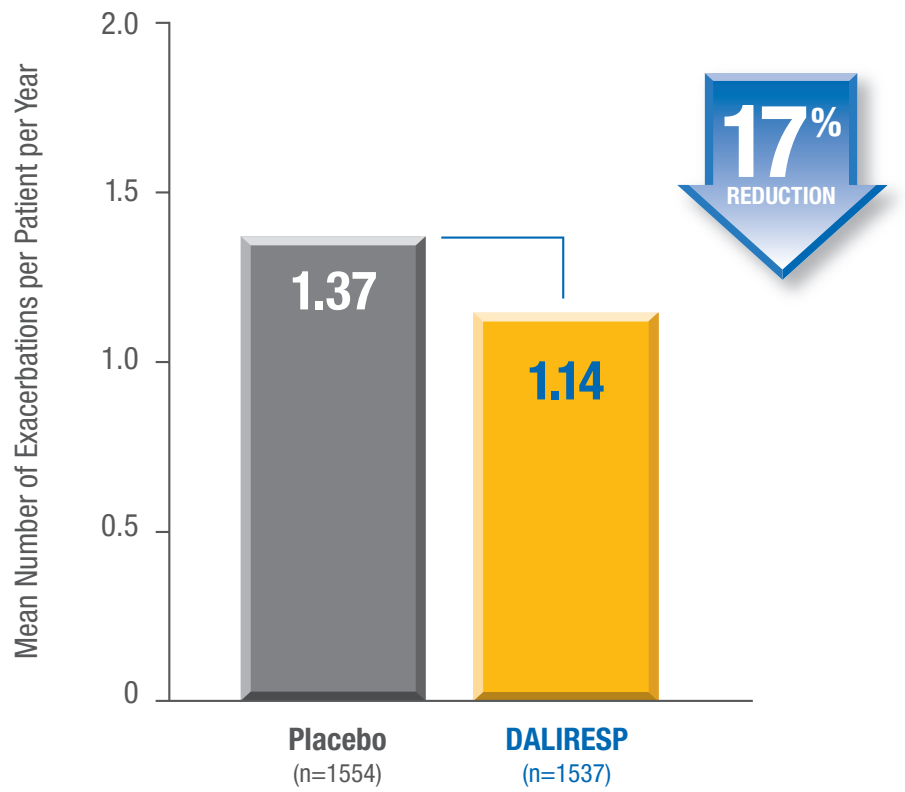
- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight).
  - During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost.
- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP.

Daliresp®
(roflumilast) tablets
500 mcg

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

DALIRESP significantly reduces exacerbations

REDUCTION IN THE RATE OF MODERATE OR SEVERE EXACERBATIONS[3,4]



P=0.0003 vs placebo

Study design: A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs or short-acting anticholinergics were allowed as concomitant treatment. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV_1) were co-primary endpoints. Each study met both co-primary endpoints.

- Moderate exacerbations were defined as those requiring treatment with systemic corticosteroids[1]
- Severe exacerbations were defined as resulting in hospitalization and/or death[1]

INDICATIONS AND USAGE

DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.

References: 1. DALIRESP (roflumilast) Prescribing Information. Forest Pharmaceuticals, Inc. St. Louis, MO. **2.** US Food and Drug Administration. FDA approves new drug to treat chronic obstructive pulmonary disease. March 1, 2011. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm244989.htm. Accessed October 19, 2011. **3.** Data on file. Forest Laboratories, Inc. **4.** Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ; for the M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet.* 2009;374:685-694. **5.** US Food and Drug Administration. Atrovent approval history (NDA 019085, 1986). Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed October 19, 2011.

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

Effective with LABAs or short-acting anticholinergics

In the same studies:

DALIRESP significantly reduced the rate of exacerbations vs placebo in patients using a bronchodilator[1,3]

CONSISTENT EFFECT WITH A CONCOMITANT BRONCHODILATOR[1,3]

DALIRESP with LABAs (Long-acting $ß_2$ Agonists)	✓
DALIRESP with Short-acting Anticholinergics	✓

Study design: A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs and short-acting anticholinergics were allowed and were used by 44% and 35% of patients treated with DALIRESP and 45% and 37% of patients treated with placebo, respectively. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV_1) were co-primary endpoints. Each study met both co-primary endpoints.

- **The effect with concomitant LABAs or short-acting anticholinergics was similar to that seen in the overall population[1,3]**

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.

Adverse Reactions

In clinical trials the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see additional Important Safety Information on the previous pages and Brief Summary of full Prescribing Information on the following page and at www.DALIRESP.com.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Daliresp®
(roflumilast) tablets
500 mcg

 84-12000308Tr1 11/11

DALIRESP® (roflumilast) tablets **Rx Only**
Brief Summary of Full Prescribing Information

Initial U.S. Approval: 2011

INDICATIONS AND USAGE

DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following conditions:

Moderate to severe liver impairment (Child-Pugh B or C) [*see Clinical Pharmacology (12.3) and Use in Special Populations (8.6)*].

WARNINGS AND PRECAUTIONS

Treatment of Acute Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) *[see Adverse Reactions (6.1)]*. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [*see Adverse Reactions (6.1)*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (eg. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended. [*see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)*].

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Psychiatric Events Including Suicidality *[see Warnings and Precautions (5.2)]*
- Weight Decrease *[see Warnings and Precautions (5.3)]*

Adverse Reactions in Clinical Studies

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

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials *[see Clinical Studies (14.1)]*. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥ 2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP** (**N=**4438) n (%)	**Placebo** (**N=**4192) n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting

Infections and infestations - rhinitis, sinusitis, urinary tract infection,

Musculoskeletal and connective tissue disorders - muscle spasms

Nervous system disorders - tremor

Psychiatric disorders - anxiety, depression

DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [*see Clinical Pharmacology (12.3)*].

Drugs That Induce Cytochrome P450 (CYP) Enzymes

Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended *[see Drug Interactions (5.4) and Clinical Pharmacology (12.3)].*

Drugs That Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. *[see Clinical Pharmacology (12.3)].*

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3)].*

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses > 2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg^2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m^2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

Labor and Delivery

DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m^2 basis at a maternal dose of > 2 mg/kg/day).

Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use

COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use

Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3)]*.

Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

OVERDOSAGE

Human Experience

No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

Manufactured by:
Nycomed GmbH.
Production Site Oranienburg
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Manufactured for:
Forest Pharmaceuticals, Inc.
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Please also see full Prescribing Information at www.daliresp.com.

MITH Score Uses Admission Criteria to Predict VTE

Nine admission factors were significantly associated with a risk of VTE.

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO – The three most significant risk factors for venous thromboembolism among medical inpatients were a history of congestive heart failure or of rheumatologic or inflammatory disease and having a fracture in the past 3 months.

Those are findings from a study of a risk assessment model known as the Medical Inpatients and Thrombosis (MITH) score, which was developed to help clinicians assess venous thromboembolism (VTE) risk at admission for medical inpatients. The score relies on assessing risk factors at admission.

"The few current risk assessment models for hospital-acquired VTE have many limitations," Dr. Neil A. Zakai said at the annual meeting of the American Society of Hematology. "Some of these are empirically derived. Others are derived from selected medical populations such as restricting hospital stays more than 3 days and restricting patient age, and others have difficult-to-assess VTE risk factors such as anticipated bed confinement or hypercoagulable states that may or may not be documented in the medical record."

Dr. Zakai, of the department of medicine and pathology at the University of Vermont, Burlington, and associates studied an unselected medical population and included all VTE events. They conducted a frequency-matched case-control study at a 500-bed teaching hospital in Vermont. They studied 299 cases of hospital-acquired VTE that occurred between Jan. 1, 2002, and May 31, 2009, using ICD-9-CM discharge codes, and validated the cases by medical record review. A total of 601 controls were frequency matched by admission service and year.

Risk factors for VTE were collected at admission as part of routine medical care. "Models were built using clinical judgment; we didn't use automatic selection algorithms," Dr. Zakai explained. "Points were assigned for each risk factor by dividing the beta values by the lowest beta value in the model and rounding to the nearest integer. Models were validated using multiple permutation methods."

Dr. Zakai reported that the VTE event rate during the study period was 4.6 per 1,000 admissions. About half of the events (154) were DVT plus or minus pulmonary embolism.

"What's remarkable is the large number of upper-extremity DVTs, representing approximately half of all DVTs for this population," he said.

Most of the VTE events occurred on the general medicine service (an incidence of 8 per 1,000 admissions), followed by the oncology service (7.6 per 1,000 admissions) and the cardiology service (1.1 per 1,000 admissions).

Nine admission factors were significantly associated with a risk of VTE: history of congestive heart failure (odds ratio 8.6, and a score of 5 on the MITH scale), history of rheumatic or inflammatory disease (OR 7.7, and a score of 4 on the MITH scale), fracture in the past 3 months (OR 3.8, and a score of 3 on the MITH scale), history of VTE (OR 2.7, and a score of 2 on the MITH scale), history of cancer in the past year (OR 1.6, and a score of 1 on the MITH scale), tachycardia (OR 2.5, and a score of 2 on the MITH scale), respiratory dysfunction (OR 1.9, and a score of 1 on the MITH scale), white blood cell count of 11 or greater (OR 1.9, and a score of 1 on the MITH scale), and a platelet count of 350 or greater (OR 1.9, and a score of 1 on the MITH scale). Each of these risk factors was assigned a point value, which could range from 1 to 5.

A high risk of VTE was attributed to anyone with a score of 2 points or greater on the MITH scale. Using this definition, 70% of cases and 39% of controls were classified as high risk. The probability of venous thromboembolism in the absence of prophylaxis was 1.5 per 1,000 admissions in those with a MITH score of less than 2 and 8.9 per 1,000 admissions for those with a MITH score of 2 or greater.

Using validation and sensitivity analysis, the researchers determined that the c-statistic for the model was 0.73 (95% confidence interval, 0.70-0.76) and 0.71 when the lab studies on admission were excluded (95% CI, 0.68-0.74).

Limitations of the study include its single-center design and the fact that the findings are validated by statistical means only. "Patients with rare risk factors may be misclassified as low risk, and the level of VTE risk warranting VTE prophylaxis is not established," Dr. Zakai said. ■

VITALS

Major Finding: The probability of venous thromboembolism in the absence of prophylaxis was 1.5 per 1,000 admissions in those with a Medical Inpatients and Thrombosis (MITH) score of less than 2 and 8.9 per 1,000 admissions for those with a MITH score of 2 or greater.

Data Source: A frequency-matched case-control study of 299 cases of hospital-acquired VTE and 601 controls at a 500-bed teaching hospital in Northern Vermont.

Disclosures: The study was funded by a Hemophilia and Thrombosis Research Society Mentored Research Award and by the Jeffords Quality Institute at Fletcher Allen Health Care, which is affiliated with the University of Vermont.

COMMENTARY

Dr. Carl Kaplan, FCCP, comments: This is a new, thoughtful prediction and risk assessment tool for medical patients at the time of admission relating to venous thromboembolism, the Medical Inpatient and Thrombosis (MITH) score. The importance of prevention of venous thromboembolism for every hospitalized patient is highlighted in our guidelines and centers around risk assessment. We need a multicenter prospective validation study with the assessment of event reduction with adequate prophylaxis and low adverse events.

Statin May Cut Atrial Fibrillation Risk

BY BRUCE JANCIN
Elsevier Global Medical News

ORLANDO –The higher a patient's baseline high-sensitivity C-reactive protein level in the landmark JUPITER study, the greater the incidence of new-onset atrial fibrillation during follow-up, and randomization to rosuvastatin significantly reduced this risk.

VITALS

Major Finding: Apparently healthy subjects with high C-reactive protein and an LDL below 130 mg/dL who were placed on rosuvastatin at 20 mg/day had a 27% lower incidence of new-onset atrial fibrillation than placebo-treated controls during a mean of 1.9 years of follow-up.

Data Source: Double-blind, randomized JUPITER study.

Disclosures: JUPITER was sponsored by AstraZeneca. Dr. Peña reported having no relevant conflicts of interest.

Among the 17,120 apparently healthy participants in JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) with no baseline history of atrial fibrillation or other arrhythmia, those in the highest baseline tertile for C-reactive protein (CRP) – that is, more than 5.8 mg/L – had an adjusted 1.96-fold greater incidence of new-onset atrial fibrillation during follow-up, compared with those in the lowest tertile for the inflammatory biomarker, with a CRP of less than 3.2 mg/L, Dr. Jessica M. Peña reported at the annual scientific sessions of the American Heart Association.

Those in the middle tertile had a 1.7-fold increased risk of developing atrial fibrillation after adjustment for age, gender, race, exercise, alcohol intake, current smoking, metabolic syndrome, hypertension, body mass index, and glycosylated hemoglobin.

The incidence of atrial fibrillation was 0.83 cases per 100 person-years in subjects in the top tertile for baseline CRP, 0.75 per 100 person-years for those in the middle tertile, and 0.43 per 100 person-years among patients in the lowest tertile, according to Dr. Peña of Brigham and Women's Hospital, Boston.

Rosuvastatin (Crestor) proved to have a significant impact upon this risk. The crude incidence was 1.6% with placebo, compared to 1.2% with the statin, which worked out to an adjusted 27% reduction in relative risk in the rosuvastatin group.

The presumed mechanism of benefit lies in the mounting evidence suggesting that inflammation plays a role in both the initiation and maintenance of atrial fibrillation. Statins have anti-inflammatory properties that could be helpful in preventing the arrhythmia, she observed.

In this post hoc analysis, atrial fibrillation was not a prespecified study end point, Dr. Peña stressed. She and her coinvestigators undertook this exploratory analysis because other studies have yielded mixed results regarding statins and atrial fibrillation. The JUPITER analysis provided an opportunity to focus on a population with an underlying proinflammatory state as manifest by the requirement that participants had to have a baseline CRP of at least 2 mg/L.

A recent meta-analysis found that the available evidence does not support the notion that statins reduce atrial fibrillation risk (BMJ 2011;342:d1250). Dr. Peña surmised that the different study conclusions were probably due to different populations and methods of detecting atrial fibrillation. "Until we have better data we can't definitively answer the question of whether statins protect against atrial fibrillation," Dr. Peña said. ■

COMMENT

Dr. Jun Chiong, FCCP, comments: It is comforting to know that what we commonly do to slow the progression of coronary disease can also cut the risk for atrial fibrillation. However, secondary analysis only proves association and the hypothesis generated has to be tested in a randomized setting.

Flu Vaccine Facility May Not Speed Production

BY MITCHEL L. ZOLER
Elsevier Global Medical News

With the official dedication of America's first facility for making influenza vaccine in cell culture, the United States took a small but important step toward improved protection against the next flu pandemic, experts said.

But some question just how many weeks this new facility will shave off of the timeline for moving from a candidate pandemic vaccine strain to getting the vaccine into the arms of the American public. And by relying on an inherently old-fashioned approach to flu protection with limited effectiveness, some see this development as merely refining an archaic vaccine that is overdue for replacement by a newer and better method of immunoprotection against pandemic influenza.

"It's a small, incremental step in preparedness, but the current hemagglutinin-antigen based vaccine really is inadequate for providing the kind of immunologic protection we need, and so anything you do to speed up the amount of [this type of] vaccine is only a marginal improvement in protecting against influenza," commented Michael T. Osterholm, Ph.D., professor in the school of public health and director of the Center for Infectious Disease Research and Policy at the University of Minnesota, Minneapolis.

"Having a new facility of substantial production capacity in the United States is a comfort," said Dr. William Schaffner, professor of medicine and chairman of preventive medicine at Vanderbilt University, Nashville, Tenn. "When you're creating a pandemic vaccine, every week counts," and the cell culture–based technology that the new plant employs "is supposed to be somewhat faster" than conventional, egg-based production of flu vaccine, he noted. By not relying on chicken-based egg production that might conceivably be vulnerable to an avian flu pandemic, the new facility also sidesteps that potential danger.

The new vaccine plant, in Holly Springs, N.C., culminates a 7-year project by Novartis working on contract with the Health and Human Services department, which funded 49% of the construction costs. The new plant brings cell-based flu vaccine production into the United States, and eventually onto the U.S. vaccine market, for the first time and also serves to beef up U.S.-based flu vaccine production of all types.

HHS officials first envisioned the new facility in 2004, when the U.S. flu vaccine supply became threatened by many previous manufacturers going out of business, and when the supply from British-based Chiron temporarily went off line, said Robin Robinson, Ph.D., director of the HSS Biomedical Advanced Research and Development Authority. The facility uses cultured canine kidney cells to grow influenza vaccine.

COURTESY NOVARTIS

The new facility, located in Holly Springs, N.C., culminates a 7-year project by Novartis working on contract with the Health and Human Services department.

The Holly Springs plant became operational in late 2009, and now has produced several commercial-scale lots that have undergone testing in phase III trials, Dr. Robinson said in an interview. The facility is positioned to immediately start making as much as 50 million doses of pandemic flu vaccine using cell-culture production, which could receive emergency-use FDA licensing and be available to the American public.

In the absence of a pandemic, the facility will primarily focus on making seasonal influenza vaccine (as well as certain other vaccines), but with less urgency.

For pandemics, a major goal of cell-based flu vaccine production is to have "more vaccine available sooner," Dr. Robinson said. "The goal is 4 months" once a candidate vaccine strain is isolated during a new pandemic, but a more realistic expectation is that the facility will send out significant amounts of vaccine after "4-5 months," he said. That compares with the 5 months it took to have the first egg-based vaccine appear during the H1N1 pandemic of 2009, he noted.

Even saving just a couple weeks or so could make a difference, some experts said. "If the H1N1 vaccine had been available in quantity 1 month earlier, it would have made a difference in containing the [2009] pandemic," said Dr. W. Paul Glezen, a professor of molecular virology and microbiology at Baylor College of Medicine, Houston. "Using a tissue culture substrate to grow influenza viruses provides flexibility to vaccine production not available before using embryonated eggs. It should be safer as well, with less danger of contamination."

Next on the agenda for the Biomedical Advanced Research and Development Authority and HHS is to finish plans to make pandemic flu vaccine using recombinant technology. Dr. Robinson said this could produce vaccine within about 12 weeks, and that this capability is roughly 2 years away.

But recombinant vaccine may not be ideal either. Investigational recombinant vaccines have had effectiveness levels comparable to the 60% seen in trivalent inactivated vaccines. The answer, Dr. Osterholm said, lies in better understanding the immunity produced by natural flu infection and using that as a model to develop new vaccine antigens that reach much higher levels of effectiveness.

"Much of what we know about flu immunity is for hemagglutinin, and that's not much," he said. "In 2009, there was clear evidence that 65- to 70-year-olds had residual protection to H1N1 from when that virus last circulated in the 1950s. These elderly people were entering immunosenescence, but they still had good protection. Yet we can't get good protection from year to year with hemagglutinin-based vaccines. That shows something else going on immunologically that we should think about. Several possible target antigens have been identified, but so far they are not going anywhere because there has not been sufficient investment."

Dr. Osterholm and Dr. Robinson said that they had no disclosures. Dr. Schaffner said that he has been a consultant to GlaxoSmithKline, Dynavax, Novartis, and Pfizer, and that he has served on data safety and monitoring boards for Sanofi-Pasteur and Merck. Dr. Glezen said that he has received a research grant from MedImmune. ■

COMMENTARY

Dr. Stuart Garay, FCCP, comments: Hailed as a major breakthrough, the opening of a new facility to produce cell-based flu vaccine will result in "1 month less time" to produce pandemic flu vaccine. Such a "breakthrough" would not make a difference in a pandemic, arriving too late. It is a sad commentary that we cannot stimulate research toward better and more rapid techniques to produce vaccine.

Spleen, Lung Tissue Examined

Sepsis • *from page 1*

They assessed the organs of 40 patients who died while being treated for sepsis in surgical or medical intensive care units, and in control samples from 29 patients who had critical illnesses that did not involve sepsis. The control tissue came from organ donors, trauma patients who required emergency splenectomy, and non–tumor-involved lung tissue from lung cancer patients who underwent lobectomies.

The causes of sepsis included ventilator-associated pneumonia, peritonitis, necrotizing fasciitis, retroperitoneal abscess, infected intravascular catheters, urinary tract infection, intrapelvic abscess, and osteomyelitis.

IT MAY BE POSSIBLE TO IDENTIFY SEPSIS PATIENTS WHO ENTER THIS PHASE AND TREAT THEM WITH IMMUNE-ENHANCING THERAPIES.

Compared with cells from control spleens, splenocytes from sepsis patients showed profound impairment of cytokine production when stimulated in vitro. At 5 hours after collection, the secretion of cytokines from splenocytes of sepsis patients was less than 10% of that secreted by control splenocytes, the investigators said (JAMA 2011;306:2594-605).

Splenocytes from most sepsis patients showed some recovery of cytokine production at 22 hours, but they still secreted only one-third the number of cytokines produced by control splenocytes. This result was consistent for all the cytokines tested and for all subgroups of patients, regardless of the duration of sepsis, patient age, whether corticosteroids had been received, and patient nutritional status at the time of death.

The researchers identified many separate mechanisms by which immune responses were inhibited in spleen cells. They found a decrease in stimulatory molecules such as CD28 on T cells, a deficiency in antigen-presenting cells such as macrophages and dendritic cells, increased expression of inhibitory ligands that suppress immune function, and an excess of inhibitory cells such as myeloid-derived suppressor cells and regulatory T cells.

Lung tissue similarly showed significant immunosuppression in sepsis patients, compared with control patients. In particular, lung alveolar epithelial cells and endothelial cells showed an excess of inhibitory receptors and ligands.

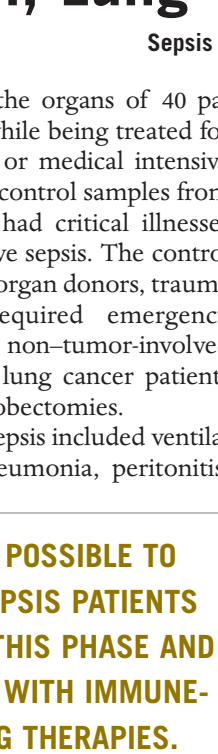
The study findings suggest that it may be possible to identify sepsis patients who enter this phase of immunocompromise and treat them with immune-enhancing therapies such as interleukin, the researchers said.

The study was limited by its small sample size and the heterogeneous nature of both the sepsis and control patients, the authors said. They further emphasized that malnutrition should be recognized for its possible effects on host immunity and that for a number of reasons, their study "must be viewed cautiously." The research "serves as a bridge between preclinical and early clinical findings," they wrote.

This study was supported by the National Institutes of Health. One coauthor reported receiving grants from Pfizer, Bristol-Meyers Squibb, and Aurigine. ■

COMMENTARY

Dr. Stephen Field, FCCP, comments: This study explores the expression of anti-inflammatory mediators in severe sepsis and appears to establish an association of the anti-inflammatory phenotype with mortality. Due to limitations of the study design, it is not possible to say whether expression of this phenotype led to death, or if progressive tissue hypoxia or other factors in the premorbid state stimulated expression of the anti-inflammatory phenotype. Nevertheless, the importance of exploring in detail the anti-inflammatory side of severe sepsis is underscored by this study, and new therapeutic avenues may open because of it.



Seeing a Seizure? Look for Pulmonary Embolism

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

BALTIMORE – A seizure was initially the only presenting symptom in 1% of patients diagnosed with pulmonary embolism during a 5-year retrospective study of cases seen at an emergency department.

Although it is an unusual presentation, pulmonary embolism–related seizure does occur, and when it does, it's a life-threatening emergency, Dr. Kimitoshi Kimura reported in a poster at the annual meeting of the American Epilepsy Society.

"With a seizure, clinical evaluation may be compromised by the postictal confusional state. Hypoxia, tachypnea, and tachycardia, which are important signs of PE, may be attributed to the seizure. This results in delayed diagnosis," said Dr. Kimura of the department of neurology at Kurashiki (Japan) Central Hospital.

He reported a retrospective study of 319 pulmonary embolism (PE) cases seen at the hospital over a 5-year period. The vast majority of these (282) did not involve any seizure activity. Most (165) had classic PE symptoms of chest pain, hypoxia, and impaired consciousness. In 75 cases, the only early symptom was swelling or tenderness in the leg, leading to a PE diagnosis. Another 42 cases were asymptomatic and were detected incidentally. No diagnostic details were available for 34 cases.

Only 1% (3 cases) initially presented as a seizure; none of these patients had a history of any seizure or cardiopulmonary disorders.

The first case was a 78-year-old man who "suddenly raised his hands over his head and stared at a fixed point for a substantial period of time," Dr. Kimura wrote. "On the next evening, he complained of increasing dyspnea and was taken to our hospital." The patient arrived already in cardiopulmonary arrest. The PE was diagnosed soon after, but the patient died the next day.

The second case was an 87-year-old woman who complained of chest discomfort while at home. The next morning, she experienced generalized tonic seizures with conjugated deviation; the seizures occurred intermittently for 4 hours. She was admitted to the hospital and received four 5-mg doses of diazepam. When the seizures stopped, the patient had persistent hypoxia and an elevated D-dimer of more than 10 mcg/mL (normal is less than 1.0 mcg/mL). Mild right ventricular overload and PE were detected.

ALTHOUGH IT IS AN UNUSUAL PRESENTATION, PULMONARY EMBOLISM–RELATED SEIZURE IS A LIFE-THREATENING EMERGENCY.

"In this case, she was treated successfully with anticoagulation therapy," Dr. Kimura wrote.

The third patient was a 78-year-old woman admitted because of a 5-minute generalized tonic-clonic seizure and drowsiness. After the seizure, she also remained hypoxic and had a D-dimer value of 2.3 mcg/mL.

"At first, we suspected the cause of the seizure was a cerebral infarction because a small subacute infarction was detected, but intermittent oxygen desaturation persisted," Dr. Kimura noted. The embolism was diagnosed 2 days later. This patient was successfully treated with heparin.

Neither of the surviving patients required any antiepileptic drugs after discharge, he added.

Dr. Kimura reported that he had no financial conflicts. ■

COMMENTARY

Dr. Vera DePalo, FCCP, comments: As a disease entity, pulmonary embolism is underdiagnosed. Too often, the diagnosis of pulmonary embolism is not premortem. A high level of suspicion is needed for timely diagnosis and the initiation of treatment. Dr. Kimura's study provides one more clinical finding that helps the clinician suspect pulmonary embolism and move rapidly toward diagnosis and therapy.

No Lung Damage Seen in Typical Marijuana Smokers

BY MARY ANN MOON
Elsevier Global Medical News

Unlike cigarette smoking, 20 years of typical marijuana smoking doesn't appear to impair lung function, according to a report in JAMA.

"With up to 7 joint-years of lifetime exposure (e.g., one joint per day for 7 years or one joint per week for 49 years), we found no evidence that increasing exposure to marijuana adversely affects pulmonary function," said Dr. Mark J. Pletcher of the department of epidemiology and biostatistics and the department of medicine, University of California, San Francisco, and his associates.

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Only at very high levels of marijuana smoking was a detrimental effect on pulmonary function suggested.

While heavier use may impair lung function, the number of such users was too small in this study cohort to allow reliable estimates, the investigators noted.

Previous studies of the pulmonary effects of long-term marijuana use have yielded inconsistent results. Some have demonstrated "consistent evidence of airway mucosal injury and inflammation, as well as increased respiratory symptoms such as cough, phlegm production, and wheeze, similar to that seen in tobacco smokers." However, these appear to be short-term effects, and there has been no clear evidence of long-term damage to lung function.

Dr. Pletcher and his colleagues used data from a large longitudinal study of coronary risk that closely followed the cigarette and marijuana smoking habits of 5,016 young adults in four U.S. communities from 1985 through 2006. As part of that study, the subjects (aged 18-30 years at baseline) underwent pulmonary function testing at baseline, 2 years, 5 years, 10 years, and 20 years.

Using that data, "we estimated both current intensity and lifetime cumulative exposure to tobacco and marijuana smoking and analyzed their associations with spirometric measures of pulmonary function over the 20 years of follow-up," the researchers said.

As expected, both current and lifetime tobacco smoking were associated with lower forced expiratory volume in 1 second (FEV_1) and lower forced vital capacity (FVC). But unexpectedly, both current and lifetime marijuana smoking were associated with higher FEV_1 and higher FVC, the authors wrote (JAMA 2012;307:173-81).

Why marijuana smoking would increase lung capacity is unknown, but other studies have also found this effect. "Some investigators have proposed that the deep inspiratory maneuvers practiced by marijuana smokers could stretch the lungs, resulting in larger lung volumes. Another speculative possibility is strengthening of chest wall musculature or another 'training' effect that allows marijuana users to inspire more fully (closer to lung capacity) on spirometry testing," Dr. Pletcher and his associates said. Only at very high levels of marijuana smoking was a detrimental effect on pulmonary function suggested.

This study was supported by the National Institute on Drug Abuse and the National Heart, Lung, and Blood Institute. Dr. Pletcher reported no conflicts of interest. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: Prior work has highlighted potential adverse consequences from smoking marijuana. The results of this observational study, however, suggest no detrimental effect in "typical marijuana smokers," although lung function was impaired with heavier usage. It is important to recognize daily-use subjects were followed for only 7 years, marijuana usage was self-reported, and spirometry may not be the most sensitive test for the early detection of abnormalities. Nonetheless, while the definition of a typical marijuana user can be debated, these results will be reassuring to some.

Recommendations Made for Off-Label Cancer Treatments

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

Prospective clinical studies that evaluate off-label uses of approved oncology drugs for advanced cancers should include patients in community settings and, whenever possible, should use actual survival as the primary outcome instead of a surrogate for survival, according to recommendations published online in the Journal of Clinical Oncology.

These and other proposed recommendations are outlined in a document intended "to guide the design of future prospective trials for off-label use of oncology drugs," wrote C. Daniel Mullins, Ph.D., professor of pharmacoeconomics at the University of Maryland, School of Pharmacy, Baltimore, and his coauthors, in the paper (doi:10.1200/JCO.2011.35.5198). The recommendations "address the needs of patients and their clinical providers, compendia, payers, and policy makers,"

The document is intended 'to guide the design of future prospective trials for off-label use of oncology drugs.'

DR. MULLINS

and focus on "the design of clinical studies to support evidence-based clinical and health policy decision making," but do not focus on changing the Food and Drug Administration–approved label of these drugs or resulting in approvals of the indications.

Referring to the "pervasive" use of oncology drugs for nonapproved indications, the authors noted that, in 2005, 50%-75% of cancer drugs were being used off label, an increase from previous years, but clinical evidence was available to support use of the drug for only about 27% of the off-label indications. Sources oncologists turn to when prescribing off-label treatments for patients include FDA-approved drug labels, medical literature, anecdotal information from colleagues, and continuing education programs, which are useful, but "reflect evidentiary gap that make it difficult for end users to gain information sufficient to make informed treatment decisions," they said.

The recommendations are based on the proceedings of a November 2009 meeting hosted by the Center for Medical Technology Policy (CMTP), with input from oncologists, drug manufacturers, the FDA, the National Cancer Institute, the Centers for Medicare and Medicaid Services, public and private payers, and other stakeholders. The recommendations apply to studies of drugs for late-stage cancers, "in which there are hypothesized survival benefits for the drugs being examined in new indications," and are most likely relevant to patients who have been pretreated and have gone beyond first-line treatments. (The CMTP is a private, nonprofit organization, which "serves as a neutral forum to promote discussion and development strategies that improve the quality of clinical research for health care decision making," according to its website. (The founder and director, Dr. Sean Tunis, is a coauthor of the paper.)

"In oncology, more so than in any other area of medicine, drugs are used outside of FDA-labeled indications," Dr. Mullins said in an interview. In some cases, there is good evidence of the drug's net health benefit for the indication that has not resulted in approval for that indication or a label change. "But oftentimes, there is very limited evidence, so physicians have to make decisions and talk with patients about important decisions that affect their lives," without adequate evidence, he noted.

To address this gap, the group provided recommendations about the conduct of clinical trials of off-label indications so that the study of a treatment and the data collected in the postapproval setting parallel what takes place in the "preapproval process for a drug being reviewed for an indication being considered for [FDA] approval, where the data are more consistent," said Dr. Mullins, who is also with the School of Pharmacy's Center of Drugs

and Public Policy. "Our goal is to help patients and their physicians make better informed decisions" by making more consistent data available, so that if, for example, two drug options have been studied in similar trials, "you can compare them more readily," he added.

The recommendations in the document are divided into four categories: trial design and data analysis, patient and site recruitment, comparators, and outcomes.

Recommendations in the section on trial design and data analysis include using a blinded reviewer, incorporating biomarkers, and designing the study protocol to test the drug for the intended therapeutic use and in the way it is expected be used (as monotherapy or as adjuvant therapy, for example). Subpopulations should be described before the study starts, not in a post hoc analysis that may not provide adequate information.

The section on patient and site recruitment includes the recommendation to develop a strategy that addresses the reluctance of patients and physicians to participate in a study of a drug that is available – and to recruit patients from different clinical practice settings, since most patients are treated for cancer in the community, although most trials are available in academic medical centers.

The section on comparators includes the recommendation to use active comparators in studies that are approved by the FDA, are commonly prescribed, and are considered as having the "greatest clinical net benefit," for the indication being evaluated – with clear definitions of other components of treatment, such as surgery radiation or palliative care.

The outcomes section states that actual survival, "whenever feasible," should be used instead of a surrogate for survival as the primary outcome in studies, referring to frustration among decision makers over the common use of surrogate markets for survival in oncology drug studies. When a survival end point is not feasible, disease-free survival or progression-free survival can be used as the primary outcome end point, but in such cases, it is important to provide evidence of a link between one of these end points and actual survival, patient-reported outcomes, or health-related quality of life for the type and stage of cancer and the treatment being studied. Studies should also collect "meaningful" patient data, such as health-related quality of life measures.

'OUR GOAL IS TO HELP PATIENTS AND THEIR PHYSICIANS MAKE BETTER INFORMED DECISIONS' BY MAKING MORE DATA AVAILABLE.

In an accompanying editorial, Dr. David Pfister of Memorial Sloan-Kettering Cancer Center, New York, described the framework provided in the paper as "an important and thoughtful start to better understanding and defining the indications for, and appropriate use of, off-label drugs in cancer care." However, more work will be needed to "address potential challenges to the implementation of the recommendations," he added (doi:10.1200/JCO.2011.38.5567).

Dr. Mullins has served as a consultant or as an adviser for Amgen, Bayer Pharmaceuticals, Bristol-Myers Squibb, Glaxo, Novartis, Pfizer, and Sanofi-Aventis, for which he received compensation; and has received funding from the CMTP, Bayer, GSK, Novartis, Pfizer, and Sanofi-Aventis. One of the other authors, Stephen Pearson of Massachusetts General Hospital, Boston, has received funding from Merck, Johnson & Johnson, and the National Pharmaceutical Council. ■

Biomarkers May Improve Lung Cancer Screening

New technologies could lead to earlier diagnosis and treatment of lung cancer.

BY DIANA MAHONEY
Elsevier Global Medical News

New noninvasive screening technologies are poised to improve the diagnostic yield of advanced imaging in lung cancer and, by so doing, improve patient outcomes, according to Dr. Paul A. Bunn.

A blood test for detecting genetic mutations in circulating tumor cells of lung cancer specimens and a colorimetric sensor array that identifies cancerous compounds in exhaled human breath are among the technologies that could lead to earlier diagnosis and treatment, said Dr. Bunn, executive director of the International Association for the Study of Lung Cancer (IASLC).

Lung cancer treatment has been hampered in the past by late diagnoses, typically achieved using invasive procedures only after symptoms have presented, said Dr. Bunn, the James Dudley Professor of Lung Cancer Research at the University of Colorado at Denver.

"But this is changing quickly," he said. "Major breakthroughs are leading to interventions that make a huge difference and make it an exciting time for lung cancer."

The first such breakthrough has been the use of low-dose helical computed tomography, which can identify early-stage disease in asymptomatic individuals while exposing them to a fraction of the radiation emitted by a standard diagnostic chest CT or x-ray, Dr. Bunn said in a press briefing on research presented at a joint conference of the American Association for Cancer Research and the IASLC.

"Spiral CT scans reduced lung cancer mortality by 20% [among current or former heavy smokers] and increased the 7-year survival rate by 20% compared with standard chest x-rays," he said, citing preliminary results of the National Lung Screening Trial (NLST) (N. Engl. J. Med. 2011;365:395-409).

"The low-dose CT screening also increased the diagnosis of stage I cases and surgical cures while they decreased the number of stage IV diagnoses because patients were diagnosed earlier and cured," he said.

Unfortunately, the value of CT scans as a routine screening tool is limited by the technology's low specificity. In the NLST study, approximately 24% of the participants screened positive based on abnormal CT scan findings, but only 4% of the abnormalities were confirmed as lung cancer. This has led to controversy over whether smokers should be routinely screened for lung cancer.

"The remaining 96% were false positives," said Dr. Bunn, who maintained that the technology, on its own, is currently not cost effective enough to recommend for routine annual screening. "Working up those nodules is incredibly expensive and complicated, and often leads to surgery for something that is benign, not malignant," he said.

The cost/benefit ratio stands to improve substantially, however, as some of the noninvasive screening technologies presented at the conference come to fruition, Dr. Bunn predicted.

For example, Heidi S. Erickson, Ph.D., and her colleagues at the University of Texas M.D. Anderson Cancer Center in Houston have developed a highly sensitive method for detecting cancer mutations in DNA isolated from circulating tumor cells of non–small cell lung cancer (NSCLC). They use the mass spectrometry–based technology to look for any of 135 mutations among 13 genes representing multiple pathways known to be involved in lung cancer.

The methodology requires a simple blood test, which makes it less intrusive than a biopsy. The information will ultimately help investigators understand the molecular characteristics of lung cancer treatment and progression, Dr. Erickson said in an interview. When perfected, it will also complement the information attained via spiral CT scans by providing important insight into diagnostic, prognostic, and predictive markers of disease, thus aiding management decisions, she said.

Similarly, a test identifying lung cancer biomarkers through exhaled breath may also help clinicians and researchers identify which patients with abnormal CT scans need more aggressive follow-up, according to Dr. Bunn.

Dr. Nir Peled of the Sheba Medical Center in Tel Hashomer, Israel, presented data from a cross-sectional comparative survey using breath analyses, in which investigators captured the "metabolic biosignatures" – the pattern of volatile organic compounds (VOCs) – of 74 patients with solitary pulmonary nodules to determine the VOC profiles for malignant and benign lung nodules.

For the analyses, a patient's breath is drawn across an array of nanomaterial-based sensors, and the patterns are captured using digital cameras. Of the 74 high-risk patients, 53 had malignant nodules and 21 had benign growths, Dr. Peled reported. Within the malignant group, 47 samples were NSCLC and 6 were small cell lung cancer. Further, 30 of the patients had early-stage (I/II) disease and 23 had advanced disease (stage III/V), he said.

"On analysis, two [VOCs] in patients' exhaled breath showed statistically significant differences in concentration for benign and malignant lung nodules, and the sensor array distinguished between the corresponding collective VOC patterns with nearly 90% accuracy," Dr. Peled said in an interview.

Further, looking specifically at the malignant nodules, "the sensor array distinguished between small and non–small cell lung cancer with an accuracy approaching 94% and between early and advanced disease with nearly 90% accuracy."

Although the test is a work in progress and not yet ready for clinical application, the findings suggest the possibility that a noninvasive breath analysis tool would be a useful, cost-effective diagnostic tool for managing nodule-positive patients, Dr. Bunn said. "We make advances one step at a time, and these are first steps, but they're important," he added.

Dr. Bunn disclosed financial relationships with numerous pharmaceutical companies. Dr. Peled said she had no relevant financial disclosures. No disclosures were received from Dr. Erickson. ■

COMMENTARY

Dr. Lary Robinson, FCCP, comments: Highly accurate, noninvasive screening for early-stage lung cancer is the Holy Grail of thoracic oncologists and pulmonologists. While low-dose spiral CT scanning has been proven effective, there are high costs involved to separate true cancers from the large number of false-positive nodules. Still, at the research level, Dr. Bunn describes two novel screening techniques that offer exciting promise for improving accuracy with a greater cost-benefit ratio. Further studies will define whether these new methods prove to be clinically useful.

Depression, Impairment Common

ALI • *from page 1*

Johns Hopkins University, Baltimore, and his coauthors.

"Depressive symptoms could affect functioning through direct neurobiologic pathways, including neuroendocrine and inflammatory mechanisms."

The study comprised 2-year follow-up data on 186 patients. All of the patients were mechanically ventilated for acute lung injury (ALI). Baseline depression was present in 21% and baseline physical impairment in 40% (Am. J. Respir. Crit. Care Med. 2011 Dec. 8 [doi: 10.1164/rccm.201103-0503OC]).

The patients' mean age was 49 years; 56% were male. The mean length of stay in the intensive care unit (ICU) was 19 days. Patients were assessed for depression and physical function at 3, 6, 12, and 14 months after discharge.

During the entire follow-up period, 40% of the patients experienced new-onset depression and 66% had new-onset physical impairment. Remission occurred in 39% of those with depression and 54% of those with physical impairment, but there was recurrence in 20% and 14%, respectively. Most of those who developed depression or physical impairment had symptoms at 24 months (69% and 58%).

Patients who did remit, however, tended to do well. In those with remitted depression, the mean score on the Hospital and Anxiety Depression Scale remained about 5, indicating normal mood. In those whose symptoms did not remit, the score remained 10 or higher, indicating moderate to severe depression. Similarly, those with remission of physical impairment had a mean of 1 impaired activity of daily living, compared with a mean of 4 or more in those with unremitted impairments.

When the authors looked at potential risk factors for new-onset depression and physical impairment, only two remained statistically significant in multivariate analyses. Education of 12 or fewer years increased the risk of new-onset depression threefold. Only depression at last follow-up significantly correlated with new-onset physical impairment (odds ratio, 2.7).

"Our analyses indicate that depressive symptoms are not only relatively persistent in ALI survivors, they are also an independent risk factor for subsequent impairment in physical function," the authors wrote. "Hence, early identification and treatment of depressive states should be evaluated as a potential intervention to minimize the suffering and impairment that affect too many of these patients."

The National Institutes of Health supported the study. None of the authors reported any financial conflicts. ■

COMMENTARY

Dr. Marcos Restrepo, FCCP, comments: This interesting study shows our limited understanding of the complexity of interactions that may occur with prior comorbid mental health illnesses and physical impairment and the appearance of new events during hospitalization and after discharge. These data suggest that transitions of care of ALI survivors who are likely to develop depression and physical impairment during the hospitalization or after discharge requires clinicians' awareness and further evaluations. In addition, follow-up strategies focused on appropriate diagnosis, management, and prevention may be important to decrease morbidity in ALI survivors.

Pages 18a—18b

ACCP Publishes 9th Edition of Antithrombotic Guidelines

BY SANDRA ZELMAN LEWIS, PH.D.

The *Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: ACCP Evidence-Based Clinical Practice Guidelines*, were published in the February print and online issues of *CHEST*. This edition's print version provides the Executive Summary and all recommendations, the Introduction, and Methods. The online version provides the complete supplement, with all full chapters and many special features, including supplemental tables and podcasts, mobile-optimized/app views, and much more.

Since the first edition of these guidelines in 1986, the ACCP antithrombotic guidelines have become one of the most widely followed and cited guidelines in the medical community. The 8th edition has had several million accesses from the journal's Web site and over 120,000 additional page views retrieved through the National Guideline Clearinghouse.

The 9th edition guidelines mark a significant advance in the field of evidence-based medicine. Innovative procedural and methodological (Guyatt et al. *Chest*. 2012;141[2][suppl]:53S) advancements have resulted in many changes in the recommendations, both clinically and in terms of the strength of the recommendations.

Many of the strong recommendations in the 8th edition have been downgraded to moderate or weaker levels for two major reasons:

- Today's more rigorous assessments of the quality of the evidence have led to lower confidence in the estimates of effect.
- A systematic review has demonstrated the considerable heterogeneity of patient values and preferences, resulting in less certainty that most patients would chose the same option (a hallmark of a strong recommendation) when provided with choices.

With this set of the guidelines, the ACCP is refining the selection of outcomes to specify that they must be patient-important outcomes. This patient-focused improvement impacted the body of evidence by allowing for additional studies to be included in some areas, whereas in other areas, literature previously relevant no longer met the inclusion criteria. Some of the recommendations most affected by this advance involve the use of risk stratification and aspirin for prophylaxis. Refer to the three prevention articles in the guideline publication for specific recommendations (Kahn et al. *Chest*. 2012;141[2][suppl]:53S; Gould et al. *Chest*. 2012;141[2][suppl]:e227S; Falck-Yttr et al. *Chest*. 2012;141[2][suppl]:e278S).

The new guidelines delve further into prevention, which has been separated into three major areas: medical patients, orthopedic surgery patients, and all other surgical patients. This edition includes an article on diagnosis (Bates et al. *Chest*. 2012; 141[2][suppl]:e351S) for the first time. Frontline clinicians helped to define clinically important areas in which evidence-based guidance was needed. Physicians with health economic expertise consulted on a methodology to consider whether and how resource use might change the direction or strength of recommendations (Guyatt et al. *Chest*. 2012;141[2][suppl]:53S).

The ACCP Health and Science Policy Committee took a stricter approach to the review of nominees' conflicts of interest and final approval. However, the Executive Committee of the guideline panel also monitored and managed intellectual conflicts of interest, employing unconflicted volunteer methodologists to lead each of the chapter committees and allowing only unconflicted individuals to have full recommendation drafting and voting rights (Guyatt et al. *Ann Intern Med*. 2010;152 [11]:). Readers will note many other advancements in the new guidelines.

Watch for related clinical resources and educational programs coming out soon and during CHEST 2012. Access www.chestnet.org often.

The ACCP is working hard to produce the very best evidence-based clinical guidelines in chest medicine. In the end, it is the patients who benefit the most. ■

For more information, contact Sandra Zelman Lewis, PhD, slewis@chestnet.org.

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

Consultations Popular at CHEST 2011

BY DIANE KRIER-MORROW, MBA, MPH, CCS-P; AND MARLA BRICHTA

The ACCP Practice Management Department has offered two unique educational opportunities for CHEST annual meeting attendees for the past 6 years: one-on-one practice management consultations and practice management roundtable discussions.

One-on-One Practice Management Consultations

Diane Krier-Morrow, MBA, MPH, CCS-P, the ACCP's coding and reimbursement consultant, met with 35 attendees to discuss practice management, coding, and/or billing issues relevant to their practices. Attendees who met with Ms. Krier-Morrow on the first day also had the unique opportunity of also meeting with Arthur Lurvey, MD, Medicare Director, Medicare Administrative Contractor (MAC) Palmetto GBA, Jurisdiction I (American Samoa, California, Guam, Hawaii, Nevada, and the Northern Mariana Islands). Ms. Krier-Morrow and Dr. Lurvey met with a number of constituents from California and Hawaii, as well as from practices from other states.

One attendee shared that he had stopped reporting the 6-minute walk (CPT **94620**) because payment was denied by Medicare on the same day reported with an evaluation and management (E/M) code. Ms. Krier-Morrow and Dr. Lurvey advised the attendee that, indeed, a 6-minute walk test is reportable on the same day with an E/M, with an appended modifier 25. All that was needed by the contractor was the Medicare Summary Notice showing the inappropriate denial, which is true for any errors. The answer to this question can also be found in the *ACCP Coding for Chest Medicine 2011* book.

We had a very interesting discussion on inpatient billing of subsequent hospital care. Dr. Lurvey cautioned that every day the patient would not warrant the highest level of E/M. He suggested that on the first subsequent day, you would document and appropriately report a **99233**; the next day, the patient might be a bit better and your documentation would support a **99232**; the third day he/she is not better, so it might be documented and reported as a **99233**, the patient is then better the next day, and again, and a couple days of **99232**, until discharged.

Many of the physicians and their staff did not know about the new 4th and 5th digits for diagnosis coding for interstitial lung diseases that became effective on October 1, 2011. They were cautioned to check with their staff or external billers to see if the correct diagnosis codes were reported. If the new 4th and 5th digits are missing on claims, the claim will be denied. Many also wanted to know more about the four new pulmonary function testing codes that replaced 10 existing pulmonary function codes (written about in the November and December issues of *Chest Physician*. The 1:1 consultations covered many different topics. Discussions during the 3 days included discussions with fellows going into practice, retiring, interventional bronchoscopists and navigational bronchoscopy; and reporting of CPT Category III codes, such as bronchial valves and acoustic PFTs, critical care and use of NP/PA in the ICU, new sleep introductory language and diagnosis coding, documentation in an electronic medical record, Physician Quality Reporting System (PQRS), and RAC audits.

It is very important for anything heard at the annual meeting or anywhere related to coding is checked with a reliable resource and shared with coding and billing staff and external billers. You do not want to change a coding practice unless you are sure of the change.

Practice Management Roundtable Discussions

Several practice management discussions were led by members of the Practice Management Committee and the Practice Operations NetWork. Attendees had many diverse practice management issues they were able to address in the forums provided by the ACCP Practice Management Department. Throughout the meeting, attendees were encouraged to purchase the most recent version of *ACCP Coding for Chest Medicine*. A 2012 edition of the book was not published, and new information was transmitted through *CHEST Physician* articles and the weekly e-mail *ACCP NewsBrief*. We are beginning to work on the coding book for 2013. This publication is an invaluable practice management resource tool for any pulmonary, critical care, or sleep medicine practice in the United States. ■

ACCP Practice Administrators/Managers (PAM) Meet at College Headquarters

BY MARLA BRICHTA

With the ACCP Headquarters located in the Chicago area, the idea was proposed to pilot a face-to-face quarterly meeting of practice administrators (PAs)/practice managers (PMs) at the ACCP in Northbrook, Illinois. On December 9, 2011, the third Chicagoland PAM meeting was held.

This gathering of PAs/PMs began at the first meeting with four individuals attending and has increased steadily at subsequent meetings. The practice type and size vary from two- to three-physician pulmonary groups to 250 multispecialty practices. The PAs/PMs attending enthusiastically discuss how they are all working toward running effective and efficient pulmonary medical practices.

After introductions and some background practice information, the group has had robust discussions about the following topics and many others:

- Size of practice
- Type of services provided: pulmonary, critical care, sleep, and any ancillary-related services
- Use of physician extenders in your practice
- Hiring physicians
- High deductible insurance collections
- In-house or outsourced billing services
- Electronic health records
  - –What you need to know when investigating
  - –What products fit your practices needs
  - –Implementation plans and training
  - –Challenges faced during implementation and after
  - –Lessons learned along the way
- Equipment-diagnostic
  - –Due diligence before purchase
  - –What you need to due for ROI
  - –What equipment is obsolete or will be
- Documentation practices, challenges
- Reimbursement issues, challenges, denials
- eRX
- PQRS program participation and reporting
- Audits
- Surprise visits by regulatory agencies
- Coding procedures properly
- Determining awareness of the practice management resources, educational courses, and products that the ACCP has available to members, including a membership category for practice administrators; access to *CHEST Physician* and coding updates; practice management section in the *CHEST* journal; and the ACCP CAC.

Many have expressed their surprise at "not knowing what they need to know." One major recommendation resulting from these Chicago PAM meetings was to plan an informal meeting of regional practice administrators/managers at each annual CHEST meeting. The goal would be to market this meeting to PAMs in the vicinity of the CHEST meeting site (Atlanta 2012, Chicago, 2013). This could be a valuable networking opportunity and align with the mission and values of the ACCP. Watch for more information to come.

Register today for the **ACCP Business of Medicine** course. http://www.chestnet.org/accp/events/american-college-chest-physicians-business-medicine. ■

Access 2012 coding updates in *CHEST Physician* at www.chestnet.org/accp/chest-physician.

This Month in *CHEST*: Editor's Picks

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

EDITORIAL

- **Introducing the Future of ACCP Clinical Practice Guidelines.** *By Dr. M. L. Metersky, FCCP; and Dr. I. Nathanson, FCCP.*

ORIGINAL RESEARCH

- **A 12-Year Follow-up Study of Patients With Newly Diagnosed Lone Atrial Fibrillation : Implications of Arrhythmia Progression on Prognosis: The Belgrade Atrial Fibrillation Study.** *By Dr. T. S. Potpara et al.*
- **Fluticasone/Salmeterol Combination Confers Benefits in People With Asthma Who Smoke.** *By Dr. K. L. Clearie et al.*

TOPICS IN PRACTICE MANAGEMENT

- **Understanding the Economic Impact of Introducing a New Procedure: Calculating Downstream Revenue of Endobronchial Ultrasound With Transbronchial Needle Aspiration as a Model.** *By Dr. N. J. Pastis, FCCP, et al.*

COMMENTARY

- **Prevention of Embolic Strokes: The Role of the American College of Chest Physicians.** *By Dr. J. E. Dalen, Master FCCP.*
- **Will Performance Measurement Lead to Better Patient Outcomes? What Are the Roles of the National Quality Forum and Medical Specialty Societies?** *By Dr. J. M. O'Brien, FCCP, et al.*

SUPPLEMENT

- **Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.**

Pulmonary Perspectives

Update on Mesothelioma

Malignant pleural mesothelioma (MPM) is an orphan disease that has been challenging researchers and clinicians since it was first recognized as a distinct disease entity in the 1960s. There are approximately 3,500 new cases of mesothelioma diagnosed yearly in the United States. Pleural mesothelioma accounts for approximately 80% of cases, peritoneal mesothelioma accounts for 10% to 15% of cases, and there are rare reports of cases originating in the pericardium, testes, and tunica vaginalis.

Asbestos exposure has been directly linked to the development of malignant mesothelioma. The male to female incidence of mesothelioma is reported as 4:1, due largely to workplace exposure to asbestos. Secondhand exposure, due to fibers brought home on clothing and non-workplace exposure during home remodeling/repair, often leads to a diagnosis at a younger age rather than the average age of diagnosis, which is reported as 70 years. Mesothelioma can also develop following radiation exposure, and a genetic predisposition has been implicated. Erionite, a mineral in the zeolite family with properties similar to asbestos, was found to be the causative agent in the development of mesothelioma with alarming mortality rates in villagers on the Anatolian plateau in Turkey. Geological surveys have also discovered erionite in at least 12 US states, and it has recently been reported that 300 miles of roads in North Dakota, over the past few decades, were surfaced with erionite-containing gravel, thus exposing potentially countless citizens (Carbone et al. *Proc Natl Acad Sci U S A*. 2011;108[33]:13618). The latency period from exposure, primarily to asbestos, to the development of disease has been reported to be between 20 and 60 years.

The development of accurate studies of early detection seems to be an important aspect of management because the vast majority of patients are still today diagnosed at late stages of the disease, which contributes to the ongoing high mortality. Serum proteins such as mesothelin and osteopontin, though promising, have not achieved the specificity and sensitivity required for routine screening. Tissue biopsy remains the standard for confirming the diagnosis of mesothelioma and distinguishing it from adenocarcinoma of the lung and other malignant conditions. Fluorodeoxyglucose F18 PET-CT imaging is superior to both CT scan and MRI in overall staging and monitoring the response to therapy.

Chemotherapy

In 2004, pemetrexed and cisplatin were granted a US FDA indication for the treatment of malignant mesothelioma. No other agents have been approved thus far in either the first-line or second-line setting. In a randomized controlled trial, Vogelzang and colleagues (*J Clin Oncol*. 2003;21[14]:2636) reported the results of 456 patients randomized to receive either cisplatin plus placebo vs cisplatin coupled with pemetrexed. In the pemetrexed arm, median survival was reported at 12.1 months vs 9.3 months in the control arm (P =.020, two-sided log-rank test). Median time to progression was also significantly improved: 5.7 months in the doublet vs 3.9 months (P =.001). Response rates were 41.3% in the pemetrexed/cisplatin arm vs 16.7% in the control arm (P < .0001). Smaller trials have evaluated the combination of pemetrexed and carboplatin, with response rates ranging from 19% to 22% and median survival ranging from 13 to 15 months. Substitution of carboplatin for cisplatin in patients for whom cisplatin is not thought to be tolerable remains a viable option. The role of maintenance therapy with pemetrexed is currently under investigation in the Cancer and Leukemia Group B (CALGB) 30901 trial. The overall goal of this trial will be progression-free survival. In this study, patients receive four cycles of pemetrexed and cisplatin, and those who have demonstrated any response or stability of disease will be randomized to receive pemetrexed every 3 weeks vs no further treatment. The patients who receive maintenance therapy will then be compared with those who do not, with regard to disease progression or the development of unacceptable toxicity requiring discontinuation of the chemotherapy. It is expected that up to 96 patients will be enrolled in this multicenter trial. A recent multicenter, multinational trial (Abstract 1LBA. Abstract presented at: 2011 European Multidisciplinary Cancer Congress; September 24, 2011; Stockholm, Sweden), in which 660 patients who were previously treated but had a relapse were randomized to receive vorinostat (a suberoylanilide hydroxamic acid) vs placebo, reported that it did not meet its criteria for response at the study endpoint, which was increased overall survival. Referral to chemotherapy clinical trials should be considered for either first-line therapy or following failure of the now standard pemetrexed/cisplatin regimen.

Surgery

Some would argue that there is no role for surgery based upon the recently reported results of the Mesothelioma and Radical Surgery (MARS) trial. Others debate the optimal nature of surgery for mesothelioma, that is, extrapleural pneumonectomy (EPP) vs a radical pleurectomy and decortication (PD). Questions addressing the timing of chemotherapy, neoadjuvant vs adjuvant therapy, performance of radiation therapy, and the role of intensity-modulated radiation therapy all complicate the development of a standard treatment protocol for patients with mesothelioma. Is it the failure of chemotherapy or the surgery that prevents patients from enjoying a long remission or even a cure in this disease? These are questions that need to be addressed. However, unfortunately, in a rare disease, randomized trials to answer these many disparate questions are not feasible, and we must look at clinical data from large referral centers where the vast majority of surgical patients are treated.

The MARS trial was designed to be a feasibility study to determine if patients could indeed be randomized to either a surgical or chemotherapy arm. The trial was designed to accrue 50 patients in 1 year to determine if randomization to such radically different arms was feasible, thus paving the way for a much larger trial. The goal was not met in that it took 3 years to accrue 50 patients. Patients were to receive three cycles of a platinum-based chemotherapy (neoadjuvant chemotherapy), and if they met surgical criteria, subsequently randomized to receive an EPP followed by radiation therapy vs the physician's choice of treatment. Between October 2005 and November 2008, 112 patients were registered, of whom 50 were randomly assigned to EPP (n=24) vs no surgery (n=26). Of those who did not go on to randomization, 33 patients had disease progression, 5 patients had an inoperable status, and 19 patients withdrew from the study. Sixteen of the 24 randomized patients underwent a complete EPP. Of those eight patients who did not complete the EPP, surgery was not even attempted in five patients, and it was abandoned in three patients. Eight of the 16 patients who underwent EPP completed radiation therapy. Median survival was reported at 14.4 months for the EPP group vs 19.5 months for the non EPP group (Treasure et al; MARS trialists. *Lancet Oncol*. 2011;12[8]:763). Many criticisms have been leveled at this much-advertised study. The number of patients was, in fact, smaller than most published series; the overall survival was lower than presently reported in tertiary care centers; and the morbidity and mortality rates fall outside those that have come to be acceptable (2%-5%) among surgeons who operate on large numbers of patients with mesothelioma.

A recent paper (Flores et al. *J Thorac Cardiovasc Surg*. 2008;135[3]:620) describing the surgical experience in 663 consecutive patients from three large referral centers was analyzed in an attempt to define the overall survival difference among patients who underwent either PD or an EPP between the years 1990 and 2006. The study concluded that patients who underwent an EPP had a poorer survival than those undergoing a PD, although the author concluded that the reasons for this difference in survival were multifactoral and subject to selection bias. Operative mortality for PD was reported at 4% vs 7% for EPP. The median survival of patients with stage I mesothelioma undergoing either EPP or PD was 38 months vs 7 months for those assessed as stage IV. Others have reported that, for those patients with epithelial disease who have early-stage disease, 45% will be alive at 5 years. This is a significant improvement over the dismal figures that were reported in earlier series of patients. Operative morbidity is limited, and mortality is reported at 3% to 5% by surgeons with a vast experience in operating on patients with this disease. Unfortunately, advanced-stage disease is the first diagnosis for the majority of patients, and, for this group, new strategies need to be developed.

Research and Clinical Trials

In mesothelioma, it is important that patients, if at all possible, be referred to clinical trials, from which data regarding the development of methods of early detection and the optimization of treatment can be derived. This treatment may involve surgery, chemotherapy, and radiation therapy vs a varied combination of these different modalities. These modalities are potentially administered in a varying order with the aim of ultimately defining the best approach to management.

New and often molecularly targeted therapies are being developed on a much more regular basis. There is hope that we will ultimately develop an approach to treatment that will be helpful in prolonging the lives of those with mesothelioma and even potentially curing the disease. Refer to www.cancer.gov/clinicaltrials for a list of trials currently accruing patients diagnosed with mesothelioma.

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CHEST Foundation Awards Program 2012

The CHEST Foundation provides funds for volunteer service, leadership, and clinical research through its annual awards program. In 2012, awards are offered in several areas. The CHEST Foundation offers 1-, 2-, and 3-year awards for ACCP members' projects.

Fourth Eli Lilly and Company Distinguished Scholar in Critical Care Medicine award is open to ACCP members who are FCCPs. The individual selected as Distinguished Scholar would develop an original education project that will help disseminate new knowledge about critical care medicine and advance the creation of best practices in patient care. The recipient would investigate innovative treatment of critical care patients and create, manage, and evaluate a project over a 3-year period. This award is intended to fund the investigation of issues that are not easily supported through traditional funding. The award grants $150,000 over the course of 3 years.

Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency. This 1-year $25,000 award supports research focused on COPD and AAT deficiency. Research projects primarily in usual COPD (not associated with AAT deficiency) are allowed. Projects with a focus on AAT deficiency are encouraged.

The CHEST Foundation and the Respiratory Health Association of Metropolitan Chicago Clinical Research Award in Women's Lung Health and The Sheila J. Goodnight Clinical Research Award in Women's Lung Health (NEW). These two, 1-year $10,000 awards support clinical researchers' projects related to women's lung health, which may include research on gender differences in various lung diseases. The Sheila J. Goodnight Award was established this year in memory of Dr. Goodnight who died in 2011. Dr. Goodnight served as Professor of Medicine and Chief of the Section of Pulmonary, Critical Care, and Sleep Medicine at the Michael E. DeBakey VA Medical Center. Among many leadership roles within the ACCP, she served as chair of the Women's Health NetWork.

The CHEST Foundation California Chapter Clinical Research/Medical Education Award. This award supports a $5,000, 1-year clinical research or medical education project proposed by an ACCP member who lives in California. Candidates must be members of the ACCP and hold the degree of MD, DO, MBBCh, PharmD, PhD, or its equivalent.

OneBreath® Clinical Research Award in Lung Cancer. This 2-year $100,000 award ($50,000 annually) supports a project that is focused on medical and/or surgical detection, and treatment of lung cancer that is based on clinical and/or translational research. Applicants must be ACCP members who have completed at least 2 years of pulmonary or critical care fellowship or a thoracic surgery residency and be within 7 years of completing training.

The CHEST Foundation Clinical Research Award in Pulmonary Arterial Hypertension (NEW). This 1-year $50,000 award supports an outstanding researcher in the formative stage of his or her career who proposes an innovative PAH research project. This award is new for 2012 and has been established through a generous grant from Actelion Pharmaceuticals, US, Inc. Criteria for applicants will be posted at OneBreath.org.

Roger C. Bone Advances in End-of-Life Care Award. This 1-year award of $10,000 supports an ACCP member's project that stresses importance of communication, compassion, and effective listening. The award is given for leadership in end-of-life care—on the international, national, or local level—and does not fund research or provide seed money for new projects.

The D. Robert McCaffree, MD, Master FCCP Humanitarian Awards support the volunteer efforts of those who give time and expertise to improve the health of people in communities throughout the world. The award provides funds to nonprofit and nongovernmental organizations where ACCP members give pro bono service. Awards in amounts of $5,000, and up to $15,000, to a total of $50,000 will be granted in 2012, plus a $5,000 Ambassadors Group Humanitarian Award.

Learn more and apply for an award at OneBreath.org. The application deadline is May 4, 2012. ■

PCCSU Lesson for February

▶ Excessive Sleepiness: Evaluation and Management.
By Dr. Alon Y. Avidan

PCCSU
Pulmonary, Critical Care, Sleep Update

Looking Beyond The CHEST Foundation Awards

BY DR. RAGHU R. SUNDARAM

Editor's Note: *Dr. Sundaram is a 2011 D. Robert McCaffree, MD, Master FCCP Humanitarian Award Winner for his project, "Asthma Clinic: Comprehensive Care Delivery to Indigent/Poor Population Across Different Ages and Cultures. One Breath for Life, Once Life to Live, One Source to Trust. Prakasam District, India.*

We are all excited to receive The CHEST Foundation awards. It is good that good community service is recognized; good that opportunity has come across to help others; good that a helping hand has come from The CHEST Foundation, located thousands of miles, across many oceans, almost from the other side of the world, to folks in remote corners of the world lacking basic health care, health education, and basic human standards of life that they deserve.

When I started looking around, I observed men and women with asthma and COPD exacerbations, struggling for breath. I observed children who started to smoke at the tender age of 9 or 10 years. There were teens smoking at public places; elderly folks wondering why they are cursed to struggle for good breath, in spite of the fact that they smoked "good quality cigarettes," which they double-checked by reading the labels. Children abound with malnutrition, on the verge of blindness; women and men with severe osteoporosis. There is a lack of basic maternal care, and so on. The ugly reality is that these people who need the most were surrounded by the very rich, living in mansions, with excessive wealth. The thought came to me that what is needed, without much cost, is motivation and education that leads to the realization that something can be done which will make a difference in the lives of the less fortunate, and, in turn, will make a difference in our own lives.

All of the above thoughts of what one would call "self realization" stimulated me to do things that cost less but make the biggest impact on the very less fortunate folks I see, and I feel that something must be done NOW, and I should not procrastinate. This has led to health education, including information on healthy nutrition; smoking prevention; healthy lifestyles; exercise; preventive measures, such as regular checkups that include pulmonary function testing, chest radiographs, and blood pressure monitoring; prenatal maternal care; and vaccinations for polio and other diseases— without looking for any governmental help. These thoughts have led to a focus on education of physicians and other medical providers, so that the less fortunate folks will benefit and, in the long run, asthma, COPD, lung cancer, and many smoke -related heart problems will be controlled and prevented.

In one of the community education sessions I conducted, one recently retired physician asked me, " What is flu vaccine?" I answered patiently and realized the fact that health education is as important as all preventive and treatment aspects. Thanks goes to the ACCP and The CHEST Foundation, as their educational material has become so useful and convenient. As everybody knows, the ugly fact is that education, in all fields, has become a business, especially in developing countries. But the ugliest fact is that quality suffers, compounded by the other ugly fact that the result and outcomes of implementation of health-care standards are low, and the ultimate suffering comes to the less fortunate folks.

This has led me to ponder what else can be done in the midst of a bad economy, politicians who only preach, and rampant corruption in so many forms? What is it that we can do ... without expense? The answer is that we can influence our colleagues across the globe, as we all share common values. With technology, we can share our journals, have teleconferences with our colleagues, and e-mail each other. Most importantly, we can educate and encourage them to actively implement quality education and industry health standards with a focus on access to care for the less fortunate. The prime time has come for "global education."

It is inspiring to go through the powerful slides sent by our ACCP President, and the thought that has come to me after review is, "Yes, we have come a long way baby," but we have a long way to go.

On behalf of the millions who continue to benefit from the ACCP and its philanthropic arm, The CHEST Foundation and One Breath (the new "baby"), we bow our heads in reverence, and salute all those involved with the above institutions—the ACCP, The CHEST Foundation, and OneBreath. As the ebb and tide of "breath" keeps us going , we keep values that the above institutions give us close to our "hearts."

God bless all who care and share. ■

The CHEST Foundation is grateful for Dr. Sundaram's recognition of the benefit of The CHEST Foundation's humanitarian awards and pro bono service.

The D. Robert McCaffree, MD, Master FCCP Humanitarian Awards gave Dr. Sundaram and hundreds of ACCP members over the past 15 years an opportunity to expand physician education and improve patient care globally. To learn more about what others have achieved to benefit their community through a CHEST Foundation Humanitarian Award, go to OneBreath.org and click on the Education tab. The 2012 Humanitarian Awards applications are due on May 4, 2012, and the online application is accessible at OneBreath.org.

Marilyn Lederer
Executive Director
The CHEST Foundation

New Membership Benefit Connects Members Virtually

Introducing the ACCP e-Community

Sharing with members around the block, across the country, and around the world, the new ACCP e-Community offers a private platform for members to connect and share with other members virtually. ACCP members can use the e-Community to share resources, discuss clinical issues, or collaborate with other members from around the globe—without leaving their home or office.

Through the ACCP e-Community, NetWork members will be able to:

- Maintain a personalized profile, including specialty, subspecialty, and areas of interest.
- Manage and search for member contacts.
- Initiate and comment on discussions.
- Share resources, including documents, photos, and video.
- Collaborate on NetWork projects, such as CHEST annual meeting planning, through a "live doc" capability.
- Subscribe to topic-specific content alerts and RSS feeds for news and articles.
- Create and comment on simple polls.

"ACCP NetWorks have been requesting a tool that would allow their special interest groups to collaborate and exchange ideas and resources in a closed setting. The new ACCP e-Community will provide these opportunities and more," said Jay I. Peters, MD, FCCP, Council of NetWorks Chair.

In March, the e-Community will be open to members of all NetWorks. Future plans include opening it to all ACCP committees and members. Not a member of ACCP NetWorks? Join or update your NetWork preferences today by logging into your ACCP profile at www.chestnet.org. ■

Critical Care Commentary

Management of Trauma-Associated Coagulopathy: New Strategies and Controversies

Hemorrhage is the major preventable cause of mortality in trauma patients with otherwise potentially survivable injuries (Eastridge et al. *J Trauma*. 2011;71[2] [suppl 2]:S4). Coagulopathy is an obvious contributor to uncontrolled bleeding and is an independent risk factor for multiple organ failure and death (MacLeod et al. *J Trauma*. 2003;55[1]:39). Trauma surgeons, critical care specialists, and first responders must work together closely to manage severely injured trauma patients, and a working understanding of recent practice advances and management controversies is critical to effective communication and collaboration.

Patients at risk for uncontrolled hemorrhage and trauma-associated coagulopathy typically present in shock with multiple serious injuries. The exact mechanisms and their relative contributions to trauma-associated coagulopathy are complex and controversial. Ongoing bleeding combined with tissue injury result in direct loss and consumption of coagulation factors. Hypoperfusion and injury-related inflammation also increase coagulation cascade activation, and excessive protein C-mediated clotting factor consumption and fibrinolysis may occur. Acidosis limits the formation of coagulation factor complexes, and hypothermia reduces von Willebrand factor-mediated platelet activation (Murthi et al. *Expert Rev Hematol*. 2011;4[5]:527).

Many experts argue that these pathologic mechanisms have been exacerbated with the historical shift from whole blood in the 1970s, to initial resuscitation with crystalloid and blood component therapy, with a heavy emphasis on packed red blood cells (PRBC) to maximize oxygen delivery. This modern strategy has resulted in significant reductions in early plasma administration and may cause further iatrogenic dilution of factor levels. Combined with prolonged surgery to repair multiple severe injuries, these trauma patients frequently develop progressive coagulopathy, hypothermia, and acidosis, a so called "lethal triad," with a high subsequent risk of death (Cosgriff et al. *J Trauma*.1997;42[5]:857).

In 2004, Como and colleagues published a retrospective review of blood product utilization in trauma patients. The authors noted that the relatively small percentage of patients requiring transfusion (8% received RBCs, 6% plasma) utilized a relatively similar number of units of RBCs and plasma and suggested that the later use of plasma and platelets may have been necessary to address worsening coagulopathy caused by early use of crystalloid and PRBCs (Como et al. *Transfusion*. 2004;44[6]: 809).

Early transfusion of plasma with PRBCs, combined with recombinant activated factor VIIa (rFVIIa) and fresh whole blood, has been employed in military combat support hospitals in Iraq and Afghanistan for casualties with severe injuries and uncontrolled hemorrhage. Based on the dramatic observed responses and consensus recommendations of an international group of trauma experts, the US Army issued a clinical guideline recommending early resuscitation with a 1:1 ratio of plasma and PRBCs (Malone et al. *J Trauma*. 2006;60[6 suppl]:S91). Subsequent military data also demonstrated a survival advantage with the early utilization of platelets, prompting current recommendations to transfuse either 6 units or a single unit of apheresis platelets for every 6 units of PRBCs and plasma (1:1:1 ratio) (Perkins et al. *J Trauma*. 2009;66(suppl):S77).

These concepts have been further refined in a strategy coined "damage control resuscitation" (DCR). DCR includes the early and increased use of fresh frozen plasma (FFP), platelets, and RBC over crystalloid, rapid control of surgical bleeding with delayed definitive repair ("damage control surgery"), and hypotensive resuscitation strategies that utilize adjuncts like rFVIIa, calcium, and tris(hydroxymethyl)aminomethane (Tris) to avoid the development of hypothermia, acidosis, and coagulopathy (Holcomb et al. *J Trauma*. 2007; 62[2]:307).

There has been extensive literature published from both military and civilian trauma centers suggesting benefit from DCR, and many trauma centers have adopted these concepts in their clinical resuscitation practices. However, the variable quality of most data supporting this practice has led to mixed adoption of DCR principles in two recent trauma resuscitation guidelines (Rossaint et al. *Critical Care*. 2010;14:R52; Dzik et al. *Critical Care*. 2011;15[6]:242). The importance of rigorous validation is underlined by recent prospective trials demonstrating no benefit from rFVIIa in hemorrhage from blunt or penetrating trauma, and a potential increased risk of thrombosis (Curry et al. *Critical Care*. 2011;15:R92). Optimal plasma:platelet:PRBC ratios in trauma patients have been deemed one of the most important areas in need of a clinical trial by the NHLBI, and a number of prospective studies have now been funded to examine this issue (Josephson et al. *Transfusion*. 2011;51[4]:828).

In this rapidly changing landscape of trauma resuscitation, what lessons are safe and effective to apply to clinical practice today? Early control of hemorrhage, an early, more balanced transfusion strategy, and use of tranexamic acid (TXA) are three key concepts to consider.

Clearly, patients with extensive trauma coagulopathy at presentation are at increased risk for massive transfusion and death. Rapid control of ongoing hemorrhage with pressure bandages and tourniquets, when possible, followed by early "damage control" surgery, is a rational strategy supported by strong guideline-based recommendations (Rossaint et al. *Critical Care*. 2010;14:R52).

Initial lactate and base excess values and their trends have been shown to be predictive of mortality in trauma patients. It is reasonable to use these markers of end organ perfusion with vital signs, initial clinical assessment, and injury pattern to identify individuals who would benefit from early transfusion therapy (Rossaint et al. *Critical Care*. 2010;14:R52).

The majority of recent literature supports early transfusion over crystalloid resuscitation, with increased ratios of plasma and platelets to PRBCs. Platelet counts, activated prothrombin time (aPT), and international normalized ratio (INR) may underestimate the presence of trauma-associated coagulopathy, prompting significant interest in functional coagulation assessments, such as thromboelastography to guide transfusion therapy. A recently published study demonstrated that 20% of severely injured patients had critical coagulation factor deficiencies on presentation, which were predictive of increased transfusion requirements and mortality. Abnormalities of INR, aPT, and thromboelastography had a sensitivity of only 32%, 36%, and 35%, respectively, to detect these deficiencies (Rizoli et al. *J Trauma*. 2011;71[5] [suppl 1]:S427) Clearly, more work is necessary to determine the optimal strategy to guide transfusion therapy.

Treatment of trauma-associated fibrinolysis with antifibrinolytic agents appears to be beneficial. The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) trial was a large, multicenter, prospective trial that randomized over 20,000 trauma patients to receive tranexamic acid (TXA), or placebo. Patients receiving TXA demonstrated a reduction in 30-day all-cause mortality (14.5% vs 16.0%; RR, 0.91; confidence interval [CI], 0.85– 0.97; P=.0035). Although TXA administration did not impact transfusion requirements, the relative risk of death from hemorrhage was reduced by 15%, with the greatest benefit seen in patients treated within 3 h of injury and with systolic blood pressure $\leq$ 75 mm Hg. There was no difference in the frequency of thrombotic events observed within the two study arms (1.7% for TXA vs 2.0% for placebo, P = .084) (CRASH-2 trial collaborators; Shakur et al. *Lancet*. 2010;376[9734]:23). In an online update, the majority of hemorrhage-associated reduction in mortality with TXA was seen only if the drug was given in the first hour, and a significant increase in mortality was seen if TXA was given more than 3 hours after injury (CRASH-2 trial collaborators; Roberts I et al. *Lancet*. 2011;377[9771]:1096). Although the results of this trial remain controversial, they represent perhaps the highest level of evidence of an intervention demonstrating survival benefit in the management of trauma-related hemorrhage to date.

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The views expressed herein are those of the author alone and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US government.

Editor's Comment

Traumatic injury with significant hemorrhage still has an elevated mortality. Approximately 2.5 million deaths are attributed to massive hemorrhage worldwide.

As we went from whole blood resuscitation in the 1970s to a component-based approach, the ideal formulation still is unclear. The well-described lethal triad certainly plays a role in the mortality of severe hemorrhage. Coagulopathy seems to be biphasic in trauma; an acute phase seen within 30 min, and then part of the acquired lethal triad as discussed. In major cities with quick response time and transport to a trauma center, the approach as described in the commentary above is appropriate. In rural settings or with significant delayed transport, TXA delivered on-site by first responders may be of benefit.

Active multicenter trials in the United States and Europe are ongoing to try and clarify the appropriate mix and to decrease mortality.

–Dr. Peter Spiro, FCCP

You Should Know About...

Dr. Kalpalatha Guntupalli, FCCP, Past President of the ACCP, received the "Pravasi Bharatiya Samman" Award.

ACCP Past President Honored by President of India

Kalpalatha (Kay) Guntupalli, MD, FCCP, Past President of the ACCP, was the recent recipient of the "Pravasi Bharatiya Samman" Award, presented to her by the President of India. This is the highest award conferred by the Indian government to honor and celebrate the achievements of expatriates of Indian origin. She was also invited to respond to the honor on behalf of all the recipients. The award is conferred on 15 distinguished members of the Indian Diaspora globally each year to honor exceptional and meritorious contributions in their chosen field/profession and for enhancing the prestige and visibility of India. Congratulations, Dr. Guntupalli, for this prestigious international recognition of your many contributions to improving patient care throughout the world.

IMAGES COURTESY ACCP

With thanks to all who signed during CHEST 2011.

Surfing With CHEST 2011

An 8-foot surfboard now hangs in the lobby of the ACCP headquarters in Northbrook, Illinois, compliments of the Hawaii Convention Center. Attendees at CHEST 2011 in Honolulu had the opportunity to sign the board while at the meeting. The ACCP staff was treated to breakfast back in Northbrook and the Hawaii Midwest Team brought with them this great memento from the successful ACCP meeting in Honolulu. Mahalo!

ACCP President Makes the News

The *Brooklyn Daily* recently posted a story about Dr. Suhail Raoof, FCCP, and his new role as the President of the ACCP. To read the story, go to the newspaper's Web site at http://www.brooklyndaily.com/stories/2012/2/all_standingoside_2012_01_13_bk.html.

Don't Miss the January *CHEST* Editorial: "Spread the Word About the Journal in 2012"

Highlighting the successes of 2011, including a record number of submissions, an impact factor that continues to rise, and over 31,000 downloads of the journal app, this editorial also offers a preview of what is ahead in 2012. *CHEST* welcomes the new year with a renewed commitment to the highest standards in scientific quality and ethics, as demonstrated by the adoption of plagiarism-detection software for submitted manuscripts and the implementation of a process to screen submitted figures for potential image manipulation. *CHEST* will continue to develop its successful series, including the popular podcasts that give listeners the opportunity to hear authors and editorialists speak in depth about important new work just published in the journal. Want to know what else is coming up? Read the full editorial to learn more at http://chestjournal.chestpubs.org/content/141/1/1.full. ■

Dr. Suhail Raoof, FCCP, is in the news.

NETWORKS

IPF Clinical Trials, NW Name Change, New GOLD Grades

Interstitial and Diffuse Lung Disease

The Year that Was: An Update on Clinical Trials in IPF in 2011

The past year saw the conclusion of several important clinical trials in IPF. There were two notable negative trials. At CHEST 2011, the IPFnet reported that the ACE-IPF Trial (AntiCoagulation Effectiveness in Idiopathic Pulmonary Fibrosis), which compared warfarin and placebo in IPF, was terminated by the Data and Safety Monitoring Board (DSMB) for futility. Excess mortality in the warfarin arm made benefit unlikely and created concerns for safety.

Similarly, the IPFnet-sponsored PANTHER-IPF (Evaluating the Effectiveness of Prednisone, Azathioprine, and N-acetylcysteine (NAC) in People With Idiopathic Pulmonary Fibrosis) trial closed one arm of the three-arm trial. Excess mortality in the azathioprine arm led to discontinuation of this portion of the trial only. The other two arms (prednisone and NAC) continue to recruit. By contrast, a phase 2 clinical trial examining safety and efficacy of four doses of the tyrosine kinase inhibitor, BIBF 1120, in 432 patients with IPF showed a statistically significant decrease in the frequency of acute exacerbations and a trend toward decreased rate of decline in forced vital capacity. Patients in the BIBF arm also showed a lesser decline in St. George's Respiratory Questionnaire, a quality of life measure. The results of this study will need to be replicated in a larger population in a phase 3 study powered to detect not only statistically but clinically significant differences in physiologic and patient-centered outcomes. In sum, these studies show that definitive clinical trials in IPF are both feasible and necessary. A future goal will be to better define the clinically significant physiologic and patient-centered endpoints, which will serve as endpoints for future clinical trials.

Dr. Sonye Danoff, FCCP, Vice-Chair

Clinical Research (Formerly Members in Industry)

A NetWork Comes of Age

We in the NetWork formerly known as Members in Industry, or MII, have formally broadened our mission to being a place that "offers a clinical research, research ethics, and regulatory issues multidisciplinary discussion forum for all ACCP members interested in these activities." To represent this mission better, we are excited to announce that the College's Executive Committee has approved our name change to "Clinical Research NetWork."

What does this mean to our current NetWork members and the ACCP membership overall? The focus of our NetWork has always been such topics in clinical research as methods, statistics, alternative trial designs, and ethics of clinical research. However, the name "Members in Industry" did not adequately communicate these broad areas of interest and expertise that reside within our group. We believe that the new name, along with our newly articulated mission, will sound a welcome to both the current MII members and other members of the College to get more involved with our day-to-day operations.

Within the last 2 decades, we have witnessed an increased emphasis on clinical research skills among clinicians. As the HIT infrastructure blossoms and creates volumes of data, there will be a parallel need for competent and skilled researchers to deal with these data. It is our vision that the Clinical Research NetWork will serve as a think tank to attract many clinician investigators and be a place where innovative ideas in chest medicine are born.

Dr. Marya Zilberberg, FCCP, Chair
Dr. Roslyn Schneider, FCCP, Vice-Chair

Airways Disorders

Forecast for the New GOLD Grading System: Hazier or Clearer?

COPD is the third leading cause of death, and its mortality is rising (American Lung Association Fact Sheet. http://www.lungusa.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html. Accessed January 28, 2012). The international committee of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) statement significantly changed the grading system of COPD in 2011 (Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated edition December 2011. http://www.goldcopd.org/. Accessed January 28, 2012.). A summary of the major changes and their implications follow.

The definition of COPD is still based on a postbronchodilator fixed ratio of FEV_1/FVC of <0.70; however, the committee now places more emphasis on the systemic effects of COPD. Previously, GOLD statements (2001-2010) classified COPD stages and severity exclusively on the degree of airflow obstruction (postbronchodilator percent predicted FEV_1). Multiple other tools assessing COPD risk and severity are now included and the term "stages" of COPD was changed to "grades." The new grading system includes assessment of symptoms (by the COPD Assessment Test or the Modified Medical Research Council dyspnea scale) and the number of acute exacerbations of COPD within the prior year. The Committee further recommends that treatment algorithm be based on the Grades A, B, C, or D reflecting on these assessment tools.

Although these changes are more intuitive to specialists and approach real-life COPD management, disseminating and explaining this new grading system to primary care clinicians will be problematic. As it is now, dissemination of the original GOLD recommendations has been difficult as evidenced by the fact that most primary care clinicians remain unaware of their existence (Foster et al. *Medscape General Medicine.* 2007;9:24; Adams et al. *Chest*. 2011;140 [4]:978A). Therefore, it is imperative for us to translate these new recommendations into clinical practice in an easy-to-understand and practical format.

Dr. Sandra G. Adams, FCCP
Dr. Rubin Cohen, FCCP
Dr. Nicola A. Hanania, FCCP, Chair

Global Education and Development

BY DR. MARK J. ROSEN, FCCP
Director, Global Education and Strategic Development

Approximately 20% of ACCP's 18,000 members are clinicians, teachers, and investigators in 100 countries outside the United States and Canada. The ACCP is acknowledged around the world as a leader, and, arguably, *the* leader, in providing the best clinical education in pulmonary, critical care, and sleep medicine. The *CHEST* journal, the annual international CHEST meeting, and our simulation programs and board review courses are among our most widely known and respected activities, among many others, but these resources are not easily accessible to thousands of current and potential new ACCP members.

ACCP's leadership has identified the importance of expanding educational efforts around the world. The Board of Regents committed the College to promoting such opportunities through increasing collaboration with local and regional leadership, institutions, and professional societies. In 2011, the Global Education and Development Committee was established by the Board and charged with evaluating current programs, initiating new ones, and providing strategic recommendations on our scope of activities. The committee is chaired by ACCP Immediate Past-President Dr. David D. Gutterman, FCPP; Dr. Darcy D. Marciniuk, FCCP, ACCP President-Elect is Vice-Chair.

The Council of International Regents and Governors, with about 160 international members, had those who attended CHEST 2011 offer recommendations on how to develop new educational activities and products that respond to the needs of local clinicians and their patients. Dr. Panagiotis Behrakis, FCCP, from Greece, is the Chair of the Council, and Dr. Paraschiva Postolache, FCCP, of Romania, is Vice-Chair.

Several of ACCP's educational activities have already had international exposure. Simulation courses and train-the-trainer programs on difficult airway management were conducted in Saudi Arabia, and courses on mechanical ventilation in three cities in India. A simulation course on interventional pulmonary medicine is planned for Israel and others on critical care ultrasound in India. International "board beview" courses are on the drawing board.

I was honored to be selected and hired to serve as the ACCP Director of Global Education and Strategic Development, working with Prachi Sharma and Mark Nagasawa. We will assist the Board, the new Committee, and the International Regents and Governors to fulfill the College mission of being the global leader in providing education in cardiopulmonary, critical care, and sleep medicine. We look forward to hearing your ideas and working together. ■

CHEST 2011 Media Update

The ACCP garnered strong news coverage during CHEST 2011. Over 60 abstracts were promoted to hundreds of consumer and trade/medical media, resulting in numerous print, broadcast, and Internet articles within the United States and around the world. The most noteworthy press coverage related to an NCI lung cancer screening study that was simultaneously published in *JAMA* and presented at CHEST 2011 by Dr. Paul Kvale, FCCP. The AP wire service published a story related to this session, which led to subsequent media coverage in: *USA Today, Wall Street Journal, Chicago Tribune, Los Angeles Times,* CBS and FOX News, and others. Additional news related to CHEST 2011 abstracts/sessions and OneBreath® activities have been featured in the following media outlets: *Wall Street Journal, US News and World Report, Daily Mail (UK),* and *Honolulu Reporter*. Plus, Hawaii News Now featured CHEST 2011 highlights, featuring television interviews with Dr. Kevin Chan, FCCP, and Dr. Doreen Addrizzo-Harris, FCCP.

Stay tuned for more ACCP and OneBreath news coverage. ■

TYGACIL is in the IDSA/SIS guidelines for cIAI and the SIS guidelines for cSSSI.[1,2]

Expanded broad-spectrum coverage[3]* is on your side

***TYGACIL does not cover *Pseudomonas aeruginosa*.**

TYGACIL is indicated for the treatment of adults with:

- **Complicated skin and skin structure infections** caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*
- **Complicated intra-abdominal infections** caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*
- **Community-acquired bacterial pneumonia** caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*

Important Safety Information

- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics
- Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function. Adverse events may occur after the drug has been discontinued
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options**
- **TYGACIL may cause fetal harm when administered to a pregnant woman**
- **The use of TYGACIL during tooth development may cause permanent discoloration of the teeth.** TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated
- Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- Monotherapy should be used with caution in patients with clinically apparent intestinal perforation
- TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi
- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, infection, headache, and abdominal pain
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

Please see brief summary of Prescribing Information on adjacent page.

References: 1. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133-164. **2.** May AK, Stafford RE, Bulger EM, et al. Surgical Infection Society Guidelines: Treatment of complicated skin and soft tissue infections. *Surg Infect*. 2009;10:467-499. **3.** TYGACIL® (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.

Pfizer

Tygacil® tigecycline IV

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