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PATRICE WENDLING/IMNG MEDICAL MEDIA

"This study, for its design and results, is a remarkable achievement" and may change practice, Dr. Giancarlo Agnelli said.

Extra year of apixaban cuts recurrent VTE

BY PATRICE WENDLING
IMNG Medical News

ATLANTA – An extra year of apixaban reduced the risk of recurrent events in patients with venous thromboembolism by 80%, while keeping major bleeding rates in line with placebo in the randomized AMPLIFY-EXT trial.

The number needed to treat with apixaban (Eliquis, Bristol-Myers Squibb) to prevent one fatal or nonfatal recurrent VTE was 14, while the number needed to treat to cause one episode of major or clinically relevant nonmajor bleeding was 200, Dr. Giancarlo Agnelli reported in a late-breaking abstract at the annual meeting of the American Society of Hematology.

"We really believe this study, for its design and results, is a remarkable achievement, and [may lead to a] change in clinical practice," he said during a press briefing at the meeting.

Apixaban was approved by the Food and Drug Administration in late December for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, based largely on data demonstrating superiority to warfarin in patients with

See **AMPLIFY-EXT** • *page 25*

Antibodies linked to lung disease in rheumatoid arthritis

For some, RA may begin in the lungs.

BY HEIDI SPLETE
IMNG Medical News

WASHINGTON – Specific anti-cyclic citrullinated peptide antibody levels were significantly higher in rheumatoid arthritis patients with interstitial lung disease than in those without lung disease, based on data from 177 patients.

Complications and death are common in rheumatoid arthritis (RA) patients with interstitial lung disease (ILD), and the findings "may implicate the lung as a site in which protein citrullination initiates epitope spreading and propagation of RA," said Dr. Jon T. Giles of Columbia University in New York. He spoke at the annual meeting of the American College of Rheumatology.

To determine the association of anti-cyclic citrullinated peptide antibodies with ILD, Dr. Giles and his colleagues reviewed data from multidetector computed tomography images and concurrent serum samples for 177 RA patients. The mean age of the patients was 59 years, 60% were women, and 11% were smokers.

A total of 57 patients (32%) showed some evidence of ILD on imaging, and 32 (18%) had ILD scores of 3 U or higher.

See **Antibodies** • *page 3*

Indacaterol broadly beneficial for COPD

BY SHARON WORCESTER
IMNG Medical News

ATLANTA – Indacaterol significantly improves bronchodilation and health status in patients with chronic obstructive pulmonary disease, and is safe and well tolerated, according to findings from studies presented at the annual meeting of the American College of Chest Physicians.

In a pooled analysis of efficacy and safety data from two randomized controlled studies, the inhaled long-acting beta$_2$-agonist bronchodilator given at the approved dose of 75 mcg daily was found to be of benefit regardless of age, sex, smoking status, or severity of airflow limitation.

In another analysis of

See **Indacaterol** • *page 6*

INSIDE

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FDA panel wants expanded indication for telavancin

BY ELIZABETH MECHCATIE
IMNG Medical News

SILVER SPRING, MD. – The approval of the antibacterial drug telavancin should be expanded to include patients with nosocomial pneumonia, but only in limited situations, according to the majority of a Food and Drug Administration advisory panel.

The FDA's Anti-Infective Drugs Advisory Committee voted 13-2 that the available data on telavancin provided substantial evidence that it was safe and effective for treating nosocomial pneumonia, "when other alternatives are not suitable."

Panelists agreed that telavancin should be reserved to treat patients with nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) – not methicillin-sensitive *S. aureus* (MSSA) or *Streptococcus pneumoniae*, because there are many other treatments available for those infections.

Most panelists did not support approval of the broader indication requested by the manufacturer: treatment of patients with nosocomial pneumonia, including ventilator-associated pneumonia (VAP), caused by susceptible isolates of the gram-positive microorganisms *S. aureus* (including methicillin-susceptible and methicillin-resistant isolates) or *S. pneumoniae*. The panel voted 9-6 that the data from the two studies did not provide substantial evidence that the drug was safe and effective for this indication.

Telavancin is a lipoglycopeptide antibacterial that is administered intravenously, with bactericidal activity that results from inhibition of cell wall synthesis and disruption of bacterial plasma membrane function, according to Theravance, the drug's manufacturer. It was approved in 2009 for the treatment of adults with complicated skin and skin structure infections caused by susceptible gram-positive bacteria, and is marketed as Vibativ.

The current labeling for telavancin includes warnings and precautions in the prescribing information about the increased risk of nephrotoxicity associated with treatment, based on experience in patients treated for the skin infection indication. A boxed warning cites the potential fetal risks.

Among the other points made by panelists were that labeling should include statements about use in patients with reduced creatinine clearance and renal failure, and that the company should aggressively collect postmarketing safety and efficacy data.

The panel considered data that included analyses of clinical cure and 28-day all-cause mortality from two noninferiority studies. These studies comprised 1,503 patients with nosocomial pneumonia, and compared telavancin for 7-21 days (10 mg/kg every 24 hours administered intravenously in patients with normal renal function and mild renal impairment or an adjusted dose for patients with moderate or severe renal insufficiency) with vancomycin (1 g IV every 12 hours).

Telavancin has been approved in the European Union for the treatment of nosocomial pneumonia caused by MRSA.The FDA usually follows the recommendations of its advisory panels, which are not binding. Panelists have been cleared of potential conflicts of interest related to the topic of the meeting, although a panelist may occasionally be given a waiver, but not at this meeting.

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VIEW ON THE NEWS

Dr. Marcos I. Restrepo, FCCP, comments: The FDA approval of telavancin limited to "nosocomial pneumonia when other alternatives are not suitable" is due to the safety concerns and efficacy seen in the original randomized trials. However, multidrug-resistant pathogens continue to affect our patients, and antimicrobial therapies available to manage patients with MDR pathogens are few. Thus, decisions regarding the wise use of available antimicrobials are perhaps the best approach at this time.

IN THIS ISSUE

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Interstitial lung disease in RA

Antibodies *from page 1*

Overall levels of anti-cyclic citrullinated peptide and of 17 specific anti-cyclic citrullinated peptide antibodies ranged from 46% to 273% higher in patients with ILD than in those without ILD. Patients with ILD were more likely to be male, to smoke, to have a history of prednisone and leflunomide use, to be seropositive for rheumatoid factor and anti-CCP.

Anti-cyclic citrullinated peptide

Anti-cyclic citrullinated peptide antibodies were 46%-273% higher in interstitial lung disease.

DR. GILES

seropositivity was significantly more common in patients with any ILD than in those without ILD (89% vs. 69%). Seropositivity was evident in 94% of patients with ILD scores of 3 U or higher. High levels of seven or more anti-cyclic citrullinated peptide antibodies were seen in 40% of patients with reticulation, honeycombing, or traction bronchiectasis and in 18% of those with no ILD.

Further, high levels of seven or more anti-cyclic citrullinated peptide antibodies were seen in 39% of patients with restriction on a pulmonary function test or decreased diffusing capacity on a carbon monoxide test and in 20% of those without ILD. The differences were significant after adjustment for age, sex, smoking status, RA disease activity score, and prednisone and leflunomide use.

Levels of antibodies targeting noncitrullinated proteins were not significantly higher in patients with ILD, which "suggests a specificity for anti-cyclic citrullinated peptide antibodies in the association," Dr. Giles said.

Also, anti-cyclic citrullinated peptide antibodies may mediate remote pathogenic effects upon circulating to the lungs, where their cognate citrullinated proteins may also be present.

The findings were limited in part by the use of multidetector computed tomography, which differs in slice thickness from high-resolution CT. The strengths include the multiple measures of pulmonary disease.

Dr. Giles had no financial conflicts. The study was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the American College of Rheumatology's "Within Our Reach" campaign.

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VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: These data offer promising possiblities for a better understanding of the pathogenesis of rheumatoid arthritis in general and specifically how the lung may be involved. More study is needed to determine the potential clinical significance.

Beriplex outdoes plasma for rapid warfarin reversal

BY BRUCE JANCIN

IMNG Medical News

DENVER – A four-factor prothrombin complex concentrate bettered plasma for urgent reversal of warfarin and other vitamin K antagonists in patients experiencing major bleeding.

Marketed as Beriplex, the product had a higher rate of INR reversal than did plasma at 30 minutes after the start of infusion, based on results from a phase IIIb prospective, multicenter, randomized clinical trial.

The prothrombin complex concentrate (PCC) also proved more successful than plasma at early replacement of depleted coagulation factors and was noninferior to plasma in terms of blinded investigator–rated hemostatic efficacy in the first 24 hours, Dr. Joshua N. Goldstein said at the annual meeting of the American College of Emergency Physicians.

The study included 202 adults on warfarin or another vitamin K antagonist who presented with acute major bleeding. Participants were randomly assigned to INR- and weight-based dosing of the PCC or to plasma on top of background vitamin K given by slow intravenous infusion in all cases.

The higher the baseline INR, the greater the benefit of the prothrombin complex concentrate.

DR. GOLDSTEIN

Thirty minutes after the start of the infusion, the mean INR was significantly lower in patients on the PCC than in those given plasma. The higher the baseline INR, the greater the benefit of the PCC. For example, in 58 patients with a baseline INR above 6, the mean INR dropped from 10.6 preinfusion to 1.5 at 30 minutes in the PCC group and to 3.7 in the plasma recipients, reported Dr. Goldstein of the University of Rochester (N.Y.).

In 44 patients with a baseline INR of 4-6, the INR fell from a mean of 4.6 preinfusion to 1.4 at 30 minutes in the PCC group and to 3.2 in patients on plasma.

And in patients with a baseline INR of 2 to less than 4, mean INR fell from 2.9 preinfusion to 1.6 in the PCC group and to 2.2 in the plasma recipients.

One hour after the start of infusion, roughly 70% of PCC recipients had corrected their INR as defined by an INR of 1.3 or less, compared with less than 5% of plasma recipients.

Blinded investigators rated hemostatic efficacy in the first 24 hours as good or excellent in 72% of the PCC group and in 65% of patients on plasma, a nonsignificant difference.

Thromboembolic event rates through 51 days of follow-up were 7.8% with PCC and 5.5% with plasma.

Dr. Goldstein reported that he serves as a consultant to and advisory board member for CSL Behring, which markets Beriplex and sponsored the study.

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EHR REPORT: EHRs as tools to facilitate medical humanism

BY NEIL SKOLNIK, M.D., AND CHRIS NOTTE, M.D.

"We cannot get to where we need to go by remaining where we are."
–Adopted from Max de Pree Leadership Is an Art

A recent article published in JAMA showed a crayon drawing that was given to a doctor by a 7-year-old girl (JAMA 2012;307:2497-8). The drawing showed the girl sitting on the exam table, with her sister and mother in nearby chairs, while the doctor was sitting hunched over a computer with his back to the patient and her family.

The message of the drawing was clear: that the way we are viewed by our patients is changing. What is remarkable though, when you view the picture from the girl's perspective, is that there was nothing sad about the drawing. The colors where vivid and all the figures in the room were smiling. Why would there be anything sad about this encounter? This is the world that the 7-year-old knows, it's her reality, a world in which attention is regularly divided, and electronic devices are how information is stored and through which communication occurs. This fact is difficult to integrate and understand for those of us who are a bit older but is simply an ordinary part of life, like milk in a jar or plastic lids for those young enough to know no other world. Nonetheless, the concern remains that we need to be careful that the patient's needs do not become buried under the machine's clicks and hums.

There are many physicians who are sad about the demise of the paper chart. We hear from those people daily. If we acknowledge the complexity of our needs, then we see that the old paper-based chart system, while easier to use than an electronic chart,

DR. SKOLNIK AND DR. NOTTE

simply does not allow us to record information in a form that is retrievable for the evolved purposes for which we are now keeping records. Population management is not just a buzzword, it is the area toward which our care of patients is evolving if we are to truly make an impact on improving their health. So EHRs are a necessary component of this evolution.

Our challenge, as physicians who are now beginning to care for populations as well as individual patients, is how to balance and integrate the immediate needs that occur in the exam room – the need to provide the proper diagnosis and treatment, to record data, and to truly listen to the patient. To make sure that the patient feels heard. A colleague of ours who has thought a lot about electronic records, Dr. Keith Sweigard, feels that the EHR will eventually be a tool that will facilitate medical humanism. To use his words:

"Technology will paradoxically foster humanism in medicine. As we implement [EHRs] with standardized templates, care pathways, and order sets, patients will more likely receive the same work-up and evidence based interventions from any care provider. In that scenario, what will become the distinguishing factor that a patient selects one physician over another? Access will certainly be a factor, but ongoing relationships will depend on connecting with the patient on a humanistic level – warmth, sensitivity, compassion, and empathy."

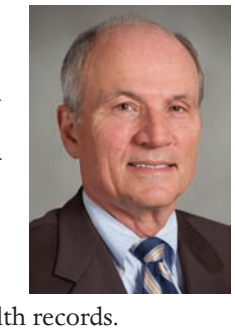
The literature supports that how well a doctor communicates influences patients' satisfaction, sense of well-being, overall health, and malpractice suits, and may even influence health care costs. When we are ill, we yearn for two things – to be well, and for someone to understand our suffering. Science and technology improve our chances of being well, but do not address our need to be understood. The doctor is in a unique position to provide for both aspects of what the ill person needs: to help alleviate their suffering and to understand their unique human position in the world, as all suffering is unique. In order to fulfill this role, there has to be ongoing reinforcement of the "centrality of relationships" in medical care (Ann. Intern. Med. 2008;149:720-4).

We agree with Dr. Sweigard's assessment that, as the protocols and decision support become easier to use and as the quality tools that EHRs will provide become more sophisticated, what will distinguish us from one another and what payers will increasingly support, is our attention to the patient and his or her needs as a person. That attention to the person will be measured through patient satisfaction, and that quality measure will be reimbursed. It will not be difficult to figure out what medication to use next for this person's hypertension or elevated glucose. The decision support will be there, integrated and easy to use, and our smile and perhaps our attentiveness to the small tear welling in the corner of a patient's eye, will again distinguish us and allow us to connect as human beings.

DR. SKOLNIK *is associate director of the family medicine residency program at Abington (Pa.) Memorial Hospital and professor of family and community medicine at Temple University, Philadelphia. He is also editor in chief of Redi-Reference, a software company that creates medical handheld references.* DR. NOTTE *practices family medicine and health care informatics for Abington Memorial Hospital. They are partners in EHR Practice Consultants, helping practices move to EHR systems. Contact them at info@ehrpc.com.*

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: "This sobering commentary by Dr. Skolnik and Dr. Notte reflects on the changes in the interaction of physicians and their patients that are occurring with the move toward the advancing technology of electronic health records. The challenges and opportunities are highlighted in this intriguing discussion, and bear careful consideration by physicians of any specialty who are engaged in active clinical practice."



COPD prevalence varies by state, peaks above 9%

COPD is three times as likely in people making less than $25,000/year versus more than $75,000/year.

BY HEIDI SPLETE
IMNG Medical News

The prevalence of chronic obstructive pulmonary disease is 6% nationwide, but varies from less than 4% in Washington and Minnesota to more than 9% in Alabama and Kentucky, according to data from the Centers for Disease Control and Prevention. The findings were published in the CDC's Morbidity and Mortality Weekly Report.

The prevalence was lower among employed individuals, homemakers, and students than among those who were unemployed, retired, or otherwise unable to work.

A total of 13,306 adults who reported having chronic obstructive pulmonary disease (COPD) in the national survey also responded to the COPD module. Of these, 76% reported undergoing a diagnostic breathing test, 64% reported that COPD symptoms (specifically shortness of breath) had an adverse effect on their quality of life, and 51% reported taking at least one COPD medication (MMWR 2012;61:938-43).

In age-adjusted comparisons, women were more likely than men to report COPD (7% vs. 5%, respectively). COPD prevalence decreased from a mean of 10% among individuals making less than $25,000 per year to 3% in those making more than $75,000 per year, and the prevalence was lower among employed individuals, homemakers, and students than among those who were unemployed, retired, or otherwise unable to work.

The prevalence of COPD was highest in current smokers (13%) compared with former smokers (7%) and never smokers (3%).

Data were taken from the 2011 Behavioral Risk Factor Surveillance System (BRFSS) survey. Additional COPD data were collected in an optional COPD module about COPD diagnosis and quality of life. This module was part of the BRFSS in 21 states, the District of Columbia, and Puerto Rico.

The 2011 BRFSS was conducted via telephone, either landline or mobile. The survey population included adults aged 18 years and older throughout the United States.

The findings were limited by several factors including the absence of data on individuals in institutions or nursing homes and by the use of self-reports for COPD diagnosis, the researchers said. However, the report is the first to analyze data on COPD prevalence in all 50 states, the District of Columbia, and Puerto Rico, they noted.

State-level health officials should focus surveillance efforts, educational campaigns, and interventions on areas of highest COPD prevalence, they added.

The study was supported by the CDC and the National Heart, Lung, and Blood Institute of the National Institutes of Health.

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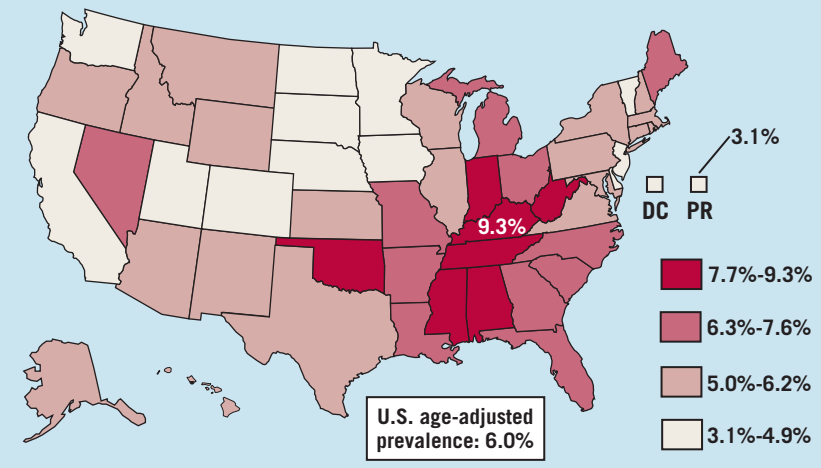
DATA WATCH

Adult COPD Prevalence Highest in Kentucky, 2011



Note: Based on data from the Behavioral Risk Factor Surveillance System.
Source: MMWR 2012;61:938-43

IMNG Medical Media

Wide range of COPD responders

Indacaterol *from page 1*

pooled data, treatment with indacaterol was shown to have an acceptable cardiovascular and cerebrovascular safety profile.

The efficacy analysis included 640 patients from two identically designed studies who were randomized to receive indacaterol or placebo for 12 weeks.

Trough (24 hours post dose) forced expiratory volume in 1 second (FEV_1) improved by least-squares mean differences of 150 and 110 mL among men and women, respectively; by 110 and 150 mL among those under age 65 and those aged 65 or older; by 150 and 110 mL among those with moderate and severe airflow limitation; and by 140 and 130 mL in ex-smokers and current smokers, Dr. Thomas Siler, FCCP, of Midwest Chest Consultants in St. Charles, Mo., reported.

Health status scores, as measured using the St. George's Respiratory Questionnaire, improved similarly in both men and women (by 3.8 and 3.7 units, respectively), and the scores also improved in all of the other groups.

Improvement was greater, however, in those aged 65 years and older (by 4.5 units vs. 3.3 units in those under age 65), those with severe airflow limitation (by 4.6 units vs. 3.3 units in those with moderate airflow limitation), and in ex-smokers (by 4.1 vs. 3.5 units in current smokers), according to Dr. Siler.

These improvements come without an increase in the risk of cerebro- and cardiovascular adverse events.

Adverse events occurred in 44%-57% of patients receiving indacaterol, and in 40%-48% of patients receiving placebo.

More adverse events in both groups occurred in older patients, women, those with moderate disease, and ex-smokers.

Patients in this study had a mean age of 63 years, and a mean post-albuterol FEV_1 of 54% predicted. About 40% were receiving inhaled corticosteroids.

The findings suggest that indacaterol can be successfully used to treat a range of COPD patients, Dr. Siler concluded.

Treatment can be expected to lead to "substantial and worthwhile improvements in bronchodilation and health status," he added.

According to findings from a separate analysis of pooled data from nearly 2,500 patients, these improvements come without an increase in the risk of cerebro- and cardiovascular adverse events (CCV AEs).

The overall frequency of CCV AEs was similar in 449 patients treated for up to 3 months and 2,012 control patients who received placebo (2.0% and 2.58%, respectively), and no type of CCV AE occurred in more than 2 patients in the active treatment group, Dr. James Donohue reported.

Serious CCV AEs occurred in 2 patients in the treatment group and 13 patients in the placebo group, and an Antiplatelet Trialists' Collaboration (APTC) event (a cerebrovascular accident not believed to be related to study treatment) occurred in 1 patient in the treatment group, compared with 8 patients in the control group, said Dr. Donohue of the University of North Carolina, Chapel Hill.

The overall frequency of patients with CCV AEs in a 6-month study population ranged from 3.3% to 5.8%, and no dose-response relationship was seen between the 75-mcg dose and up to 600 mcg daily for CCV AEs.

No deaths were reported in those receiving indacaterol 75.

These findings, which used pooled data from previous studies and a database of U.S. and Canadian patients, indicate that indacaterol given at the 75-mcg dose has an acceptable CCV safety profile in patients with moderate to severe COPD, Dr. Donohue said.

When considered in the context of the efficacy data, the findings should be very reassuring to clinicians, he said.

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New therapies emerging for malignant pleural disease

BY SHARON WORCESTER
IMNG Medical News

ATLANTA – New approaches are emerging in the treatment of malignant pleural disease.

Until recently, talc pleurodesis, the standard of care, and repeated thoracentesis were the only options for treating symptomatic patients with malignant pleural disease established by cytology or biopsy, Dr. Najib Rahman said at the annual meeting of the American College of Chest Physicians.

"We need more novel, less toxic, and more effective agents," said Dr. Rahman, noting that these are exciting and important areas of research, especially given how common malignant pleural disease is – and how the incidence is increasing because of the aging of the population.

One newer option is the use of an indwelling catheter, said Dr. Rahman of the University of Oxford (England). "We can completely bypass the whole idea of pleurodesis and go for an indwelling catheter." As for the continued use of talc pleurodesis, the focus should be on identifying the best agents and improving upon current practices.

"All of us feel talc isn't as good as it could be," he said, noting that the procedure is painful and is associated with various toxicities.

Nonetheless, talc pleurodesis is considered the most effective agent for the treatment of patients with malignant pleural effusion, and data suggest that the success rate is about 75%.

In a meta-analysis of 46 randomized controlled trials comprising over 2,000 patients, talc was shown to be superior to bleomycin and tetracycline (risk ratios of 0.63 and 0.50, respectively).

However, some questions remain about how to best use talc pleurodesis. For example, it is unclear whether poudrage or slurry is the best approach for instillation, he said. Further, talc is associated with significant toxicity; 8 (4%) of 196 patients in one study experienced acute respiratory distress syndrome and 5 of them died; 41 of 4,030 patients (1%) in another study experienced acute respiratory failure.

'We can completely bypass the whole idea of pleurodesis and go for an indwelling catheter.'

DR. RAHMAN

Although studies have suggested better safety with graded talc (French talc), compared with nongraded talc (U.S. talc), limitations of those studies raise questions about the findings. Also lacking with respect to talc is information on the best analgesic strategy, appropriate tube size, and predictors of outcomes, he said.

Newer options under consideration for pleurodesis include the bacterial proteins OK-432, staphylococcal superantigen, and lipoteichoic acid (LTAT).

Bacterial proteins

Bacterial proteins are promising for pleurodesis because they are proinflammatory and potentially less toxic than other agents.

OK-432, or Picabinil, is a bacterial protein commonly used in Japan (where talc is not available), but not yet available in the western hemisphere, Dr. Rahman said.

In a single randomized controlled trial, the radiological complete response rate in 23 treated patients was 73%, compared with 41% for those treated with mitomycin C. OK-432 was associated with a longer effusion-free survival (7 months vs. 1.5 months) but was also associated with greater toxicity.

"So, clearly there are some interesting ideas there, but certainly no definitive data," he said.

Staphylococcal superantigen

Staphylococcal superantigen has been shown to induce cytotoxic T-cell differentiation in animal models of melanoma, and is associated with anti-tumor cytokine production, as well as with evidence of tumor regression. The complete response rate was 79% in one small study in 14 consecutive patients with non–small cell lung cancer. Patients were treated with repeated intrapleural instillation of staphylococcal superantigen at 100-400 pg once or twice per week until effusion resolved.

Furthermore, median survival was 2.0 months for 13 patients with malignant pleural effusion treated with talc pleurodesis, versus 7.9 months for 14 patients treated with staphylococcal superantigen. While these are not comparative data, the survival with staphylococcal superantigen was better than one might expect.

"Potentially there are some interesting signals here that might suggest this stuff may do more than just seal the pleural space, and may help to regress the cancer," Dr. Rahman said.

Lipoteichoic acid

LTAT has various immune effects, including activating toll-like receptor pathways. In a dose-escalation study, he and his colleagues found that at 1-month follow-up, the overall success rate was 75%, while the success rate in those receiving more than 750 mcg of LTAT was 86%, suggesting that this treatment is "doing something to pleural fluid production," he said.

No significant toxicity occurred at doses below 3,000 mcg. This early evidence of efficacy requires confirmation in additional studies, he said.

Another innovative area in the treatment of malignant pleural disease is the direct biological control of pleural fluid production with profibrotic cytokines such as TGF-beta.

"So rather than sealing the cavity, this is turning off the tap at the source," Dr. Rahman said.

Although this approach has not yet been studied in humans, it has significant potential advantages including low toxicity and robust pleurodesis. Also, it is not affected by steroids. "I think maybe in the next 5 or 10 years this will be an interesting area of research," he said.

Currently, about 300,000 cases occur in the United Kingdom and the United States each year, and an estimated 100,000 additional cases each year are expected by 2055. The average hospital will see about 250 new cases per year, he said.

Dr. Rahman has received drugs and matched placebos for clinical trials, technical equipment for trials, and/or funding for trials or research from Roche, Genentech, Boehringer, Lunamed, Syder-Med, Rocket Medical UK, GE Medical, NIHR, HTA Trials, MRC, UKCRN, CRUK, BLF, and UNKRCI. He has also served as a consultant to Rocket Medical.

Lung symptoms vary throughout menstrual cycle

BY ELIZABETH MECHCATIE
IMNG Medical News

Significant variations in respiratory symptoms at different stages of the menstrual cycle were identified in a study of nearly 4,000 women in Northern Europe, with patterns that varied by body mass index, asthma, and smoking status.

"The findings suggest substantial hormonal influences in interplay with metabolic factors on airway physiology and on pathophysiological processes in respiratory diseases like asthma," said Dr. Ferenc Macsali of the department of gynecology and obstetrics at Haukeland University Hospital, Bergen, Norway, and his associates.

They obtained information from questionnaires mailed to the Nordic-Baltic population of women, about respiratory symptoms, menstrual symptoms, BMI, and smoking status. The study, reported in the American Journal of Respiratory and Critical Care Medicine, comprised 3,926 women (mean age 39 years) with regular cycles no greater than 28 days, who were not on hormonal medications. It is part of Respiratory Health in Northern Europe (RHINE), a population-based multicenter questionnaire study. Almost 29% of the women were regular smokers and almost 8% said they had been diagnosed with asthma. Mean BMI was 23 kg/m^2.

Based on their analysis of the responses, the researchers identified significant variations during the menstrual cycle for each of the three symptoms analyzed – wheezing, shortness of breath, and coughing – including reports of wheezing that were higher during cycle days 10-22, with a "dramatic" drop in the middle of the cycle at about days 14-16, the "putative time of ovulation," in most subgroups.

Wheezing was lower before and after menses. The daily incidence of shortness of breath was highest on days 7-21, dropping just before the middle of the cycle "in a number of subgroups." And there were peaks in the incidence of cough before and after midcycle, around the time of "putative" ovulation, and before the onset of menses; the incidence of coughs was lower after menses (Am. J. Respir. Crit. Care Med. 2012 [doi: 0.1164/rccm.201206-1112OC]).

Use of the questionnaire for the data, as well as variations in the lengths of menstrual cycles, were cited as study limitations.

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FDA approves bedaquiline for resistant tuberculosis

BY MICHELE G. SULLIVAN
IMNG Medical News

The Food and Drug Administration has granted an accelerated approval for bedaquiline – the first antituberculosis drug to target the key energy enzyme, adenosine triphosphate.

Because of its novel method of action, bedaquiline fills a previously unmet need, FDA officials said.

"Multidrug-resistant tuberculosis (MDR-TB) poses a serious health threat throughout the world, and [bedaquiline] provides much-needed treatment for patients who have don't have other therapeutic options available," Dr. Edward Cox, director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research, said in a statement. "Because the drug also carries some significant risks, doctors should make sure they use it appropriately and only in patients who don't have other treatment options."

Bedaquiline carries a boxed warning about its potential effect on heart rhythm; it has been associated with QT-segment prolongation, which could lead to a potentially fatal dysrhythmia. According to materials submitted to the FDA Anti-Infective Drugs Advisory Committee, 26 patients taking the drug died during the two pivotal phase II studies, compared with four who took placebo. Three deaths were cardiac related, including one from hypertension, one from cardiac arrest associated with pneumonia, one from congestive heart failure, according to the materials submitted by manufacturer Janssen Therapeutics.

The two studies upon which FDA based its approval involved almost 400 patients, all of whom had pulmonary MDR-TB. The first compared a standard, four-drug regimen plus placebo to the same regimen plus 400 mg bedaquiline daily for 2 weeks, followed by 200 mg three times a week for 22 weeks.

At 24 weeks, 78% of those treated with bedaquiline had a culture conversion, vs. 58% of those on placebo, a significant difference. Treatment failure occurred in 23% of the active group and 43% of the placebo group.

The second study was an open-label trial of 233 previously treated patients who still had culture-positive MDR-TB. They received the same dosing regimen of bedaquiline combined with an individualized background regimen. At 24 weeks, sputum conversion was 80%, with negative cultures appearing in a mean of 57 days.

The accelerated approval program allows provisional approval to drugs showing a positive treatment effect for serious disease, based on data from a surrogate endpoint likely to predict clinical benefit – in this case, sputum conversion. Bedaquiline will be available while Janssen conducts confirmatory phase III trials.

The FDA also granted bedaquiline a fast-track designation, priority review, and an orphan drug designation.

The drug will be marketed under the trade name Sirturo.

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Targeted CT follow-up proposed for incidental nodules

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – Limiting CT follow-up of incidental pulmonary nodules to a small area around the suspicious nodule may help resolve a common clinical dilemma and an Achilles heel of lung cancer screening, researchers suggest.

It could also reduce the radiation dose by more than 80%.

"Why should we radiate the entire thorax on follow-up?" Dr. Gregory D. Pearson asked rhetorically at the annual meeting of the Radiological Society of North America.

In the pivotal National Lung Cancer Screening Trial, annual low-dose CT reduced lung cancer deaths by 20% and all-cause mortality by 6.7% among heavy smokers, compared with traditional x-rays. Approximately 40% of the CT group, however, had findings of small, indeterminate pulmonary nodules that were considered suspicious for lung cancer on at least one scan, with 1.4% experiencing a complication as a result of additional testing (N. Engl. J. Med. 2011;365: 395-409).

Follow-up CT scans contribute to a patient's cumulative radiation burden, said Dr. Pearson, a thoracic radiologist at New York-Presbyterian Hospital/Columbia University in New York.

In an effort to develop a practical solution, he and his colleagues analyzed the variability in nodule location among 50 patients with subcentimeter nodules identified on CT screening for lung cancer and emphysema, and then devised a protocol for targeted CT follow-up that was validated in 50 additional patients.

Two experts and one novice reader, a medical student, independently measured the distances of the nodules from two anatomical landmarks, the lung apex and carina, on baseline and follow-up scans by cross-referencing the axial images with the CT scanogram on a PACS (picture archiving and communication system) workstation.

The interobserver variability was quite low, with mean differences of just 2-3 mm when the two experts were paired together or individually paired with the novice reader, Dr. Pearson said. Results were significantly better measuring from the apex than from the carina for two of the three reader pairings ($P = .005$ and .03), although the absolute difference was just 1 mm.

Interscan variability between the baseline and follow-up scans was slightly larger, averaging 5.3 mm from the apex and 6.2 mm from the carina. The maximal difference in nodule location between the two scans was 24 mm from the apex and 29 mm from the carina. Both outcomes significantly favored the measurement from the apex ($P = .01$).

"The measurements were highly reproducible, [there was] no benefit in measuring from the carina, and we figured that if the nodules were normally distributed throughout the lungs, that 99% of nodules should range between the mean plus three standard deviations, which would be about a 38-mm range," Dr. Pearson said.

To allow for a greater margin of error, measurements in the validation phase of the study were only from the ipsilateral lung apex and covered a 60-mm range. At baseline, the expert identified the nodule and placed a cut line on the scan to measure the distance from the apex. Medical students then measured the distance of the nodule from the apex on the follow-up scan, and reviewed a region of about 6 cm to determine whether the nodule would have been included in its entirety if the range of the CT scan had been narrowed to just 60 mm.

"The results here are pretty simple; 100% of the nodules in follow-up were scanned in their entirety," Dr. Pearson said. The mean craniocaudal coverage on follow-up CT was 363 mm.

With use of a targeted 60-mm range, the mean craniocaudal coverage and radiation dose would be reduced by 83%, although the actual dose reduction will depend on the location of the nodules, he added.

The technique needs to be validated prospectively in larger groups, and would require buy-in from radiologists, medical societies, and Medicare and private insurers, he said.

Dr. McAdams reported a research grant from General Electric, serving as a consultant for American College of Radiology Image Metrix, and working as an author for Reed Elsevier and UpToDate Inc.

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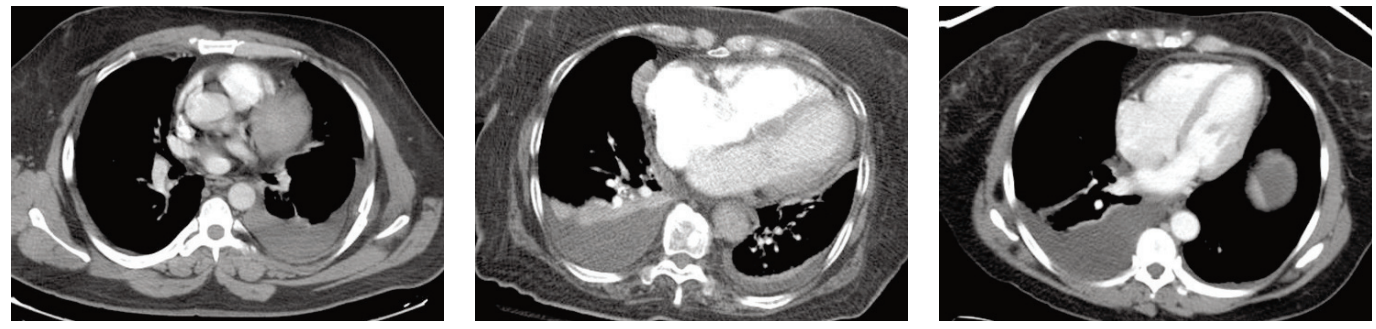
Tool helped to standardize sizing of pleural effusions

BY PATRICE WENDLING
IMNG Medical News



IMAGES COURTESY MONTEFIORE MEDICAL CENTER

Although these pleural effusions are similar in size, the sizes were reported as "small-moderate" (left), "moderate" (middle), and "large" (right). Such variation in terminology among radiologists can confuse interpretation of CT reports.

CHICAGO – Researchers have developed and validated a simple two-step rule to quantify pleural effusion size on computed tomography – something currently not standardized.

Use of the rule improved interobserver agreement, from a kappa coefficient of 0.56 to 0.79 (P less than .0001), among nine physicians ranging in skill from cardiothoracic radiologists and pulmonologists to radiology residents.

"It's practical for any physician with access to the images and the referent tool," Dr. Matthew Moy said at the at the annual meeting of the Radiological Society of North America.

Computed tomography (CT) is highly sensitive for detecting small effusions, and differentiating pleural and parenchymal disease. The problem lies in the subjective grading of pleural effusion size, which can lead to confusion among physicians when reading CT reports or comparing effusions based on different reports, he said. (See image.)

In an effort to improve this communication, investigators at the Albert Einstein College of Medicine, New York, selected 34 adult CT scans with a range of pleural effusion sizes, and measured the volume of each effusion and ipsilateral hemithorax using a morphometric segmentation tool.

The effusion and ipsilateral hemithorax were then manually traced on each axial slice, and the effusion volume calculated as a percent of the volume of the hemithorax.

The mean effusion volume was 37.42% of the hemithorax (range, 5.59%-89.05%). The patients' mean age was 64 years, and 74% had undergone noncontrast CT.

Two cardiothoracic fellowship–trained radiologists then reviewed the CTs to identify qualitative and quantitative features that correlated with effusion volume. Several features emerged, but only anteroposterior (AP) quartile, maximum AP depth, and degree of atelectasis remained significant in multivariate analysis. The last was dropped, however, because it was not useful for differentiating large effusions, said Dr. Moy, now with Massachusetts General Hospital in Boston.

A classification rule was then developed in which first AP quartile (0-25%) effusions are small, second quartile (25-50%) moderate, and third or fourth AP quartile (50-75% or 75-100%) large.

To validate the rule, nine physicians assessed the 34 CT scans; the reviewers were not involved in the initial CT analysis. Interobserver agreement improved from a kappa of 0.59 to a kappa of 0.73 for radiology residents, 0.54 to 0.76 for pulmonologists, and 0.74 to 0.85 for cardiothoracic radiologists.

The new two-step rule is currently in use at Albert Einstein, and has been published online (Chest 2012 Nov. 8 [doi: 10.1378/chest.12-1292]).

Dr. Moy reported no conflicts of interest. A coauthor reported investments in Ortho SpImages courtesy Montefiore Medical Center and Kryon Systems.

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With COPD

Limited lung function makes breathing more difficult

INDICATIONS AND USAGE

TUDORZA™ PRESSAIR™ (aclidinium bromide inhalation powder) is an anticholinergic indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Please see Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

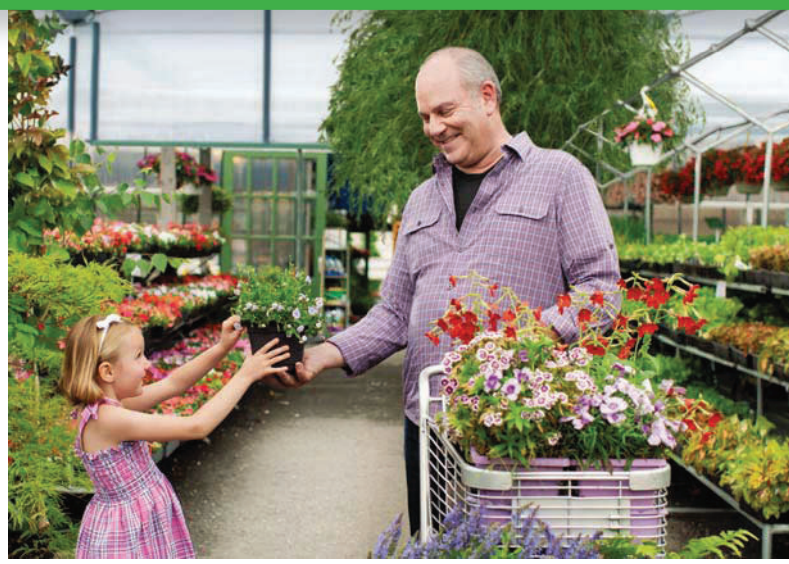
New

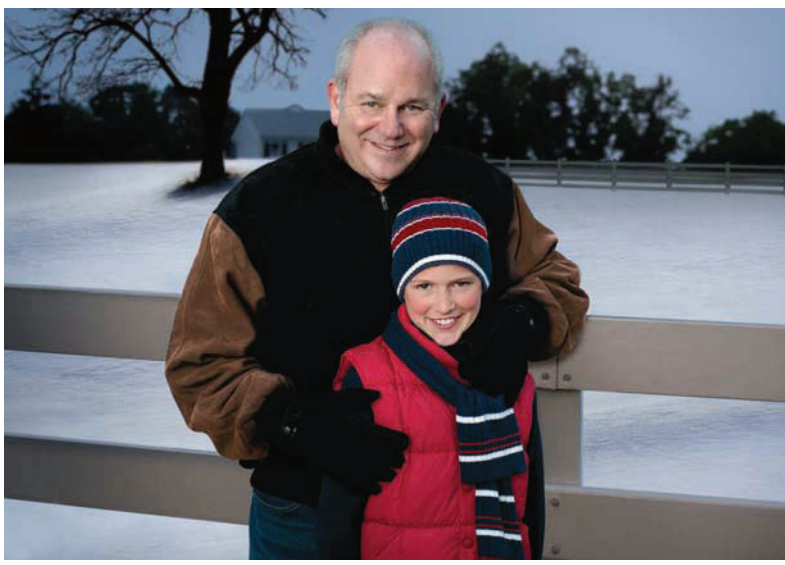
Tudorza™ Pressair™

(aclidinium bromide inhalation powder)

400 mcg

TUDORZA™ can help





IMPORTANT SAFETY INFORMATION

- TUDORZA PRESSAIR is not indicated for the initial treatment of acute episodes of bronchospasm (ie, rescue therapy).
- Inhaled medicines, including TUDORZA, may cause paradoxical bronchospasm. In addition, immediate hypersensitivity reactions may occur after administration of TUDORZA. If either of these occurs, treatment with TUDORZA should be stopped and other treatments considered.
- TUDORZA should be used with caution in patients with narrow-angle glaucoma or urinary retention. Instruct patients to consult a physician immediately should any signs or symptoms of narrow-angle glaucoma or prostatic hyperplasia or bladder-neck obstruction develop.

Introducing TUDORZA™ PRESSAIR™
A new long-acting anticholinergic treatment

For the long-term maintenance treatment of bronchospasm in patients with COPD

TUDORZA provides statistically significant improvements in bronchodilation that are consistent over time[1]

- Statistically significant improvements in morning predose lung function (forced expiratory volume in one second [FEV_1]) at 12 weeks (primary endpoint) or 24 weeks vs placebo[1-3]
- Mean peak improvements in FEV_1 relative to baseline observed after the first dose on day 1 were similar at 12 weeks[1]
- No overall differences in efficacy or safety were observed between older (≥70 years) and younger (<70 years) adult patients in 3 placebo-controlled studies[1]
- Common side effects occurred at rates of <7%[1]
  - The most common side effects (≥3% incidence and greater than placebo) were headache (6.6% vs 5.0%), nasopharyngitis (5.5% vs 3.9%), and cough (3.0% vs 2.2%), for TUDORZA vs placebo, respectively[1]
  - The incidence of common anticholinergic side effects was <1%, including dry mouth (0.8% vs 0.6%), constipation (0.0% vs 0.9%), tachycardia (0.3% vs 0.0%), and urinary retention (0.2% vs 0.0%), for TUDORZA vs placebo, respectively[2]
- Preloaded, multiple-dose inhaler with dose indicator and colored control window that confirms correct inhalation[1]
  - For a complete description of how to use the TUDORZA PRESSAIR inhaler, see the step-by-step Instructions for Use within the full Prescribing Information, available at www.TUDORZA.com
- The recommended dose is one oral inhalation of 400 mcg, twice daily[1]

IMPORTANT SAFETY INFORMATION

- Patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to TUDORZA. Use with caution in patients with severe hypersensitivity to milk proteins.
- The most common adverse reactions (≥3% incidence and greater than placebo) were headache, nasopharyngitis, and cough.

Please see Brief Summary of full Prescribing Information at the end of this ad.

New

Tudorza™ Pressair™

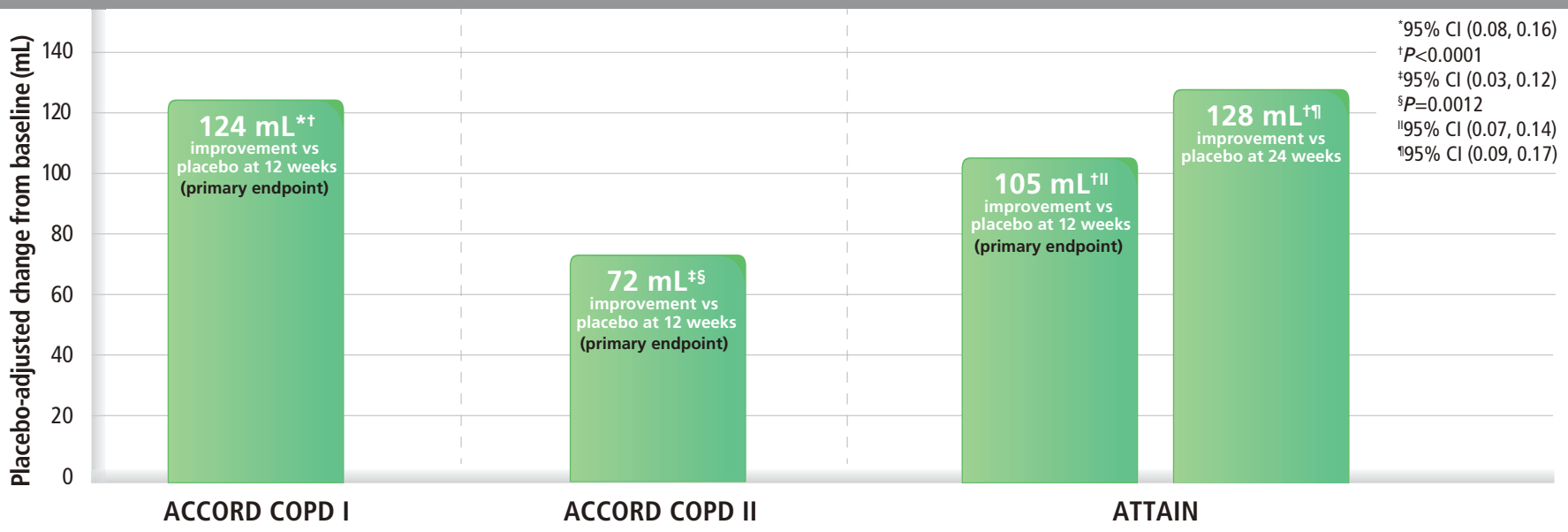
(aclidinium bromide inhalation powder)

400 mcg

In placebo-controlled studies

TUDORZA provided statistically significant improvements in morning trough (predose) lung function at 12 or 24 weeks

Morning trough (predose) FEV_1 treatment difference vs placebo at 12 or 24 weeks across 3 studies[2,3]



Please see study descriptions below, including results for individual treatment arms.

The primary endpoint for all 3 studies was the change from baseline in morning trough (predose) FEV_1 at 12 weeks. Morning trough (predose) FEV_1 was defined as FEV_1 measured 12 hours after the previous evening dose of TUDORZA. A secondary endpoint of change from baseline in morning trough (predose) FEV_1 at 24 weeks was measured in the ATTAIN study.[1-3]

Study design for ACCORD COPD I: A randomized, double-blind, 12-week study in patients with moderate to severe COPD (N=375; n=190 [TUDORZA] and n=185 [placebo]) that assessed the bronchodilator efficacy and safety of inhaled TUDORZA. Mean patient age was 65 years; 52.1% male, 94.7% Caucasian. Rescue medication, corticosteroids, methylxanthines (theophylline), and oxygen therapy were allowed as concomitant treatments. Major relevant medication classes not allowed included long-acting beta agonists, short-acting muscarinic antagonists, long-acting muscarinic antagonists, and long-acting beta agonist/inhaled corticosteroid combinations.[1-3]

Mean baseline values for morning trough (predose) FEV_1 were 1.33 L for the TUDORZA study group and 1.38 L for the placebo study group. The change from baseline in morning trough (predose) FEV_1 at 12 weeks was 99 mL for the TUDORZA study group and -25 mL for the placebo study group.[1-3]

Study design for ACCORD COPD II: A randomized, double-blind, 12-week study in patients with moderate to severe COPD (N=359; n=177 [TUDORZA] and n=182 [placebo]) that assessed the bronchodilator efficacy and safety of inhaled TUDORZA. Mean patient age was 62.5 years; 52.6% male, 91.4% Caucasian. Rescue medication, corticosteroids, methylxanthines (theophylline), and oxygen therapy were allowed as concomitant treatments. Major relevant medication classes not allowed included long-acting beta agonists, short-acting muscarinic antagonists, long-acting muscarinic antagonists, and long-acting beta agonist/inhaled corticosteroid combinations.[1,2]

Mean baseline values for morning trough (predose) FEV_1 were 1.25 L for the TUDORZA study group and 1.46 L for the placebo study group. The change from baseline in morning trough (predose) FEV_1 at 12 weeks was 64 mL for the TUDORZA study group and -8 mL for the placebo study group.[1,2]

Study design for ATTAIN: A randomized, double-blind, 24-week study in patients with moderate to severe COPD (N=542; n=269 [TUDORZA] and n=273 [placebo]) that assessed the long-term bronchodilator efficacy and safety of inhaled TUDORZA. Mean patient age was 62.5 years; 68.5% male, 95.4% Caucasian. Rescue medication, corticosteroids, methylxanthines (theophylline), and oxygen therapy were allowed as concomitant treatments. Major relevant medication classes not allowed included long-acting beta agonists, short-acting muscarinic antagonists, long-acting muscarinic antagonists, and long-acting beta agonist/inhaled corticosteroid combinations.[1,2]

Mean baseline values for morning trough (predose) FEV_1 were 1.51 L for the TUDORZA study group and 1.50 L for the placebo study group. The change from baseline in morning trough (predose) FEV_1 at 12 and 24 weeks was 58 mL and 55 mL, respectively, for the TUDORZA study group and -47 mL and -73 mL, respectively, for the placebo study group.[1,2]

Peak lung function in all 3 studies

Mean peak improvements in FEV_1 relative to baseline observed after the first dose on day 1 were similar at 12 weeks[1]

IMPORTANT SAFETY INFORMATION

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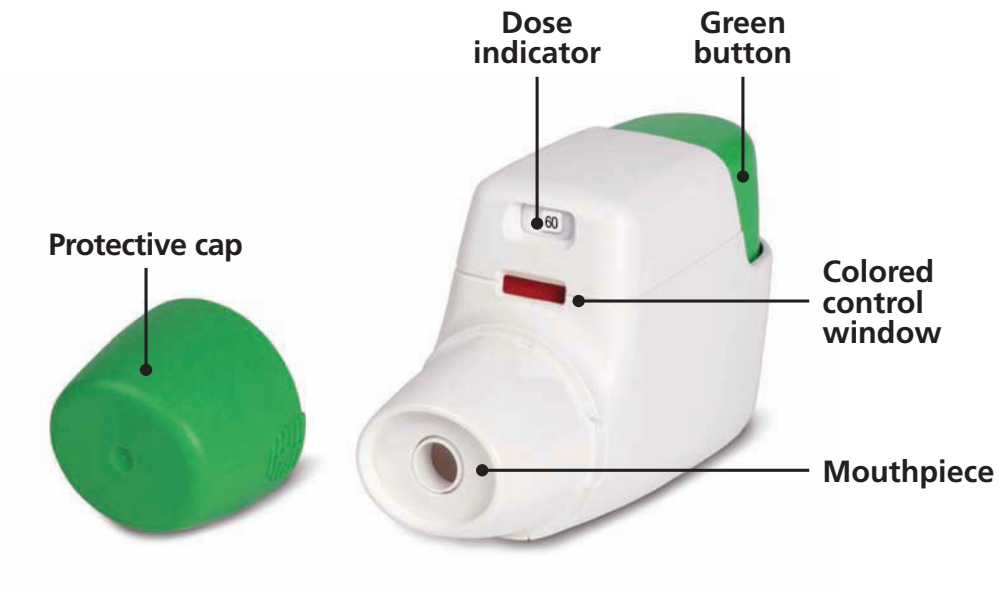
- TUDORZA should be used with caution in patients with narrow-angle glaucoma or urinary retention. Instruct patients to consult a physician immediately should any signs or symptoms of narrow-angle glaucoma or prostatic hyperplasia or bladder-neck obstruction develop.

The new PRESSAIR™ inhaler

TUDORZA is administered using a preloaded, multiple-dose, dry-powder inhaler[1]



- **Preloaded** with 60 doses for 1 month of treatment[1]
- **Colored control window**—provides confirmation of successful inhalation[1]
  - Turns from red to green when the dose is ready, and from green to red when the patient has inhaled the full dose of medication correctly
- A **"click"** sounds during inhalation when the patient is using the inhaler correctly[1]
  - Patients should keep breathing in after the "click" to be sure they get the full dose
- **Dose indicator**—shows patients approximately how many doses remain in the inhaler[1]
  - Number of doses counts down in intervals of 10 (60, 50, 40, 30, 20, 10, 0) with use
- Taking a dose from the PRESSAIR inhaler requires patients to press and release the green button, and then inhale[1]
  - For a complete description of how to use the TUDORZA PRESSAIR inhaler, see the step-by-step Instructions for Use within the full Prescribing Information, available at www.TUDORZA.com

IMPORTANT SAFETY INFORMATION

- Patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to TUDORZA. Use with caution in patients with severe hypersensitivity to milk proteins.
- The most common adverse reactions (≥3% incidence and greater than placebo) were headache, nasopharyngitis, and cough.

Please see Brief Summary of full Prescribing Information at the end of this ad.

References: 1. TUDORZA PRESSAIR (aclidinium bromide inhalation powder) Prescribing Information. Forest Pharmaceuticals, Inc. St. Louis, MO. **2.** Data on file. Forest Laboratories, Inc. **3.** Kerwin EM, D'Urzo AD, Gelb AF, et al, on behalf of the ACCORD I study investigators. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD.* 2012;9:90-101.

New

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12/12

Mild creatinine increase may bode ill after surgery

BY DOUG BRUNK
IMNG Medical News

SAN DIEGO – Patients who have minor elevations in serum creatinine after noncardiac surgery may be more likely to require a longer postoperative hospital stay and face a twofold increased risk of dying during that stay, preliminary data from a German study have shown.

"This is a big problem, because minor kidney dysfunction may not be noticed postoperatively," Dr. Felix Kork said in an interview during a poster session at Kidney Week 2012.

"About 2% of people in general have a small increase in serum creatinine. They are at greater risk of dying and staying longer in the hospital."

Dr. Kork of the department of anesthesiology and intensive care medicine at Charité Hospital in Berlin and his associates reviewed the records of 27,616 patients who had noncardiac surgery at Charité during 2006-2012.

Analysis showed that minor elevations in serum creatinine (0.25-0.50 mg/dL) were independently associated with a prolonged hospital length of stay (hazard ratio for early discharge, 0.81) and a twofold risk of death during the postoperative hospital stay (odds ratio, 1.99), compared with patients without an increase in serum creatinine. Both findings were significant. In addition, receiving a radiographic contrast agent before surgery was independently associated with a greater risk of mortality and a longer hospital stay, even without kidney dysfunction after the contrast agent.

Dr. Kork said that he had no relevant financial conflicts to disclose.

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VIEW ON THE NEWS

Lary Robinson, FCCP, comments: In a retrospective study of 27,616 noncardiac surgery patients in Berlin, 2% developed mild renal dysfunction with serum creatinine elevations of 0.25-0.50. The intensivist/anesthesiologist author, Dr. Kork, reports that this apparent mild change in creatinine in the perioperative period in this group of patients was associated with a significant doubling of operative mortality and an increase in hospital stay. Additionally, just receiving radiographic contrast media prior to surgery, even without renal dysfunction, also increased postoperative mortality and hospital stay. This study documents the critical role of renal function and fluid balance in the perioperative management of the surgical patient that is a strong determinant of morbidity and mortality. Experienced surgeons have always emphasized this principle to reduce complications, and this study underscores its importance.

Ultrafiltration flops for acute cardiorenal syndrome

BY BRUCE JANCIN
IMNG Medical News

LOS ANGELES – Mechanical venovenous ultrafiltration proved inferior to drug therapy in diuretic-responsive patients hospitalized with acute decompensated heart failure and cardiorenal syndrome in a major multicenter randomized trial.

In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF), weight loss due to elimination of excess fluid was similar at 96 hours in the two treatment arms. However, renal function was significantly worse in the ultrafiltration group at that time point, and it remained so even 60 days from baseline, Dr. Bradley A. Bart reported at the annual scientific sessions of the American Heart Association.

Moreover, the combined rate of the secondary endpoint comprising death or serious adverse events at 6 months was 72% in the ultrafiltration group, compared with 57% in patients treated with a standardized pharmacologic regimen, for an adjusted 50% increased risk in the ultrafiltration group. Serious adverse events included kidney failure, bleeding complications, and IV catheter problems.

"Neither group was adequately decongested at the time of hospital discharge. This is a challenging group of patients to treat. The 60-day event rates are very high," said Dr. Bart of the Hennepin County Medical Center, Minneapolis.

The CARRESS-HF trial randomized 188 affected patients who were diuretic responsive to a stepped pharmacologic care algorithm or to ultrafiltration at a rate of 200 mL/hr using the commercially available Aquadex System 100 device manufactured by CHF Solutions.

Both treatment groups lost about 12 pounds through 96 hours. However, while mean serum creatinine was unchanged from baseline in the drug therapy group, it climbed by 0.25 mg/dL in the ultrafiltration group.

Discussant Dr. Milton Packer agreed with the investigators that the findings offer no support for the use of mechanical ultrafiltration in patients who are responsive to diuretics. "I still think there's a role for ultrafiltration in patients who are diuretic unresponsive," added Dr. Packer, professor and chairman of the department of clinical sciences at the University of Texas Southwestern Medical Center, Dallas.

He called CARRESS-HF "a really terrific study and an important one." Ultrafiltration can be programmed to pull fluid off of patients more rapidly than is possible with drug therapy. Had mechanical ultrafiltration performed better than well-managed drug therapy in CARRESS-HF, the message to physicians would have been that they shouldn't spend much time fiddling with diuretic therapy in such patients, but should instead turn to ultrafiltration much earlier during the hospitalization, even in diuretic-responsive patients.

"What is striking about this study is that the difference in renal function was present not only during the ultrafiltration but afterward. That's something that, frankly speaking, gives us pause," according to Dr. Packer.

Simultaneous with Dr. Bart's presentation of the CARRESS-HF results at the AHA conference, the study findings were published online (N. Engl. J. Med. 2012 [doi: 10.1056/NEJMoa1210357]).

In an accompanying editorial, Dr. W.H. Wilson Tang of the Cleveland Clinic called the outcomes in CARRESS-HF "overall dismal," with more than one-third of patients dying or being readmitted for acute decompensated heart failure within 60 days, regardless of their treatment arm. But that's representative of what happens in everyday clinical practice when acute cardiorenal syndrome occurs (N. Engl. J. Med. 2012 [doi: 10.1056/NEJMe1212881]).

CARRESS-HF was sponsored by the National Heart, Lung, and Blood Institute and carried out by the Heart Failure Clinical Research Network. Dr. Bart, Dr. Packer, and Dr. Tang reported having no relevant financial disclosures.

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Nonpayment fails to improve hospital infection rates

BY MARY ANN MOON
IMNG Medical News

The 2008 Medicare policy to withhold payment for treating certain hospital-acquired infections failed to decrease infection rates in U.S. hospitals, according to a report published in the New England Journal of Medicine.

In a study involving 398 hospitals or medical systems across the country, implementing a Centers for Medicare and Medicaid Services policy of nonpayment for the treatment of preventable catheter-associated bloodstream infections and catheter-associated urinary tract infections appeared to have no impact at all on the acquisition of those infections, according to Dr. Ashish K. Jha of the department of health policy and management, Harvard School of Public Health, Boston, and his associates.

"As CMS continues to expand this policy to cover Medicaid through the Affordable Care Act, require public reporting of National Healthcare Safety Network [NHSN] data through the Hospital Compare website, and impose greater financial penalties on hospitals that perform poorly on these measures, careful evaluation is needed to determine when these programs work, when they have unintended consequences, and what might be done to improve patient outcomes," Dr. Jha noted.

Dr. Jha and his colleagues assessed data from the NHSN, a public health surveillance program for monitoring health care–associated infections across the country. A total of 1,166 nonfederal acute-care hospitals report their infection rates to this Centers for Disease Control and Prevention–sponsored network every month.

A possible explanation for these findings is that the amount of this financial disincentive was quite small.

DR. JHA

Dr. Jha and his colleagues assessed NHSN data on three types of infection at 398 of those hospitals in 41 states. They examined central catheter–associated bloodstream and catheter-associated urinary tract infections because these are the two hospital-acquired infections for which CMS currently does not pay. They also looked at ventilator-associated pneumonia, which is not targeted by the CMS policy, as a control.

Rates of central catheter–associated bloodstream infections were already decreasing at the time the CMS policy was implemented, likely because the federal government, national organizations, and accrediting agencies had already focused attention on preventing these nosocomial infections.

The rate of these infections was 4.8% per quarter before the policy was implemented and 4.7% afterward, a nonsignificant difference, the investigators said (N. Engl. J. Med. 2012 [doi: 10.1056/NEJMsa1202419]).

This pattern also was seen with catheter-associated UTIs, in which there was a small, nonsignificant increase in the infection rate after implementation of the CMS policy. For the control condition of ventilator-associated pneumonia, the infection rate was 7.3% before implementation and 8.2% after implementation of the policy, also showing no significant impact on infection rates.

These findings were consistent across all hospital types, regardless of size, regional location, type of ownership, or teaching status.

To assess whether any benefit of the nonpayment policy may have been offset by strategies to lower infection rates, such as mandatory reporting, the researchers performed a separate analysis involving only the hospital units located in states that didn't have mandatory reporting. Again, no demonstrable effect on infection rates was seen.

To allow more time for hospitals to adapt to the policy change, the investigators performed a sensitivity analysis comparing infection rates 2 years after implementation with those before implementation. Again, they found no further decreases in the rates of any infections.

A possible explanation for these findings is that the amount of this financial disincentive was quite small. "Reductions in payment may have been equivalent to as little as 0.6% of Medicare revenue for the average hospital," Dr. Jha and his associates said. "Greater financial penalties might induce a greater change in hospital responsiveness to the CMS policy."

The study results are particularly important given the increasing use of financial disincentives to improve the quality of health care, they said.

This study was supported by the Agency for Healthcare Research and Quality. No financial conflicts of interest were reported.

Pertussis vaccine loses efficacy after fifth dose

BY MARY ANN MOON
IMNG Medical News

The odds of a child developing pertussis increase as the interval since he or she received the fifth and final dose of the DTaP vaccine increases, according to a report published in JAMA.

This pattern indicates a progressive waning of vaccine effectiveness every year after completion of the vaccine series, which would explain the recently noted surge in pertussis cases among 7- to 10-year-olds in at least 34 states, said Lara K. Misegades, Ph.D., of the Meningitis and Vaccine Preventable Disease Branch of the Centers for Disease Control and Prevention, and her associates.

These are the findings of "the first large-scale assessment of the U.S. five-dose DTaP schedule conducted in the setting of a mature vaccination program and allowing for a comparison of fully vaccinated and unvaccinated children." Together with the findings of previous studies that used different methods to examine this issue, the results "suggest that waning of immunity following DTaP vaccination may have resulted in a much larger pool of susceptible individuals" than previously realized.

"In periods of increased pertussis transmission, the burden of disease attributable to the vaccinated but susceptible population is high," noted Dr. Misegades and her colleagues.

The investigators examined the durability of the protection provided by the DTaP vaccine by using a case-control study design to compare pertussis incidence between fully vaccinated and unvaccinated children aged 4-10 years who were living in California during the 2010 pertussis epidemic there. The study population comprised 682 cases who developed confirmed, probable, or suspected pertussis and 2,016 controls who did not, enrolled from the offices of 265 clinicians.

All the vaccinated children had received their first three doses before the age of 1 year, a fourth dose at 1-2 years of age, and a fifth dose at 4-6 years of age.

Compared with controls, children who developed pertussis had a lower chance of having received all five doses of DTaP, with an odds ratio of 0.11. This study finding was not unexpected.

When the study subjects were categorized by time since completion of the vaccine series, using unvaccinated subjects as the reference group, those who developed pertussis were less likely to have received their fifth dose within the preceding 12 months. The rate of pertussis was 2.8% among children who had received their final dose of vaccine during the previous year, compared with 17.6% among children who had received their final dose of vaccine more than 1 year previously, the investigators said (JAMA 2012;308:2126-32).

This association not only persisted but became stronger with increasing time since receipt of the final vaccine dose, so that vaccine effectiveness declined further with each succeeding year.

These findings, together with those of previous studies using different methods of analysis, "have raised concerns about the current U.S. pertussis vaccine program and may prompt consideration of alternative schedules. Options include delaying administration of the fifth DTaP dose or administering the Tdap booster at earlier than 11 years of age," Dr. Misegades and her associates said.

No financial conflicts of interest were reported.

VIEW ON THE NEWS

The DTaP vaccine may afford less than optimal protection, but it is still quite effective. The overall incidence of pertussis remains "a small fraction" of what it was in the prevaccine era, said Dr. Eugene D. Shapiro.

[Dr.] "Misegades et al. found that, compared with 4- to 10-year-olds who had received five doses of DTaP vaccine, the odds of receiving a pertussis diagnosis were nine times higher for unimmunized children, and the estimated vaccine effectiveness was 89% and was even higher in years 1, 2, and 3 after the fifth dose," he noted.

DR. SHAPIRO *is in the department of pediatrics, epidemiology, and investigative medicine at Yale University, New Haven, Conn.* *His work is supported by the National Center for Research Resources and the National Center for Advancing Translational Science. He reported no financial conflicts of interest. These remarks were taken from his editorial accompanying Dr. Misegades' report (JAMA 2012;308:2149-50).*

PCV13 vaccine benefits extend to nonimmune children

BY SUSAN LONDON
IMNG Medical News

SAN DIEGO – Children who receive just one of the recommended two doses of the 13-valent pneumococcal conjugate vaccine still derive indirect protection, new data suggest.

Colonization rates were similar for immune and nonimmune children, based on surveillance data for the first 2 years after the vaccine's introduction. The findings come from a study at the Boston Medical Center of 4,338 children under age 60 months. Roughly one-third were considered nonimmune because they did not receive sufficient doses of the vaccine.

Nasopharyngeal colonization with PCV13-unique serotypes fell in the overall population after the introduction of the vaccine. Importantly, colonization declined by at least 50% in the nonimmune group at about 1.5 years after the vaccine was introduced, when roughly 75% of eligible children had received it.

Although it took time for the nonimmune group to catch up with their immune peers, the vaccine reduced serotype-specific colonization in children regardless of their immune status, commented Dr. Stephen I. Pelton, a professor of pediatrics and epidemiology at the Boston University School of Medicine and Public Health.

"No change in overall prevalence of pneumococcal colonization is observed," he said at IDWeek, the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

Introduction of the similar PCV7 vaccine was associated with a greater reduction of cases of pneumococcal disease in nonimmunized children than in their immunized counterparts (MBio. 2011;2:e00309-10). The researchers in that study attributed the shared benefits to the vaccine's impact in reducing nasopharyngeal carriage and transmission of vaccine serotypes.

The records of children aged 59 months or younger who received care at the Boston Medical Center's primary care center were reviewed to determine vaccination status. Children under age 12 months were considered immune if they received two doses of PCV13 vaccine, and older children were presumed immune if they received one dose.

Pneumococcal colonization was based on the serotypes of *Streptococcus pneumoniae* isolates obtained from nasopharyngeal swab samples. Colonization analyses used 25-week rolling intervals, for example, weeks 1-25, weeks 2-26, and so on.

Analyses showed good uptake of the vaccine in all age groups. The percentage of children considered immune rose steadily over the 2-year period and peaked at 80%, Dr. Pelton reported.

On average, 32% of children were considered nonimmune during the study period, but the proportion decreased over time.

The overall prevalence of colonization was essentially stable during the study period, but the prevalence of colonization specifically with PCV13-unique serotypes fell. A distinct seasonal pattern was also evident.

"By week 28, we could already see a difference between the unimmunized group and the immunized group," Dr. Pelton explained. "We saw a rapid increase in PCV13 carriage during the fall, projecting on into the winter season [in the former], whereas we have a blunting in the children who are immunized in terms of the acquisition of PCV13 serotypes."

An indirect effect of the vaccine – a reduction by at least 50% in colonization with PCV13-unique serotypes that persisted among nonimmune children during a comparable season – was achieved at week 81. At that point the prevalence stood at about 3 cases per 100 nonimmune children. This outcome occurred when vaccine uptake reached 75%.

Colonization among nonimmune children fell to the levels seen among immune children at week 52 after the PCV13 vaccine was introduced. By this time, vaccine uptake hit 65%.

Dr. Pelton disclosed that he has received honoraria and research funding from Merck, GlaxoSmithKline, and Pfizer. The study was funded by the Thrasher Research Foundation and Pfizer.

Drug plus CPAP improved high-altitude sleep apnea

BY TARA HAELLE
IMNG Medical News

Using a combination treatment of acetazolamide and auto-CPAP therapy in patients with obstructive sleep apnea traveling to high altitudes was more effective than CPAP use alone, according to a study published in JAMA.

Patients with OSA who took acetazolamide and used CPAP at two different altitudes higher than baseline had lower apnea/hypopnea index scores and higher nighttime oxygen saturation percentages than patients who took a placebo and used CPAP.

Dr. Tsogyal Latshang and associates at the University Hospital Zurich reported the results of their randomized, placebo-controlled, double-blind crossover study with 51 OSA patients (JAMA 2012 Dec. 12 [doi: 10.1001/jama.2012.94847]).

All the patients, who normally live below 800 meters altitude and use CPAP regularly, underwent sleep studies during the summer of 2009, first at the University Hospital Zurich (490 m) and then at two Swiss mountain resorts, one at 1,630 m and one at 2,590 m, during two 3-day trips.

The patients took either acetazolamide or a placebo while spending 2 days at 1,630 m and 1 day at 2,590 m. The acetazolamide was dispensed as one 250-mg dose each morning and two 250-mg doses each evening before meals; the placebo looked identical.

After 2 weeks spent below 800 m following the first 3-day trip, the patients then spent another 3 days at the high-altitude resorts to take the other intervention (acetazolamide or placebo). During the sleep studies, instead of using their own CPAP devices, the patients all used the same type of autoadjusting CPAP machine with their own masks.

The combination therapy of acetazolamide and CPAP increased the patients' median nighttime oxygen saturation at 1,630 meters by 1%, from 93% with placebo to 94% with combination therapy. At 2,590 meters, the increase was 2%, from 89% with placebo to 91% with combination therapy. At the higher altitude, patients receiving combination therapy spent a median 13% of nighttime sleep with oxygen saturation below 90%, compared to a median of 57% (*P* less than .001) below 90% oxygen saturation with placebo.

Patients receiving combination therapy also had lower apnea/hypopnea index scores at both altitudes, compared with placebo. The median at baseline, in the hospital at 490 meters with CPAP only, was 6.6 events/hr. At 1,630 meters, patients with placebo had a median 10.7 events/hr, compared with 5.8 when taking acetazolamide. At 2,590 m, patients' median apnea/hypopnea index improved from 19.3 events/hr with placebo to 6.8 with acetazolamide. (All *P* values were less than .001)

"The reduction in the apnea/hypopnea index was mainly related to a lower number of central apneas/hypopneas, particularly during nonrapid eye movement sleep, but obstructive apneas/hypopneas were

Continued on following page

Continued from previous page

slightly reduced as well (at 2,590 m)," the researchers reported.

Secondary outcomes measured included sleep time, exercise performance, vigilance symptoms, and adverse effects. Patients taking acetazolamide slept a median 24 minutes more (451 minutes, versus 427) at 1,630 m and 34 minutes more (446 minutes, versus 412) at 2,590 m (*P* less than .001). Sleep efficiency and nonrapid eye movement sleep were also higher with combination therapy than placebo, although self-reported daytime sleepiness was not significantly different.

Patients' heart rate was slightly lower with combination therapy (59 beats per minute, versus 60 at 1,630 m; and 61 bpm, versus 64 at 2,590 m), and patients taking acetazolamide had lower blood pressure at altitude than with placebo (96 mm Hg, versus 101 mm Hg at 1,630 m; and 99 mm Hg, versus 104 mm Hg at 2,590 m; *P* less than .05)

The most common adverse effects with acetazolamide were an unpleasant taste in the mouth and mild to moderate paresthesias, but no patients discontinued therapy.

The study was funded by grants from the Swiss National Science Foundation, Lung Leagues of Zurich and Schaffhausen, Center for Clinical Research, University of Zurich, University Hospital Zurich, and Philips Respironics (unconditional grant) in Switzerland. The only disclosure reported was Dr. Bloch's consultancy for IMT Medical and his receipt of unconditional institutional grants from Philips Respironics and ResMed.

VIEW ON THE NEWS

Dr. Paul A. Selecky, FCCP, comments: These are very interesting findings that will be useful to physicians with OSA patients who want to go to higher altitudes.

Adenotonsillectomy helped quell some OSA, bed-wetting

BY HEIDI SPLETE
IMNG Medical News

WASHINGTON – Adenotonsillectomy reduced obstructive sleep apnea and bed-wetting in half of 35 children diagnosed with both conditions.

The study was limited by its small size, but it suggests that children with severe OSA and nocturnal enuresis might benefit on both counts with adenotonsillectomy, Dr. Prasad Thottam said at the annual meeting of the American Academy of Otolaryngology – Head and Neck Surgery Foundation.

The mean age of the children was 8 years, and their mean BMI was 24 kg/m^2. Proper bladder function was documented in all children, and none had chronic conditions such as cerebral palsy. All wet their bed more than 3 nights/week, according to Dr. Thottam of Children's Hospital of Michigan, Detroit.

Four children had adenoidectomies, 2 had tonsillectomies, and 29 had adenotonsillectomies. A mean of 10 weeks post surgery, 51% of the children had reductions in bed-wetting. Girls were five times as likely as boys to have bed-wetting resolve.

Dr. Thottam had no financial conflicts to disclose.

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SLEEP STRATEGIES: The link between OSA and chronic lung disease

The rising prevalence of obstructive sleep apnea (OSA) and the realization that its treatment can impact the course of cardiovascular disease and metabolic syndrome has led to the call for sleep as a health imperative (Luyster et al. Sleep. 2012;35:727). Although most OSA is managed by pulmonologists board-certified in sleep medicine, the impact of treating OSA on comorbid respiratory disease has not received a commensurate degree of attention.

Sleep is a multistage behavioral state that has been preserved through evolution from unicellular organisms to the more complex mammalian life. Fragmentation of sleep continuity, as can occur during apneic events, induces profound physiologic abnormalities, including changes in arterial and tissue oxygenation, global neurohormonal perturbations, and disruptions in quiescent sleep-related brain electrical activity. As a result of the local physiologic changes and the systemic disturbances, there is significant impact on thoracic and pulmonary structures that includes the following:

1. Changes in cardiac, pulmonary, vascular, and hemodynamic status

As a result of increased upper airway resistance, ventilatory efforts increase with progressively more negative intrathoracic pressures. This leads to an increase in left ventricular afterload that can induce ventricular hypertrophy and diastolic dysfunction and increases in left atrial filling pressures. The associated arousals and increase in sympathetic tone can lead to tachycardia and hypertension that, over time, can also fuel left ventricular hypertrophy and remodeling (Dempsey et al. Physiol Rev. 2010;90:47-112). The subsequent increase in pulmonary capillary wedge pressures sets the stage for pulmonary venous and arterial hypertension that is further aggravated by episodic arterial hypoxemia and hypercapnia during apneic events. Diastolic dysfunction–related pulmonary hypertension may be the commonest cause of pulmonary hypertension encountered in clinical practice, although treatments have not been studied as extensively as those for the rarer and more dangerous WHO Group 1 disease (Shah et al. JAMA. 2012;308:1366). While OSA is often treated in patients with diastolic dysfunction-related pulmonary hypertension (Colish et al. Chest. 2012;141:674), these patients experience considerable morbidity, and substantial health care resources are expended during the work-up and long-term management of their pulmonary hypertension. Whether OSA treatment can serve as prophylaxis against cardiovascular morbidity, and thus save on these costs, remains to be seen.

2. Gastroesophageal reflux (GER) and microaspiration

GER appears to be increased in subjects with OSA (Sundar and Daly. Clin Sleep Med. 2011;7:669). Although it has not been easy to demonstrate the occurrence of acidic reflux during apneic events in subjects with intact lower esophageal sphincter tone (Kahrilas. Chest. 2010;137:747), there is incontrovertible evidence about the benefit of continuous positive airway pressure (CPAP) on GER symptoms (Green et al. Arch Intern Med. 2003;163:41). Given that GER plays an important role in airway disorders, such as asthma, COPD, and chronic cough (Parsons and Mastronade. Curr Opin Pulm Med. 2010;16:60) and interstitial lung diseases (ILD), including idiopathic and connective tissue-related subtypes (Raghu and Meyer. Eur Respir J. 2012;39:242), amelioration of GER may be an important mechanism of benefit from CPAP in patients with chronic lung disease (Lancaster et al. Chest. 2009;136:772). The impact of CPAP on the microaspiration that has been proposed to be a trigger for ongoing interstitial fibrosis is yet to be understood, but it is conceivable that OSA treatment could slow progression of ILD.

3. Abnormal daytime oxygen and carbon dioxide tensions

OSA can induce impaired CO_2 sensitivity in some patients (Appelberg and Sundström. Clin Physiol. 1997;17:497), with an eventual consequence of obesity hypoventilation, which is becoming an increasingly prevalent disorder (Casey et al. Chest. 2007;131:1936). It is not uncommon for patients to have basilar atelectasis as a result of their obesity, which may contribute to V/Q mismatching and a possible need for daytime supplemental oxygen.

4. Lower airway inflammation and immunity

Recent studies have demonstrated an increase in markers of inflammation in airways of patients with OSA. This stems from a number of different mechanisms that include hypoxia-reperfusion injury, increased sympathetic tone, effects of REM deprivation on oxidant-antioxidant balance, adipokine effects, spillover from systemic inflammation, and acid reflux (Carpagnano et al. Eur Respir J. 2012;39:1547). In addition, patients with untreated OSA also seem to be prone to upper respiratory infections, especially common colds (Raghu and Meyer. Eur Respir J. 2012;39:242). The mechanisms for frequent upper respiratory infections in these patients are unclear, although they could occur through effects on systemic immunity. This susceptibility to infection is important because such infections are often the proximate cause of exacerbations of both obstructive and ILD, events that account for the bulk of the morbidity and health-care costs in COPD and are a significant driver of mortality in COPD and ILD (Suissa et al. Thorax. 2012;67:957 and Song et al. Eur Respir J. 2011;37:356).

In addition to these effects on cardiopulmonary status, OSA also results in daytime functional and mood changes that, coupled with metabolic disturbances, predispose the patient to sedentariness and deconditioning, problems that worsen outcomes from chronic pulmonary disorders. Depression is a common comorbidity for both COPD and ILD; further studies are required to understand the impact of sleep optimization on mood and other functional variables in patients with obstructive, interstitial, and vascular lung disorders.

Improved awareness of sleep-disordered breathing in patients with pulmonary disease could be achieved by including screening for OSA in disease guidelines, though current guidelines for several disorders (chronic cough and IPF) do not include any recommendations for OSA screening. The GOLD 2011 COPD guidelines (www.goldcopd.org, accessed 12/7/12) discusses OSA treatment in patients with COPD as having "clear benefits," though sleep apnea is only mentioned once in the 90-page document. The latest NHLBI and NAEP guidelines on asthma (www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf, accessed 12/7/12) recommend screening for and treating OSA in patients with poorly-controlled asthma, particularly those who are overweight or obese, though recent literature suggests that the OSA risk in this population may be independent of obesity (Teodorescu et al. Chest. 2010;138:543).

There is a critical need to understand both the true prevalence of comorbid OSA and the myriad benefits of treating it in patients with chronic lung disease. In addition to the demonstrated associations with cough and IPF derived from some of the studies referenced above, current literature has shown a significant prevalence of OSA in asthma (Teodorescu et al. Chest. 2009;135:1125), COPD (Marin et al. Am J Respir Crit Care Med. 2010;182:325), and WHO Group 1 pulmonary hypertension (Badesch et al. Chest. 2010;137:376); improved outcomes in the course of some of these disorders have been demonstrated by treating the comorbid sleep-disordered breathing. While these studies emphasize improvement in objective outcomes, such as exacerbation rate and mortality, the benefits to dyspnea, cough, need for daytime oxygen, functional status, depression, and quality of life, scores need further study. The complex relationship between upper airway dilators, diaphragmatic function, and thoracic/lung mechanics mandates a high index of suspicion for sleep-disordered breathing in patients with pulmonary disease, and the growing evidence suggests that treating comorbid OSA will yield rich dividends in terms of the functional status of these patients as well as the course of their underlying lung disease.

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From the Editor:

While the association between OSA and incident cardiovascular disease has been widely discussed, there is growing concern that untreated OSA may cause or exacerbate lung disease, as well. As Dr. Sundar outlines, there are a number of different mechanisms in play that may drive this relationship, including intermittent hypoxia. Sadly, this association has not been widely advertised, leading to the potential under-diagnosis of sleep-disordered breathing in patients with pulmonary disease. If patients with severe and refractory lung disease were routinely screened for sleep apnea in the same way we screen patients with refractory hypertension, how many additional patients with OSA would be identified? Perhaps, by helping these patients to breathe more easily at night, we may be able to similarly ease their work of breathing during the day.

Dr. David Schulman, FCCP

For twice-daily maintenance treatment of COPD

With **the right fit**, they may get back into **daily living**

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The BROVANA® (arformoterol tartrate) basics

Nebulized long-acting beta$_2$-agonist

BROVANA (arformoterol tartrate) should not be used with other medications containing long-acting beta$_2$-agonists.

12-hour bronchodilation, few daily troughs[1]

While some tolerance to the bronchodilator effect was observed after 6 weeks of dosing (at the end of the dosing interval), it was not accompanied by other clinical manifestations of tolerance.[1,2]

Requires low peak inspiratory flow rate

As with other inhaled beta$_2$-agonists, BROVANA can produce paradoxical bronchospasm that may be life-threatening.

Minimal coordination or dexterity required

Covered under Medicare Part B*

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*No guarantee of coverage.

INDICATION

BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

IMPORTANT SAFETY INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA (see WARNINGS). The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).

Please see the Brief Summary of Prescribing Information on the following pages for additional Important Safety Information.

Please visit **www.brovana.com** for full Prescribing Information.

References: 1. Baumgartner RA, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, Hanrahan JP. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. *Clin Ther*. 2007;29(2):261-278. **2.** BROVANA [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals Inc; 2012.

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BRIEF SUMMARY

WARNING: ASTHMA RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA (see WARNINGS). The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).

INDICATIONS AND USAGE

BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

CONTRAINDICATIONS

BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product.

All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication. (see **WARNINGS**).

WARNINGS

- **ASTHMA RELATED DEATH**
  Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).
  - A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13, 176 in patients treated with salmeterol vs. 3/13, 179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including BROVANA. No study adequate to determine whether the rate of asthma related death is increased in patients treated with BROVANA has been conducted.
  - Clinical studies with racemic formoterol (Foradil® Aerolizer™) suggested a higher incidence of serious asthma exacerbations in patients who received racemic formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.
- **The studies described above enrolled patients with asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.**
- **BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive pulmonary disease (COPD), and is not indicated for the treatment of acute episodes of bronchospasm, i.e., rescue therapy.**
- **BROVANA should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of BROVANA in this setting is inappropriate.**
- **BROVANA should not be used in children as the safety and efficacy of BROVANA have not been established in pediatric patients.**
- **BROVANA should not be used in conjunction with other inhaled, long-acting beta$_2$-agonists. BROVANA should not be used with other medications containing long-acting beta$_2$-agonists.**
- **When beginning treatment with BROVANA, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.**
- **See PRECAUTIONS and Information for Patients.**

Paradoxical Bronchospasm

As with other inhaled beta$_2$-agonists, BROVANA can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be discontinued immediately and alternative therapy instituted.

Deterioration of Disease

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

Cardiovascular Effects

BROVANA, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of BROVANA at the recommended dose, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. BROVANA, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS, General**).

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of BROVANA as demonstrated by cases of anaphylactic reaction, urticaria, angioedema, rash and bronchospasm.

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta$_2$-adrenergic drugs, BROVANA should not be used more often, at higher doses than recommended, or with other long-acting beta-agonists.

PRECAUTIONS

General

BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. When prescribing BROVANA, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning and evening) use of BROVANA. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated (see **Information for Patients**).

BROVANA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with arformoterol tartrate. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly though intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of BROVANA at the recommended dose.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. Patients should be given the following information:

1. Patients should be informed that long-acting beta$_2$-adrenergic agonists, such as BROVANA, increase the risk of asthma-related death. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see **CONTRAINDICATIONS**).
2. BROVANA is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if BROVANA treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA should not exceed one ready-to-use vial (15 mcg) by inhalation twice daily (30 mcg total daily dose).
3. Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness.
4. Patients should be instructed to use BROVANA by nebulizer only and not to inject or swallow this inhalation solution.
5. Patients should protect BROVANA ready-to-use vials from light and excessive heat. The protective foil pouches should be stored under refrigeration between 2ºC and 8ºC (36º–46ºF). They should not be used after the expiration date stamped on the container. After opening the pouch, unused ready-to-use vials should be returned to, and stored in, the pouch. An opened ready-to-use vial should be used right away. Discard any ready-to-use vial if the solution is not colorless.
6. The drug compatibility (physical and chemical), efficacy and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.
7. Women should be advised to contact their physician if they become pregnant or if they are nursing.
8. It is important that patients understand how to use BROVANA appropriately and how it should be used in relation to other medications to treat COPD they are taking.

Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of BROVANA may be potentiated.

When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA at steady-state, exposure to either drug was not altered. Dosage adjustments of BROVANA are not necessary when the drug is given concomitantly with potent CYP2D6 inhibitors.

Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.

BROVANA, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT_c interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QT_c interval have an increased risk of ventricular arrhythmias. The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving BROVANA has not been completely evaluated. In two combined 12-week placebo controlled trials that included BROVANA doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873 BROVANA-treated subjects received concomitant theophylline at study entry. In a 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the 528 BROVANA-treated subjects received concomitant theophylline at study entry. In these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with the overall population.

Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of arformoterol.

In a 24-month carcinogenicity study in CD-1 mice, arformoterol caused a dose-related increase in the incidence of uterine and cervical endometrial stromal polyps and stromal cell sarcoma in female mice at oral doses of 1 mg/kg and above (AUC exposure approximately 70 times adult exposure at the maximum recommended daily inhalation dose).

In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a statistically significant increase in the incidence of thyroid gland c-cell adenoma and carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure approximately 130 times adult exposure at the maximum recommended daily inhalation dose). There were no tumor findings with an inhalation dose of 40 mcg/kg (AUC exposure approximately 55 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacteria, chromosome aberration analyses in mammalian cells, and micronucleus test in mice.

Arformoterol had no effects on fertility and reproductive performance in rats at oral doses up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: Teratogenic Effects

Pregnancy Category C

Arformoterol has been shown to be teratogenic in rats based upon findings of omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above (AUC exposure approximately 370 times adult exposure at the maximum recommended daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure approximately 1100 times adult exposure at the maximum recommended daily inhalation dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC exposure approximately 2400 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol has been shown to be teratogenic in rabbits based upon findings of malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC exposure approximately 8400 times adult exposure at the maximum recommended daily inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts were observed at doses of 40 mg/kg and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. BROVANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

There are no human studies that have investigated the effects of BROVANA on preterm labor or labor at term. Because beta-agonists may potentially interfere with uterine contractility, BROVANA should be used during labor and delivery only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, arformoterol was excreted in the milk. It is not known whether arformoterol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BROVANA is administered to a nursing woman.

Pediatric

BROVANA is approved for use in the long term maintenance treatment of bronchoconstriction associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not occur in children. The safety and effectiveness of BROVANA in pediatric patients have not been established.

Geriatric

Of the 873 patients who received BROVANA in two placebo-controlled clinical studies in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Among subjects age 65 years and older, 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to ≤75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively).

A higher frequency (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical significance of this finding is not known. 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.

ADVERSE REACTIONS

Experience in Adult Patients with COPD

Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were treated with BROVANA (arformoterol tartrate) Inhalation Solution 15 mcg twice daily and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily were also evaluated. The numbers and percent of patients who reported adverse events were comparable in the 15 mcg twice daily and placebo groups.

The following table shows adverse events where the frequency was greater than or equal to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor.

Study connects aspirin 'resistance' to enteric coating

BY ELIZABETH MECHCATIE
IMNG Medical News

In a study of 400 healthy adults, measurements indicating the presence of what has been thought to be aspirin resistance were evident only with enteric-coated aspirin, not immediate-release aspirin, which the authors have described as aspirin "pseudoresistance."

The researchers used several measurements to evaluate responses reflecting the activity of cyclooxygenase-1 (COX-1), the molecular target of aspirin, including platelet aggregation and serum thromboxane formation, which could indicate a genetic cause of aspirin resistance. Still, "we failed to find a single person who satisfied" the criteria for true aspirin resistance, reported Dr. Tilo Grosser, of the Institute for Translational Medicine and Therapeutics, Perelman School of Medicine in Philadelphia, and his associates.

"By contrast, pseudoresistance, due to delayed and reduced drug absorption, was common after ingestion of enteric-coated aspirin," they said.

"These observations question the value of seeking to diagnose aspirin resistance with single point-of-care diagnostic approaches and support the finding of inconsistent platelet inhibition following enteric-coated preparations of aspirin," they concluded in a report published in Circulation (2012 [doi: 10.1161/CIRCULATIONAHA.112.117283]).

The concept of aspirin resistance has been used to explain treatment failures occurring in patients, with estimates of incidence ranging from 5% to 20% in studies, they noted.

The study had several phases, which included screening the participants, aged 18-55 years, for their response to a single 325-mg dose of immediate-release or enteric-coated aspirin, repeating testing among those who appeared to be resistant to aspirin, and comparing responses in responders and nonresponders.

Among the findings: All of the individuals who received a dose of immediate-release aspirin were responders, but up to 49% of those who received enteric aspirin were considered nonresponders. With repeated exposure, individuals categorized as nonresponders when given enteric-coated aspirin showed evidence of responses when administered immediate-release aspirin.

"What they have shown in an extremely elegant way is that aspirin resistance, at least in healthy volunteers, doesn't exist," said Dr. Deepak Bhatt in an interview. Of great interest to physicians and patients is the finding that in the individuals who appeared to be aspirin resistant, enteric coating on aspirin was delaying and reducing absorption, which is consistent with old data that indicate enteric coating can interfere with aspirin absorption, he said.

While this may have been suspected as an explanation for so-called aspirin resistance, "this is the first time someone has really nailed it down in a scientifically unassailable way," said Dr. Bhatt, professor of medicine at Harvard University, Boston, and chief of cardiology at VA Boston Healthcare System.

Although the results need to be replicated in patients with actual disease, such as diabetes or atherosclerosis, he said the results will potentially impact practice, although immediate-release aspirin is recommended for patients who are being stented or are having a myocardial infarction, for the rapid pharmacologic effect.

Another consideration, which he said is not widely appreciated, is that evidence that enteric coating reduces stomach bleeding "is quite scant, some might even say nonexistent." Because of "this issue of pseudoresistance these authors are raising, you've got to think twice about whether enteric coating is doing anything useful or good."

The study was funded by the National Heart, Lung, and Blood Institute; the National Center for Research Resources; the American Heart Association; and Bayer HealthCare. Coauthor Dr. Garret FitzGerald of the University of Pennsylvania, Philadelphia, received research funding from Bayer HealthCare to support partial funding of this study, and Dr. Grosser received consultancy fees from PLx Pharma. The four remaining coauthors had no potential conflicts of interest to disclose. Dr. Bhatt said his disclosures include being an unpaid consultant to PLx Pharma. Dr. Kaul said he had no relevant disclosures.

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Extended apixaban cuts VTE risk

AMPLIFY-EXT *from page 1*

AF in the ARISTOTLE trial.

The results of AMPLIFY-EXT (Apixaban After the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis With First-Line Therapy–Extended Treatment) provide some guidance for physicians uncertain about whether to extend or stop standard anticoagulation therapy in patients with VTE in the absence of recurrent events.

Stopping warfarin therapy increases the risk of recurrent VTE by up to 10% in patients without reversible risk factors, but also requires frequent laboratory monitoring and increases the risk of bleeding.

Apixaban, an oral factor Xa inhibitor, is given in fixed doses without the need for laboratory monitoring, said Dr. Agnelli, director of the internal and cardiovascular medicine/stroke unit at the University of Perugia, Italy.

Given the efficacy demonstrated in AMPLIFY-EXT, apixaban may also be an attractive option for those VTE patients with renal impairment, because apixaban is the least dependent on renal clearance compared with two other fixed-dose anticoagulants, rivaroxaban (Xarelto) and dabigatran (Pradaxa), said press briefing moderator Dr. Agnes Lee, medical director of the thrombosis program and associate professor of medicine at the University of British Columbia, Vancouver, and Vancouver Coastal Health.

Notably, a recent prespecified substudy of ARISTOTLE demonstrated that apixaban produced 35%-52% fewer major bleeding events in patients with renal dysfunction and atrial fibrillation.

The double-blind AMPLIFY-EXT trial randomized 842 patients to apixaban 2.5 mg, 815 to apixaban 5 mg, and 829 to placebo, all twice daily for 12 months.

Three-fourths had an initial diagnosis of deep vein thrombosis and one-fourth pulmonary embolism.

All had received 6-12 months of anticoagulation therapy and reached clinical equipoise at the continuation or cessation of anticoagulation therapy.

VTE was associated with a transient or reversible risk factor in less than 10% of patients.

Two patients from each apixaban group were excluded from the intention-to-treat efficacy analysis. Their average age was roughly 56.

The composite primary efficacy endpoint of symptomatic VTE recurrence or all-cause death occurred in 3.8% of patients on apixaban 2.5 mg and in 4.2% of patients on apixaban 5 mg, compared with 11.6% of patients given placebo, according to Dr. Agnelli.

Symptomatic recurrent VTE or death from VTE occurred in 1.7% of patients in both apixaban groups vs. 8.8% of placebo-treated patients.

Major bleeding was reported in 0.2% of the 2.5-mg apixaban group, 0.1% of the 5-mg group, and 0.5% of the placebo group.

Clinically relevant nonmajor bleeding rates were slightly higher at 3.0% and 4.2% in the apixaban groups vs. 2.3% in the placebo group, he said.

Further study will be needed to determine if the results can be directly applied to cancer patients who face an increased risk of VTE because of the disease, as only about 2% of the study population had active cancer, Dr. Agnelli said in an interview.

The study was simultaneously published in the New England Journal of Medicine ([doi: 10.1056/NEJMoa1207541]).

AMPLIFY-EXT was funded by Bristol-Myers Squibb and Pfizer.

Dr. Agnelli reported commercial relationships with Bristol-Myers Squibb, Daiichi Sankyo, and other companies. His coauthors reported relationships with the study sponsors. Dr. Lee disclosed consulting for Bristol-Myers Squibb.

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VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: This trial demonstrates a benefit to extended treatment with apixaban in patients who would likely not be anticoagulated under current guidelines. Given the relative safety of the medication, with lower rates of major bleeding than placebo, the study should prompt a re-examination of indications for long-term anticoagulation.

CABG bests multivessel stenting in diabetes patients

BY BRUCE JANCIN
IMNG Medical News

LOS ANGELES – Patients with diabetes who had revascularization for multivessel coronary artery disease fared significantly better with coronary artery bypass grafting than with percutaneous coronary intervention using drug-eluting stents in the landmark FREEDOM trial.

FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) was an international randomized trial involving 1,900 subjects who were considered candidates for both CABG and PCI. The primary outcome – a composite of 5-year all-cause mortality and nonfatal MI or stroke – occurred in 26.6% of the PCI group, compared with 18.7% of the CABG group. That's a 7.9% absolute reduction and 30% lower relative risk. The CABG advantage held up regardless of SYNTAX score, a measure of disease extent.

"The results are clear. I think this is going to change practice," FREEDOM chair Dr. Valentin Fuster predicted in presenting the study's main findings at the annual scientific sessions of the American Heart Association.

Participants in the CABG group had a 5-year mortality of 10.9%, compared with 16.3% in the PCI group. Their nonfatal MI rate was less than half of that in the PCI group: 6.0% vs. 13.9%.

BRUCE JANCIN/IMNG MEDICAL MEDIA

"I think this is going to change practice," said FREEDOM chair Dr. Valentin Fuster.

The CABG group's 5.2% nonfatal stroke rate was significantly higher than the 2.4% rate in the PCI group. However, the excess of strokes in the CABG group was confined to the first 30 days post procedure; after that, stroke rates in the two groups did not differ significantly.

Only 13% of strokes were hemorrhagic. Most strokes occurred more than 1 year post procedure, said Dr. Fuster, professor of medicine and director of the cardiovascular institute at Mount Sinai Medical Center, New York.

The repeat revascularization rate after 1 year of follow-up was 13% in the PCI group and 5% in CABG-treated patients. At 5 years, repeat revascularization had occurred in 30% of the PCI group, compared with 13% in the CABG group.

Thirteen percent of FREEDOM participants had two-vessel disease, and the rest had triple-vessel disease. Outcomes in both groups were superior with CABG. The CABG and PCI groups did not differ significantly in 30-day rates of major bleeding or acute renal failure.

Seventeen years ago, the National Heart, Lung, and Blood Institute issued a clinical alert recommending CABG over PCI for patients with diabetes on the strength of the results of BARI, the Bypass Angioplasty Revascularization Investigation (N. Engl. J. Med. 1996;335:217-25). Yet, PCI has since become increasingly popular in diabetes patients.

Persons with diabetes compose roughly 25% of the nearly 1 million patients who undergo multivessel coronary revascularization each year in the United States.

Simultaneous with Dr. Fuster's presentation at the AHA meeting, the FREEDOM results were published online in the New England Journal of Medicine (doi: 10.1056/NEJMoa1211585).

The FREEDOM trial was funded by the National Heart, Lung, and Blood Institute. Dr. Fuster said he had no relevant financial conflicts. The discussants have received research grants from medical device manufacturers.

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POLICY & PRACTICE

More doctors using social media

About one in four physicians uses social media daily or even multiple times each day to scan or explore medical information, while 14% of physicians use social media each day to contribute new medical information, according to a survey of 485 primary care physicians and oncologists. Weekly use of social media is even higher: 61% scan for medical information, and 46% contribute new information at least weekly, according to the findings from the survey. More than half of those surveyed said that they use online physician-only communities, while just 7% use Twitter professionally. The heavy use of online physician communities was surprising, says study author Dr. Robert Miller, assistant professor of oncology at the Johns Hopkins Kimmel Cancer Center, Baltimore. "It's possible that many physicians feel more comfortable with that type of social media instead of a more public space like Twitter or Facebook," Dr. Miller said in a statement.

Retail clinics gain popularity

More than 21% of U.S. adults said that they have visited a retail clinic, more than double the number found in a similar survey 6 years ago. Health care market research firm Kalorama Information, which surveyed 2,000 U.S. adults, attributed the increase to the growth of health clinics at top retail chains such as Walmart and CVS/pharmacy, along with growth in clinic traffic. Retail clinic customers said that they liked the appointment-free service and expanded hours – especially when compared with the average physician's office, according to the survey. Customers also said they liked the lower costs. Some clinics, however, have struggled to find patients during spring and summer months, and the clinics face competition from primary care physicians and urgent care centers, the report said.

ACA gifts consumers $1.5 billion

Consumers – mainly those with individual health insurance policies – saw nearly $1.5 billion in insurer rebates and overhead cost savings in 2011 as a result of an Affordable Care Act (ACA) provision that requires insurers to spend at least 80% of premium dollars on health care or quality improvement, according to a Commonwealth Fund report. Consumers with individual policies benefited the most from lower premiums and rebates when insurers reduced both administrative costs and profits to meet the new standards, according to the report. Insurers also cut administrative costs in the small- and large-group markets but mainly funneled the savings into profits, as opposed to lower premiums for the groups, since they already had medical loss ratios in the target range, according to the report. Rate regulation or more competition may be necessary to ensure that group policy prices fall along with individual policy prices, the authors said.

Medicare MD shortage feared

More than 60% of Americans worry that there will be a shortage of physicians to treat Medicare patients, and nearly half think the Medicare program needs a complete overhaul, according to a survey sponsored by health insurance brokerage firm GoHealth Insurance. An overwhelming majority (85%) said they were concerned that politicians would change Medicare benefits, according to the survey's findings. In addition, slightly more than half (53%) said that they expected to pay more toward Medicare benefits than they will receive in care.

Rx coverage to vary

Coverage for basic prescription drugs could vary dramatically from state to state under the ACA because of variations in state benchmark plans, according to an analysis from Avalere Health. The law gives each state some choice as to how to select the benchmark plans to be used in its health insurance exchange. According to the analysis, 11 states will cover only half to 75% of all drugs approved by the Food and Drug Administration, while 12 will cover almost all of them. Generally, states in the upper Midwest tended to have less generous drug benefits, while states in northern New England had the most generous benefits.

Anticompetitive activity high

In 385 metro areas studied by the American Medical Association, there was little competition in the HMO, PPO, and point-of-service markets. Two-thirds of the metro areas reported that one health insurer held more than 50% of their total HMO markets, and similar numbers were reported for the PPO and point-of-service markets. Alabama, Hawaii, Michigan, Delaware, and Alaska had the least competitive commercial health insurance markets overall.

–Jane Anderson

IOM panel calls for financial disclosure database

BY MICHELE G. SULLIVAN
IMNG Medical News

A single, harmonized database for disclosing conflicts of interest could save academic centers, researchers, and the entities that fund their work a myriad of headaches.

Rather than completing disparate disclosure forms for every research application or journal submission, users would enter their baseline information into a central system and update it as needed. Every time the information is required, those who request permission could pull a digital copy and format it according to their needs.

A new system could be launched as early as late 2013 or early 2014, said Dr. Allen Lichter, a member of the committee charged with its framing.

"The time has come for such a harmonized, centralized disclosure system to be created for the benefit of everyone who must produce or receive disclosure information," Dr. Lichter wrote in a viewpoint in JAMA (2012;308:2093-94). "Such a system can be designed and implemented as one element in a process to help ensure that research can progress in a trusted, transparent fashion, thereby increasing trust among the public and health care professionals in new medical products that are brought to the benefit of patients."

The centralized system was published in a discussion paper from the Institute of Medicine (IOM), which last year convened a stakeholders' meeting to explore the possibility.

According to the paper, a centralized system would be similar to the common application for undergraduate college admission, in which students enter all application and supporting materials in a central database, and can submit that package to any college or university.

"The harmonized system must encompass the full scope of reporting indicated by statute and regulation and most, if not all, of the reporting currently requested by organizations," the committee wrote.

The committee painted with a rather broad brush those who would need to report their financial conflicts of interest. Reporting should be required not only of the physician or researcher, but also of close family members who receive any remuneration that could be construed as a conflict.

Before such a system can be designed, however, some groundwork is necessary. Different bodies have different definitions of the same financial reporting requirement. The National Institutes of Health defines it as salary, payment, stocks and options, and ownership. The International Committee of Medical Journal Editors defines it as resources received directly or indirectly that supported work on any given manuscript.

The IOM committees suggested that data be reported separately for each financial relationship, including the start and end dates of the relationship, the name of a drug or device, and the value of each relationship.

Administering the database is an entirely different – and just as complicated – matter, according to the committee. Those who are obliged to report conflicts need to feel confident that their data can't be compromised, so each person should have full ownership and control of their information. A centralized system is one option. In this scenario, all data are stored and managed in a single repository from which users could enter and request information.

A second option is a federated system which would link many now-separate databases that would then be available through one portal. Since this approach is based on existing systems, the initial investment would probably be less. However, it would require reconfiguring almost every one of those databases in order to link them.

The Institute of Medicine supported the work. Dr. Lichter reported having no financial disclosures.

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VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: "Very interesting topic for all U.S. providers … but is anything harmonized or harmonious in the field of medicine when the government is involved?"

2013 outlook: SGR action may be on the horizon

BY MARY ELLEN SCHNEIDER
IMNG Medical Media

Could 2013 finally be the year to eliminate the Sustainable Growth Rate formula?

Officials at the American Medical Association say there's a chance that Congress could decide to permanently scrap the unpopular formula, which drives payment under the Medicare physician fee schedule, as part of a larger deal to cut the federal deficit.

"The fact that we've got this big potential deficit-reduction package would make us more optimistic that we can get [the SGR] taken care of this coming year," said Dr. Jeremy A. Lazarus, president of the American Medical Association.

On Jan. 1, lawmakers passed legislation providing a short-term, 1-year delay the scheduled 26.5% SGR cut. The bill also included a 2-month delay to scheduled tax hikes and federal spending cuts that were planned as part of a deficit reduction process known as sequestration. That gives Congress several weeks to craft a new plan to deal with the nation's debt and the growth in Medicare spending.

It wouldn't be unprecedented for a permanent SGR fix to be considered as part of comprehensive deficit reduction legislation. SGR repeal was included in bipartisan plans created by outside groups several times, including the Simpson-Bowles Commission, the Senate Gang of Six, and others, Dr. Jazarus said.

Although complete SGR repeal carries a 10-year price tag of nearly $300 billion, physicians argue that, since Congress always acts to avert the pay cuts triggered by the formula, the federal government does not save any money by keeping it on the books. The large cost of repeal, however, means that it may be easier to get the SGR fix inserted into a larger bill than to get lawmakers to approve it separately, Dr. Lazarus said.

The AMA is asking Congress not only to repeal the SGR but also to establish a period of stable Medicare payments so that physicians can begin to transition to a new payment system that focuses on quality of care, Dr. Lazarus said. In the meantime, the AMA and other groups have been working on developing new delivery and payment reform options that could offer an alternative to the current fee-for- service system.

"We do hope we can start changing the equation on reimbursement and going from fee for service to accounting for quality," said Dr. William A. Zoghbi, president of the American College of Cardiology.

ACC officials are eager to move away from the SGR but they are concerned about where the money to do so might come from. Dr. Zoghbi said that he doesn't want to see lawmakers robbing other health care priorities to pay for the fix. For instance, in December, lawmakers considered a proposal to pay for a 1-year SGR fix using money that was slated for increasing Medicaid payments to physicians providing primary care services. Instead, lawmakers financed the 1-year SGR fix mainly through cuts to hospital payments.

"These fixes cannot be on the backs of the professionals providing care," Dr. Zoghbi said.

ACA milestones

This year also will see some practice-impacting milestones under the Affordable Care Act.

The ACA established the Independent Payment Advisory Board (IPAB), which is slated to start work this year, even though its members have yet to be named by President Obama. The controversial 15-member panel is charged with making recommendations on how to reduce Medicare spending. Dr. Lazarus said the AMA will continue to work toward eliminating the IPAB.

Some of the biggest changes under the ACA – the expansion of Medicaid eligibility and the creation of state-based health insurance exchanges – are coming in 2014, but physician leaders said that doctors need to start preparing this year.

Exactly how to get ready will vary by state since both the Medicaid expansion and the exchanges will be largely state-run. The AMA is pushing to give physicians greater say by getting them seats on the boards of state exchanges. But even as physicians await more information on these changes, they can prepare by becoming more familiar with the Medicaid program since they are likely to see more of those patients, said Robert Doherty, senior vice president for governmental affairs and public policy at the American College of Physicians.

Penalties kick in

This year the Physician Quality Reporting System (PQRS) transitions from a pure incentive program to a mixed incentive/disincentive program. Previously, PQRS offered small bonus payments to physicians for successfully reporting on quality measures. Now, physicians who don't participate in the program will be assessed a penalty. The 1.5% cut to Medicare fees won't come until 2015, but it will be based on participation this year. Physicians will see a 2% penalty in 2016 if they don't successfully report data during 2014.

There are also penalties coming in Medicare's Electronic Prescribing (eRx) Incentive Program. To avoid a 2% penalty in 2014, physicians must meet Medicare's e-prescribing requirements by June 30, 2013.

Penalties from the Medicare Electronic Health Record (EHR) Incentive Program aren't coming until 2015, but physicians may wish to plan ahead to try to earn some money to offset the cost of EHR implementation.

A physician who starts participating this year can earn up to $39,000 over 4 years. Start next year and the bonus drops to $24,000. A 1% penalty takes effect in 2015, increasing to 2% the following year.

The transition to the ICD-10 coding set is another requirement that physicians need to keep in mind, ACP's Mr. Doherty said. The Department of Health and Human Services delayed the move to ICD-10 until October 2014, but Mr. Doherty said physicians can't afford to wait that long to prepare. The ACP is trying to convince federal officials to accept some alternative ways of coding that would both satisfy the ICD-10 requirements and be clinically relevant, he said.

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'Fiscal cliff' deal halts SGR cut for a year

A last-minute deal by lawmakers means that physicians won't be subject to a nearly 29% cut to their Medicare payments this year.

The deal to the avoid the so-called "fiscal cliff" will delay for 2 months an automatic 2% cut to Medicare fees that was part of an earlier plan to cut the deficit, known as sequestration. The deal also averts a 26.5% Medicare pay cut that was scheduled to take effect Jan. 1 because of the Sustainable Growth Rate (SGR) formula. The SGR cut will be delayed for 1 year, but physicians will face an even larger cut in 2014 unless Congress takes some action to alter or to eliminate the formula.

The American Taxpayer Relief Act of 2012, which delays deep cuts in federal spending and tax increases on the middle class, was passed by the House and Senate on Jan. 1; the president signed the bill Jan. 2.

Reaction from physicians has been lukewarm.

"This patch temporarily alleviates the problem, but Congress' work is not complete; it has simply delayed this massive, unsustainable cut for 1 year," Dr. Jeremy A. Lazarus, president of the American Medical Association, said in a statement. "Over the next months, it must act to eliminate this ongoing problem once and for all."

The SGR fix will be funded mainly through cuts to hospital funding, including reduced payments to disproportionate share hospitals, adjustments to documentation and coding, and cuts to end-stage renal disease payments. The cuts also include radiation oncology care and outpatient payments for radiosurgery involving multisourced cobalt-60.

The American Hospital Association objected to the cuts.

The SGR fix is not paid for by cuts to the Affordable Care Act, as had been proposed late in 2012. In December, a proposal was circulating on Capitol Hill to pay for a 1-year fix by eliminating increases in Medicaid payments for primary care services. The physician community, including both primary care and specialty societies, wrote letters to House and Senate leaders urging that the proposal be rejected because it would preserve access for seniors at the risk of access for poor patients.

Despite the deal, Congress has plenty to do in the coming weeks. H.R. 8 only delays the sequestration cuts for 2 months to allow time for another deficit-reduction deal. The sequester includes not only an automatic 2% Medicare provider cut, but also deeper cuts to funding for health professions grants, the National Health Service Corps, and public health programs.

FROM THE PRESIDENT: Looking forward to new initiatives in 2013

BY DR. DARCY D. MARCINIUK, FCCP

Let me begin by wishing everyone best wishes for 2013. May this year bring the very best for you, your families, friends, and colleagues, and especially, the very best for your patients and their families. Happy New Year!


DR. MARCINIUK

Over the next few issues, I want to share with you important issues we are addressing since I assumed my term as the 75th President of the ACCP. First, some background about the approach we will be taking during the next 12 months. During my acceptance speech in Atlanta, I related that we have been asking various individuals and groups what can the ACCP do for them, and that what we've heard back was remarkably clear. Very simply, everyone wants more of what we do: more educational offerings, more simulation, more guidelines, and more technology and innovation. They want our expertise in every corner of clinical pulmonary, critical care, and sleep medicine. Our professions want to better understand health-care reform and be better prepared to adapt to the changes that are occurring, that are inevitable. They want tools, guidance, and information to help them cope with the increasing demands for licensure and privileges. Our patients and their families want the very best care available; and barriers to that appropriate care removed or minimized. And everyone, our members, our professions, our patients and families, and also governments and health-care systems are looking for leadership and a trusted voice to help guide them through these changing times.

So, I'm going to describe an important new initiative of the ACCP to help our members and our profession understand, adapt to, and manage health-care reform. There is no denying that health-care reform is on everyone's mind and that change is coming (much more than has already occurred). While the election results provided some certainty (about who will lead the country), there is still much uncertainty (and fear, and unknowns) surrounding health-care reform in the United States. But if you step back just a little bit, the reality is that health-care reform is not just for those living in the United States but also in Canada and far beyond, as well. It doesn't matter where you live, or where you practice medicine, our health-care systems and our governments want more, for less (. . . or at least for no more), and everyone wants quality health care. But how do you define quality, how do you get there, and who is going to drive us to that destination?

The issue requires leadership and commitment. The College has been helping our members and profession navigate the vast and complex legislation and policies that will affect the practice of chest medicine and the care we provide to our patients. But we believe that even more needs to be done. It is with that understanding and firm belief that we have just formed an ACCP Royal Commission on Healthcare Reform to enhance and coordinate our efforts. The Commission's charge is to construct a comprehensive, integrated education and communication strategy and plan to assist ACCP members and our professions to understand, adapt to, and manage health-care reforms. I have appointed Dr. Scott Manaker, a long-time advocate and respected expert in the field, to Chair the Commission, which will bring together the best minds from our Chest Medicine Affairs, Practice Management, US and Canadian Governors Committees, the Practice Operations NetWork, and others for this important task. The Commission has already begun their deliberations, and outcomes suitable for implementation are expected mid-2013. I've instructed the Commission, however, to not wait if something can, or should, be done much sooner. We are more interested in meaningful results than we are in with a nicely bound report.

There is a pressing need to develop practical and useful tools and tips to help practicing clinicians provide the very best possible care to their patients during (and despite) these changing times. As I highlighted in Atlanta at CHEST 2012, as clinicians and members of the ACCP, we have the great privilege of listening to patients every single day. In fact, a

'Very simply, everyone wants more of what we do: more educational offerings, more simulation, more guidelines, and more technology and innovation.'

foundational strength of the College is that its leadership is derived from those who interact directly with patients – we work on the front lines. But I steadfastly believe that with that hallowed privilege comes responsibility, and we cannot allow health to only become a business; we must ensure that "care'" remains in health. And the ACCP wants to ensure that we are able to deliver the best possible care for our patients.

I am very grateful to Dr. Manaker, and to all the other members of the Commission – they have a very important task in front of them and to build on what has already been accomplished. If you are asked to assist them, I would be most grateful if you could provide them with all the help and support they require to ensure that their recommendations help us, and all of our patients, flourish in these changing times of health-care reform. As has been stated previously, our patients, many of them too short of breath to speak on their own behalf, deserve nothing less.

A new President-Designate elected at CHEST 2012


DR. SESSLER

Curtis Sessler, MD, FCCP, was elected as President-Designate of the ACCP at CHEST 2012, in Atlanta. Dr. Sessler is the Orhan Muren Professor of Medicine at Virginia Commonwealth University (VCU) Health System in the Division of Pulmonary and Critical Care Medicine in the Department of Internal Medicine. He currently serves as Director of the Center for Adult Critical Care, as well as Medical Director of Critical Care and the Medical Respiratory ICU at the Medical College of Virginia (MCV) Hospitals of VCU.

Dr. Sessler is an enthusiastic clinician and educator who has received a variety of teaching awards at VCU, including the School of Medicine Educational Innovation Award. He has also served on a variety of multisociety task forces addressing research, training competency, workforce shortage, and reimbursement. He is Past President of the Virginia Thoracic Society and has served on several committees for the US Food and Drug Administration, including serving as chair of the Pulmonary and Allergy Drug Advisory Committee.Dr. Sessler will transition into his 1-year term as ACCP President in October 2014, being third in the presidential lineup of Darcy D. Marciniuk, MD, FCCP (2012-2013), and Michael H. Baumann, MD, MS, FCCP, (2013-2014).

An active Fellow of the ACCP for 24 years, he has served on the Board of Regents and as Chair of the Critical Care Section, Chair of the Council of Sections, Chair of the Critical Care Institute, and Program Chair for the 2003 CHEST annual meeting. He received the Roger C. Bone Memorial Lecture award in 2010. Dr. Sessler is a member of the editorial board of *CHEST*; Editor in Chief of *ACCP-SEEK Critical Care Medicine*; and is co-section editor for Contemporary Reviews in Critical Care Medicine in *CHEST*.

ICD-10 will have an impact on productivity

BY RHONDA BUCKHOLTZ, CPC, CPMA, CPC-I, CGSC, COBGC, CPEDC, CENTC

AAPC (formerly the American Academy of Professional Coders) Vice President of ICD-10 Education and Training

The implementation of ICD-10 brings an exciting challenge. Some see it as an obstacle, but it really is an opportunity to enhance our skills and knowledge in our careers. There will be a learning curve that comes with ICD-10; the codes are very different, the guidelines have changed in some areas, and we are going to be communicating with physicians more closely to make sure all the necessary information is available. Initially, we will have to learn all the new guidelines and coding processes.

'There will be a learning curve that comes with ICD-10; the codes are very different, the guidelines have changed in some areas, and we are going to be communicating with physicians more closely . . .'

ICD-10 implementation will impact productivity on many levels. Documentation is the most obvious and largest area that will be affected, which will have a direct impact on productivity. If the documentation lacks specific elements required for accurate and precise code selection, the physician or provider will need to be queried for additional information. If they are not immediately available, the service cannot be entered or billed until the information is obtained.

Charge tickets (superbills) may become a thing of the past because of the increased amount of code choices in some areas. Physicians cannot be expected to document appropriately if they do not understand what is required in the first place.

The education process for coders and physicians should begin early to have the least impact on productivity throughout implementation. Those who do not embrace the changes, and wait until the last minute, will be at a disadvantage and may have to take extensive training classes (time away from work) to quickly learn all the changes. A coder should expect to devote around 40 to 60 hours toward ICD-10 education prior to implementation.

'Physicians cannot be expected to document appropriately if they do not understand what is required in the first place.'

Productivity will not return to normal upon implementation. There will be a delay as we assess how the payers interpret the new coding system. Payments and remittance advices will need to be closely scrutinized to ensure that claims have been processed appropriately, and when additional information is required, it must be sent in a timely manner. Staff must be prepared to focus on assessing payer responses throughout the first few months of implementation to identify deficiencies immediately.

Today, diagnosis codes are mostly numeric (with the exception of V and E codes), but with ICD-10, the codes are alphanumeric. The process of entering the new codes alone will slow productivity because we will no longer be able to rely solely on a number keypad to enter all the codes.

Also, it will be very important to distinguish between letters and numbers when a diagnosis code is written as opposed to a narrative description. For instance, depending on penmanship, it may be easy to mistake a number two for the letter Z, or the number zero for the letter O.

The key to minimizing the impact on productivity is to begin raising the awareness of each individual physician/provider regarding how documentation will specifically be affected by the changes and encouraging them to become familiar with the terms and specificity of their specialty. This will allow plenty of time to become familiar with the requirements and will not feel like such a significant change all at once.

When preparation is done early, we should expect that productivity will return to normal about 4 to 6 months after the official implementation date. The bottom line of an office will be only minimally impacted if the office has anticipated, learned, and prepared for the changes, as well as for the potential setbacks.

'It will be very important to distinguish between letters and numbers when a diagnosis code is written as opposed to a narrative description.'

An office that waits until the last minute to prepare for the changes or relies too much on outside sources (EMR, billing company, etc.) will be constantly striving to catch up with the changes.

Such an office may even experience an increase in claim denials and not be able to make corrections because of a lack of understanding the guidelines.

Timing and awareness are crucial in making a smooth transition to ICD-10.

Pages 30a—30b

NETWORKS: CRT, ventilator asynchrony, COPD attention

Cardiovascular Medicine and Surgery

Focused update on cardiac resynchronization therapy (CRT)

A focused update on CRT in the 2008 guidelines for device therapy for cardiac rhythm abnormalities was recently released by the joint committee from the American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society (*Circulation*. 2012; 126:1784). The focus of this update was on indications for device therapy and follow-up. A large number of new studies on device therapy for heart failure was reviewed for this document. The document is relevant to the daily practice of cardiologists, cardiothoracic surgeons, and intensivists caring for these patients. The important new changes are:

Class I indications:

1.Presence of left bundle-branch morphology (LBBB) on the ECG. Non-LBBB morphology is no longer an indication for CRT.

2.Duration of the QRS = 150 ms.

3.LBBB, QRS duration 150 ms, and NYHA class II

Addition of a Class IIb recommendation for patients with ischemic cardiomyopathy, LVEF 30%, sinus rhythm, LBBB, QRS duration of 150 ms, and NYHA class I symptoms.

In patients with LBBB morphology, the current evidence indicates that CRT provides substantial benefit compared with those without LBBB morphology. A class IIa indication is recommended for patients with intermediate QRS duration between 120 and149 ms and without a LBBB morphology, but with a LVEF = 35%.

The update also recommends the utility of contemporary remote monitoring that employs bidirectional telemetry with encoded and encrypted radiofrequency signals, although the office in-person visit still remains standard for most patients.

Dr. G. Hossein Almassi, FCCP
Chair

Allied Health

A collaborative approach to dealing with ventilator asynchrony

All too often, the physicians, respiratory care practitioners (RCPs), and nurses who populate the ICU team encounter mechanical ventilators that are "out of phase" with the patients to whom they are interfaced. Patients such as these generate inspiratory efforts, which fail to trigger their ventilators into the inspiratory phase, and/or experience a ventilator whose cycling into the expiratory phase is not

synchronous with their own breathing. The patients' distress and discomfort is readily apparent, and the enormous workload, which this dysfunction can impose upon patients, is not only uncomfortable but can, if severe enough, increase their morbidity and mortality.

The multidisciplinary/multispecialty environment within which these events occur renders the recognition and management of ventilator asynchrony a valuable opportunity for medical and allied health practitioners to collaborate in real-time for the tangible benefit of their patients.

I have recently created a 43-min video, "Recognition and Management of Ventilator Asynchrony," that explores the physiology and respiratory mechanics pertaining to asynchrony. It also discusses several strategies, which can be implemented to counteract it when it is encountered clinically. The video can be accessed at https://vimeo.com/53704633.

Readers are encouraged to view this video module and to share it with the physicians, RCPs, and nurses with whom they collaborate.

Bob Demers, RRT
Chair

Clinical Pulmonary Medicine

Garnering more attention for COPD

In 1981, the first cases of AIDS were reported and in 30 short years, the disease has come under control. The same cannot be said for COPD, which is now the third leading cause of death in the United States and the only condition in which the death rate has been rising. Research funding for COPD has always lagged behind other diseases, with public funding reported at about $784 per death for COPD, compared with the $15,615 per death for diabetes and $325,217 per death that is spent on human immunodeficiency virus (HIV) infections! Some of this can be attributed to a condition that carries little political clout and has always been considered a condition of white middle-aged male smokers.

However, the demographics of COPD have changed, and this public stereotype is no longer valid. Further support documenting this change can be found in the most recent report of the Behavioral Risk Factor Surveillance System (BRFSS) report from the Centers for Disease Control (CDC). The BRFSS is an annual random digit dialed telephone survey conducted by state health departments in collaboration with the CDC and include among their questions whether the subject has ever been diagnosed with COPD.

In the latest survey, those who responded in the affirmative had additional questions asked in 21 states, the District of Columbia, and Puerto Rico. In this report, about 6%, or about 15 million people in the United States, have been informed of their diagnosis of COPD, but this approaches 10% in the states of Alabama and Kentucky.

In the survey, women with COPD outnumber men by almost 2:1, and while the magnitude of this difference is related to survey methodology, other investigations have consistently found more women than men with COPD. COPD had been diagnosed in 3.2% of younger adults, defined as those <45 years of age, and almost a similar percentage (2.8%) in never-smokers. When looking only at those with COPD, 10% were <45 years of age and almost 25% were never smokers. This represents a significant portion of young adult never-smokers with a diagnosis previously confined to older smokers. About 25% had never had confirmatory spirometry, and COPD negatively impacted the quality of life in about 60% of respondents.

These and other findings of the report confirm the relatively common prevalence of this condition, impact on health, and utilization of health-care resources. This information is not necessarily new, but the magnitude of this disease has not garnered enough attention, and there needs to be greater focus on it if there is any progress to be made in stemming the epidemic of COPD.

Dr. Guy Soo Hoo, FCCP
Chair

e-Community mobile site helps ACCP members connect 'on the go'

BY TRACY SLUCIAK
ACCP e-Community Specialist

ACCP members can now connect to the ACCP e-Community whenever and wherever they want through the newly launched mobile-friendly website, accessible on all media platforms. The new website is accessed by clicking on a Web browser on any mobile device and typing in ecommunity.chestnet.org.

ACCP NetWork members have found the new site is an easy way to connect with colleagues.

"I prefer to go to the e-Community on my iPhone?," said Dr. John McIlwaine, FCCP, Critical Care NetWork Vice-Chair.

"It's an easy one click way I can stay updated on the newest discussions, and it's a useful resource when I have a clinical question or interesting topic that I want to share."

ACCP NetWork members share Dr. McIlwaine's sentiment. The average time spent on the e-Community mobile site has increased by 27%, and the average number of page views has increased by 16%.

Similar to the e-Community website that is accessible through any computer's Web browser, the new mobile site includes group discussions, a member search area, a message center, and a calendar with meetings and events.

Learn more about the ACCP e-Community and how to join on chestnet.org on the NetWorks Web page.

CHEST 2012 social media project captures members' unique perspectives

Earlier this year, the ACCP launched a full-scale social media strategy, touching all of the key initiatives of the College and The CHEST Foundation. As part of this strategy and creative direction, social media efforts for CHEST 2012 expanded beyond the standard Facebook and Twitter posts to incorporate a new social medium – Storify, a diary-style collection of social media postings. With this new social media tool, the ACCP launched its first "Day in the Life of" project, designed to highlight the activity and interactions of three annual meeting attendees from their own perspectives.

The ACCP's Facebook page has a growing number of likes. The organization is also active on Twitter and Storify.

The project followed Dr. Darcy Marciniuk, ACCP president, Dr. Chris Carroll, *CHEST* Journal Social Media Co-Editor, and Benjamin Seides, affiliate member and first-time attendee. Our attendees tweeted interesting information, took photos, videos, and provided thoughts and ideas throughout the meeting by using Twitter and hash tagging posts with "#DILCHEST2012." The project captured such fun details as the OneBreath Evening at the Georgia Aquarium, reactions to the late-breaking abstracts, thoughts from the opening sessions, and even airport sushi!

To check out the "Day in the Life of" project, visit the ACCP Storify page: www.storify.com/accpchest.

To follow along with ACCP in real time, like us on Facebook (www.facebook.com/accpchest), and follow us on Twitter (www.twitter.com/accpchest).

This month in *CHEST*: Editor's picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

The Costs of Critical Care Telemedicine Programs: A Systematic Review and Analysis. *By Dr. G. Kumar et al.*

Impact of Different Backup Respiratory Rates on the Efficacy of Noninvasive Positive Pressure Ventilation in Obesity Hypoventilation Syndrome: A Randomized Trial. *By Dr. O. Contal et al.*

Volumetric Optical Frequency Domain Imaging of Pulmonary Pathology With Precise Correlation to Histopathology. *By Dr. L. P. Hariri et al.*

COMMENTARY

Change in Sweat Chloride as a Clinical End Point in Cystic Fibrosis Clinical Trials: The Ivacaftor Experience. *By Dr. A. G. Durmowicz et al.*

Remembering CHEST 2012

Our Poster Grand Rounds are always popular.

Passing of the Presidential Medal (Dr. Suhail Raoof to Dr. Darcy D. Marciniuk)

The expanded 2012 Simulation Center offered realistic scenarios to practice skills.

The annual Outreach Event taught children at a local Atlanta school about good lung health.

Our CHEST Challenge champs from Maimonides Medical Center

CHEST 2012
October 20 - 25
Atlanta, Georgia

Congratulations to our many winners at CHEST 2012 in Atlanta

Every attendee at CHEST 2012 was a winner, but we wish to especially acknowledge these winners in the following categories:

ACCP Honor Awards

▶ *Master FCCP*
Peter J. Barnes, DM, Master FCCP
▶ *Alfred Soffer Award for Editorial Excellence*
Nicki Augustyn
▶ *Alton Ochsner Award Relating Smoking and Disease*
Jennifer R. Grandis, MD

CHEST Foundation Awards

▶ *Eli Lilly and Company Distinguished Scholar in Critical Care*
Marin Kollef, MD, FCCP
▶ *Roger C. Bone Advances in End-of-Life Care Award*
Lisa I. Mansur, MD, FCCP
▶ *OneBreath® Clinical Research Award in Lung Cancer*
Fabien Maldonado, MD, FCCP
Sunil Singhal, MD
▶ *The CHEST Foundation Clinical Research Award in Pulmonary Arterial Hypertension*
Corey Ventetuolo, MD
▶ *Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency*
Karina Serban, MD
▶ *The Sheila J. Goodnight, MD, FCCP Clinical Research Award in Women's Lung Health*
Ghada Bourjeily, MD, FCCP
▶ *The CHEST Foundation and the Respiratory Health Association of Metropolitan Chicago Clinical Research Award in Women's Lung Health*
Nirupama Putcha, MD
▶ *The CHEST Foundation California Chapter Clinical Research/Medical Education Award*
Mona Luke-Zeitoun, MD

D. Robert McCaffree, MD, Master FCCP Humanitarian Awards
Gregory Erhabor, MBBS, FCCP
Renli Qiao, MD, FCCP
Samuel Joseph, DO, FCCP
Michael Shea, MD, FCCP

Ambassadors for OneBreath® Humanitarian Award
De De Gardner, MSHP, RRT
Diane Rhodes, RRT

ACCP Honor and Memorial Awards and Lectures

▶ *College Medalist Award*
Kalpalatha K. Guntupalli, MD, FCCP
▶ *Distinguished Service Award*
Paul H. Mayo, MD, FCCP
▶ *Edward C. Rosenow III, MD, Master FCCP/ Master Teacher Honor Lecture*
Paul A. Kvale, MD, Master FCCP
▶ *Presidential Citation Honor Lecture*
David J. Prezant, MD, FCCP
▶ *Murray Kornfeld Memorial Founders Lecture*
David E. Griffith, MD, FCCP
▶ *Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation*
Norma M. T. Braun, MD, FCCP
▶ *Distinguished Scientist Honor Lecture in Cardiopulmonary Physiology*
Elizabeth R. Jacobs, MD, FCCP
▶ *Roger C. Bone Memorial Lecture in Critical Care*
Neil A. Halpern, MD, FCCP
▶ *Pasquale Ciaglia Memorial Lecture in Interventional Medicine*
Gerard A. Silvestri, MD, FCCP

Canadian Thoracic Society Awards

▶ *CTS/Institute of Circulatory and Respiratory Health Distinguished Lectureship in Respiratory Sciences*
Shaf Keshavjee, MD, FCCP
▶ *Annual Christie Memorial Lecture*
Susan M. Tarlo, MBBS, FCCP

Alfred Soffer Research Awards

$1,500 Award Winners
Mardi Gomberg-Maitland, MD, MSc
Satvik Ramakrishna, BA
$1,000 Award Winners
Vallerie McLaughlin, MD
Rui Wang
Hikmet Al-Hiti, PhD
Samjot Dhillon, MD

Young Investigator Awards

$1,500 Award Winners
Nadine Al-Naamani, MD
Gustavo Heresi, MD
Peter Moschovis, MD
$1,250 Award Winners
Jun She, MD, PhD
Matthew Churpek, MD, MPH

Top 5 Poster Awards

Mark E. Fenton, MD
Filomena Hazel Villa, MD
Robert J. Walter, MD
Kyle J. Rehder
Petch Wacharasint, MD

Case Report Award Winners

Mir Alikhan
Lalitha Pereirasamy
Siavash Farshidpanah
Ravindra Ramakrishna
Kusum Mathews
Edward McCann
Kirandeep Saini
Tayyab Rehman
Kelly Cawcutt
Fadi Safi
Sajeet Sawhney
William Hunt
Anand Kommuri
Anand Kommuri
Roger Alvarez
Bilal Safadi
Bashar Staitieh
Ariella Reinherz
Frantisek Sandor
John Kingrey
Kevyn Stroebe
William Wong (on behalf of Priyesh Mehta)
Sowjanya Duthuluru
Pankaj Mehta

Global Abstract Award Winners

Argentina–Glenda Ernst
Australia–Andrew Rosenstengel
Brazil–Ricardo Terra
China–Jie Zhang
Egypt–Gamal Agmy
Greece–Andriani Loukopoulou
India–Ashutosh Aggarwal
Italy–Alessia Verduri
Japan–Hiroaki Harada
Korea–So-My Koo
Philippines–Edelweise Merin
Romania–Roxana Nemes, Dumitrache-Rujinski, Magdalena Ciobanu
Russian Federation–Mikhail Chushkin
Singapore–Tunn Ren Tay
Turkey–Hakan Tanriverdi

Special NetWork Abstract Recognition Winners
Nayan Desai, MBBS
Andrew F. Shorr, MD, MPH, FCCP
J. Jonas Carmichael, MD
Petch Wacharasint, MD
Vince Roberts
Sanjay Mehta, MD, FCCP
Takahiro Nakajima, MD, FCCP
Jason Atticus Akulian, MD
Joseph C. Cicenia, MD, FCCP
Brian W. Carlin, MD, FCCP
Tunn Ren Tay, MBBS
Sangit Lal Kasaju, MD
Shadi B. Hijjawi, MD
Jacques Baillargeon, PhD
Thongchai Leelayuthachai, MD
Dennis Jurcevic, MD
Krishna M. Sundar, MD, MBBS, FCCP
Kyle J. Rehder, MD
Oren Fruchter, MD, FCCP

CHEST 2012 Bingo Winners

▶ *CHEST Bingo (Monday Winners)*
Carol E. Breland, RRT
Joseph Donath, MD, FCCP
Kristen Hoyord, RN
Geeta Nath, MD
Shuang Liu, MD
▶ *COPD Bingo (Tuesday Winners)*
Kathleen Kinser
Navpreet Sidhu, MD, MBBS
Elizabeth M. Hinchcliff, RRT
Ann Rutt, MS, APN
Howard Waksman, MD, FCCP
▶ *PAH Bingo (Wednesday Winners)*
Tiong G. The, MBBS, FCCP
Katja Ruh, MD
Som Lerd, MD
Zaher Qassen, MD
Kandace McCarver

CHEST Challenge Winners

▶ *1st Place: Maimonides Medical Center*
Prashant R. Gundre, MBBS
Vishesh Paul, MBBS
Uma Edupuganti, MBBS
▶ *2nd Place: Harvard Pulmonary and Critical Care Medicine Fellowship Program*
Ekaterina Gladysheva, MD
William Oldham, MD, PhD
Peter Moschovis, MD
▶ *3rd Place: University of Toronto*
Rebecca Colman, MD
Woganee Filate, MD
Althea Alexina Barthos Burrell, MD

OneBreath® 5K Walk/Run Winners

Women
1st: Jacqueline Jaworek
2nd: Name Withheld
3rd: Erinn Stubbs
Men
1st: Paul MacEachern
2nd: Jerry Hung
3rd: Franck-Olivier LeBrun

Speaking from the heart … and lungs at CHEST 2012

BY BARBARA STORMS GRANNER
Editorial Specialist
The CHEST Foundation

At the Ambassadors for OneBreath® open meeting and educational program during CHEST 2012, two very special guests spoke about their personal experiences with lung disease.

Chris Draft, former NFL linebacker and president and founder of the Chris Draft Family Foundation, explained his two very close connections to lung disease: he suffers from asthma, which during his 20-plus years as a professional football player often left him "looking for air." And, in 2011, his wife of 1 month died of lung cancer. He spoke to the Ambassadors about the work of his foundation to empower families to live healthy lives, and about the Team Draft initiative, which is dedicated to raising lung cancer awareness, shattering the misconception that lung cancer is a "smoker's disease," and increasing badly needed research funding.

Brian Callanan, executive director of the Cystic Fibrosis Lifestyle Foundation, spoke about living with cystic fibrosis, the struggles he has faced, and his dedication to an active lifestyle. Despite CF, Callanan snowboards, sails, mountain bikes, hikes, snowshoes, and cross-country skis. He founded the Cystic Fibrosis Lifestyle Foundation to inspire people with CF to pursue healthy and active lifestyles by awarding recreation grants to pay for participation in fitness, exercise, and outdoor recreation activities. The goal, he explained, is for patients with CF to thrive, not just survive. The group viewed the documentary that Callanan produced with assistance from a CHEST Foundation Humanitarian Grant. Called "Living Xtreme With Cystic Fibrosis. Brian swam with the whale sharks and is pictured second from right.

Winner Steve Welch (far right), staff members Nancy MacRae and Kevin Oronato (center two), and friends prepare for a swim with the Georgia Aquarium's "gentle giants," the whale sharks. Welch described the experience as "absolutely perfect."

A Fin-tastic Evening at the Georgia Aquarium

More than 800 OneBreath® supporters enjoyed a magical visit to the Georgia Aquarium in Atlanta, with once-in-a-lifetime private views of the Aquarium's famous exhibit tanks, food from Wolfgang Puck, and two chances to swim with the whale sharks. The lucky divers were Steve Welch, ACCP's Senior Vice President of Communications and Executive Editor of the *CHEST* journal, and Dr. Curt Sessler, FCCP, ACCP President-Designate.

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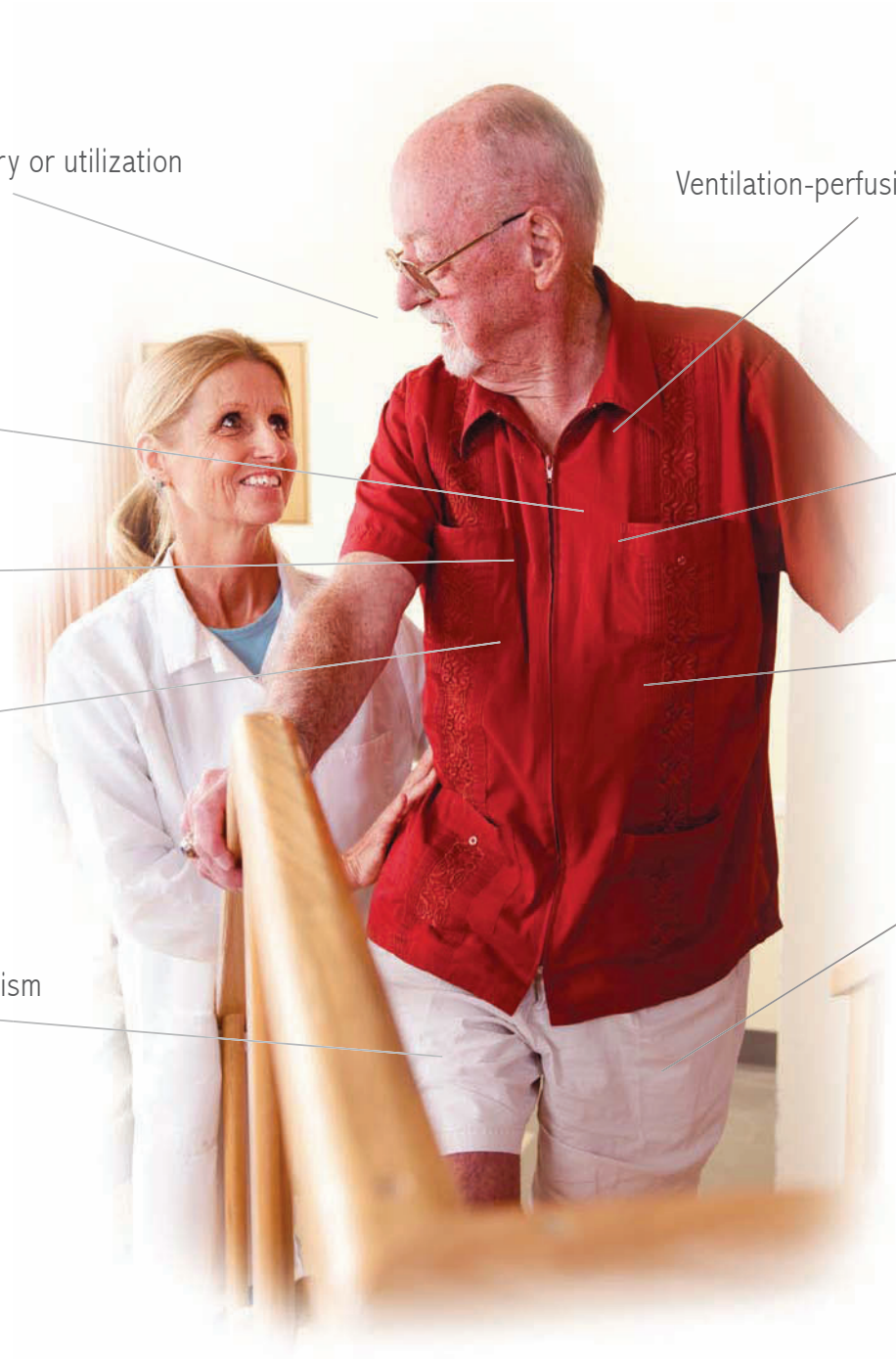

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