Celebrating 10 Years
VOL. 11 • NO. 6 • JUNE 2016

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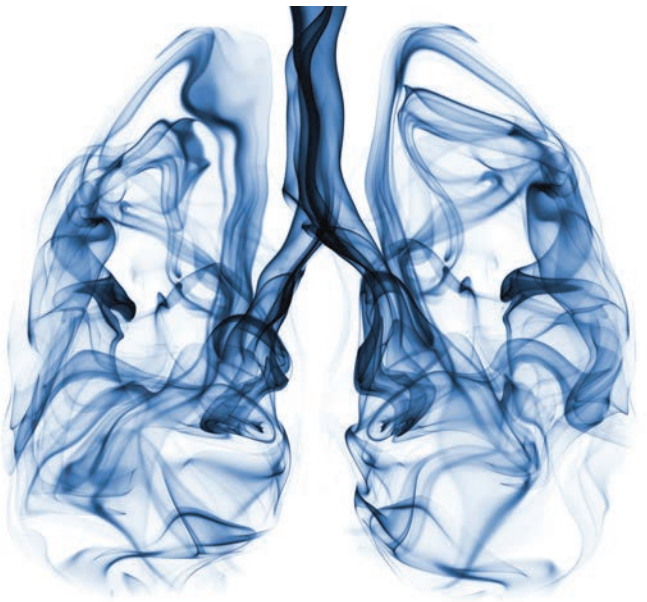

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Definition of COPD may need revision

BY KATIE WAGNER LENNON
Frontline Medical News

The clinical definition of chronic obstructive pulmonary disease (COPD) may need to be revised, based on results from a multicenter observational study of 2,736 individuals.

Respiratory symptoms of COPD were present in 425 of 849 current or former smokers who did not meet the standard spirometry criteria for diagnosing COPD.

The 425 study participants who were symptomatic for COPD but were considered to have preserved pulmonary function had a significantly higher rate of respiratory exacerbations, compared with that of the 424 current or former smokers who were asymptomatic for COPD and were not classified as having the disease (0.27 +/- 0.67 events vs. 0.08 +/- 0.31 events; *P* less than .001).

Using spirometry to define who should receive a diagnosis of COPD does not address all people with symptomatic smoking-related lung disease.

This large population needs to be studied to better define appropriate treatment strategies, Dr. Prescott G. Woodruff, a professor of medicine at the University of California, San Francisco, and his associates noted (N Engl J Med. 2016 May

See **COPD** • *page 7*

Aspirin falls short for the prevention of ARDS

Risk was 10% with aspirin or placebo

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Despite evidence implicating platelets in the development and resolution of acute respiratory distress syndrome (ARDS), the antiplatelet agent aspirin was not efficacious for prevention, according to the findings from a phase IIb trial reported at an international conference of the American Thoracic Society.

A total of 400 at-risk patients from emergency departments were enrolled in the trial, known as LIPS-A (Lung Injury Prevention Study With Aspirin), and randomized evenly to aspirin or placebo, started within 24 hours of presentation.

Overall, about 10% of patients developed ARDS by day 7, with no significant difference between the groups, according to results reported at the conference and simultaneously published in JAMA (2016 May 15. doi: 10.1001/jama.2016.6330).

"In patients at risk for ARDS, aspirin therapy administered within 24 hours of presentation to the emergency department was safe. However, it did not decrease the primary outcome of ARDS development or im-

See **ARDS** • *page 7*

INSIDE

Phrenic implant limits central apnea

BY MITCHEL L. ZOLER
Frontline Medical News

FLORENCE, ITALY – In patients with moderate to severe central sleep apnea, an implanted device that stimulates the phrenic nerve to optimize diaphragm-driven breathing met its efficacy and safety goals, based on results from a multicenter, controlled trial with 151 patients.

Among the 68 patients randomized to active treatment with the device and available for follow-up after 6 months on treatment, 35 patients (51%) had a 50% or better reduction in their apnea-hypopnea index compared with 8 of 73 patients (11%) who had this level of response following device implantation but without its active use.

This statistically significant difference in response to the study's primary endpoint should pave the way for the device's approval, Dr. Maria Rosa Costanzo said at a meeting held by the Heart

See **Apnea** • *page 4*

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  - —**2.3× as many patients on Esbriet maintained their baseline function at 52 weeks** vs placebo (23% vs 10% of patients; 13% absolute difference; *P*<0.001)
- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[2,3]**
- **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006[2,4]**
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)[2]

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- The recommended daily dosage is 3 capsules, 3 times a day (2403 mg/day) with food, titrated to full dosage over a 14-day period[2]
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  - —eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash

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Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{co}$ (percent predicted diffusing capacity of lung for carbon monoxide) between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. The primary endpoint was change in %FVC from baseline to week 72.

†Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.

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Conditional recommendation, moderate confidence in estimates of effect.[5†]

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Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

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

References: 1. Data on file. Genentech, Inc. 2015. **2.** Esbriet Prescribing Information. Genentech, Inc. September 2015. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083-2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760-1769. **5.** Raghu G, Rochwerg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline [published correction appears in *Am J Respir Crit Care Med.* 2015;192(5):644]. *Am J Respir Crit Care Med.* 2015;192(2):e3-e19.

Esbriet®
(pirfenidone) capsules 267 mg

Phrenic nerve stimulator

Apnea *from page 1*

Failure Association of the European Society of Cardiology.

Although the trial enrolled patients with a mix of disorders that caused their central sleep apnea, the majority, 80 patients, had heart failure.

Other enrollees had their breathing disorder secondary to atrial fibrillation, hypertension, and other diseases, suggesting that the implanted device, called the remede System, is suitable for patients with moderate to severe central sleep apnea regardless of the etiology, said Dr. Costanzo, medical director for heart failure at the Advocate Medical Group in Naperville, Ill.

Among the 80 heart failure patients in the trial, the percentage of patients on active treatment who had a 50% or better reduction in their apnea-hypopnea index closely matched the rate in the entire study group.

The results also demonstrated the treatment's safety, with a 9% rate of serious adverse events secondary to either the device's implantation or function during the 12 months fol-

lowing placement in all 151 patients enrolled. Patients in the control arm had a device implanted but not turned on during the first 6 months of the study. The device was turned on and they received active treatment during the next 6 months. The trial's prespecified safety goal, developed in conjunction with the Food and Drug Administration, was a 1-year rate of freedom from a serious adverse event of at least 80%; the actual rate achieved was 91%.

Successful implantation of the device by electrophysiology cardiologists occurred in 97% of enrolled patients, a procedure that took an average of nearly 3 hours. Need for a lead revision, one of the serious adverse events tallied during follow-up, occurred in 3% of patients.

The efficacy and safety shown in this pivotal trial "should be plenty" for obtaining FDA approval.

DR. CASTANZO

No patients in the study died during 1-year follow-up.

Most other serious adverse events involved lead reposition (but not revision) to better optimize the phrenic nerve stimulation. Dr. Costanzo likened the complexity of implanting and operating the device to placement and use of a cardiac resynchronization device.

The efficacy and safety of the device shown in this pivotal trial "should be plenty" for obtaining FDA approval, predicted Dr. Costanzo, the study's lead investigator, which would make it the first approved intervention for central sleep apnea. "I think this is a game changer," she said in an interview.

But coming less than a year after a report of an unexpected excess-mortality rate in heart failure patients treated for central sleep apnea with an adaptive servo-ventilation device (N Engl J Med. 2015 Sept 17;373[12]:1095-1105), heart-failure specialists are now more demanding about the data needed to prove safety and clinical benefit from an intervention that targets central sleep apnea and sleep-disordered breathing.

"I think we need an endpoint that involves hospitalizations and death" to more clearly demonstrate meaningful clinical benefit and safety, said Dr. Mariell Jessup, a professor of medicine and heart failure specialist at the University of Pennsylvania in Philadelphia.

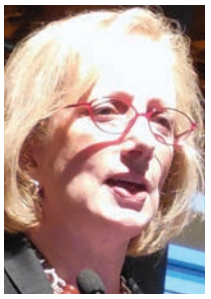
Following the experience with increased mortality from servo-ventilation "we now need to demand" more comprehensive safety data in sleep trials.

Also, the approach tested in this study involves "putting a device into

Continued on following page

Continued from previous page

patients, so it's not completely benign," she said in an interview. "A lot of things that we thought made a lot of sense, like treating a heart-failure patient's sleep apnea, turned out to cause things we didn't expect. We need to be cautious."



Dr. Costanzo agreed that there is a need for additional studies of the phrenic-nerve stimulating device in a larger number of heart failure patients that involve heart-failure-specific endpoints.

But she also stressed how life changing this intervention was for some of the patients in the study. "The transformation of their lives was unbelievable. They said things like 'I feel I have my life back.'"

She additionally noted that the mechanism of action of phrenic nerve stimulation is different from more traditional sleep-apnea treatments that have relied on positive air pressure devices.

We need an endpoint that involves hospitalizations and death to show benefit and safety.

DR. JESSUP

Phrenic nerve stimulation causes contraction of a patient's diaphragm that creates negative pressure within the chest cavity in a manner similar to that of natural breathing. The stimulation is adjusted to make it imperceptible to patients, and stimulation does not occur when a patient is standing or sitting, only when lying down.

"With positive airway pressure in patients with advanced heart failure you reduce venous return, and when a patient's heart is sick and depends on preload this can hurt the patient. Phrenic nerve stimulation does the opposite.

It contracts the diaphragm and creates negative pressure, so if anything, it facilitates venous return," she explained.

The trial, run at 31 centers, mostly in the United States with the others in Europe, enrolled patients with moderate to severe central sleep apnea with an average apnea-hypopnea index of 45 episodes per hour while sleeping. The average age was 65 years, about 90% of the patients were men, and average body mass index was 31 kg/m^2.

In addition to the primary efficacy endpoint of reduced apnea-hypopnea index, the patients on active treatment also showed statistically significant reductions compared with baseline in central apnea episodes and in daytime sleepiness measured on the Epworth Sleepiness Scale and an improvement in the patients' global assessment of their condition. The changes did not occur in the control patients. In the treated patients central apnea episodes fell from an average of 32 episodes per hour at baseline to an average of 6 central episodes an hour after 6 months on treatment.

Dr. Costanzo is a consultant to and has received research support from Respicardia, the company developing the tested phrenic-nerve stimulation device. Dr. Jessup had no disclosures.

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VIEW ON THE NEWS

Dr. David A. Schulman, FCCP, comments: Phrenic nerve and diaphragmatic pacing have historically been used in patients with respiratory failure due to neuromuscular disease to decrease the need for mechanical ventilation. Its role in the management of central sleep apnea, however, remains unclear. It is certainly unsurprising that the frequency of central sleep apnea events improves with phrenic nerve pacing. It is also encouraging that a subjective benefit to sleep quality results from such therapy. That noted, improvement in sleep quality does not necessarily predict improvement in health. While central sleep apnea has been associated with worsened outcome in several disease states, there is no evidence to date that treatment of the sleep-disordered breathing helps to improve those outcomes. Until such evidence exists, it may be difficult to justify an invasive surgical intervention to treat central sleep apnea.

IN THIS ISSUE

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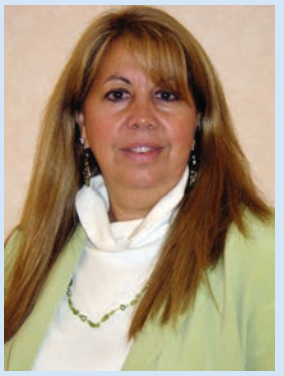

Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $230.00 per year. Phone 973-206-3434, fax 973-206-9378.

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Aspirin fell short

ARDS *from page 1*

prove any of the secondary outcomes," commented lead author Dr. Daryl J. Kor, an associate professor of anesthesiology at the Mayo Clinic, Rochester, Minn. "The results of this phase IIb trial do not support continuation to a larger phase III trial."

Nonetheless, as the first large multicenter ARDS prevention trial, LIPS-A provided an abundance of information about research in this challenging area, he stressed. For example, the information gleaned will help inform future trials on issues related to timely enrollment, risk prediction, and work flow modifications.

"In terms of limitations, we should note that there was a very low rate of ARDS, much lower than we anticipated," Dr. Kor said. Patients also had less severe disease than expected. "There are always questions about the dose and duration [of treatment], as well as whether or not the ED environment is early enough for an ARDS prevention trial. Almost 15% of our patient population had prevalent bilateral infiltrates by the time they presented to the emergency department," he noted.

Despite the negative LIPS-A findings, there may still be a role for aspirin in the treatment of ARDS, according to conference attendee Dr. Ivor S. Douglas, chief of pulmonary sciences and critical care medicine, and director of the medical intensive care unit, at the Denver Health Medical Center and the University of Colorado.

ARDS lacks a good biomarker similar to the troponin used to identify and guide aspirin treatment in myocardial infarction, he explained in an interview.

"I continue to believe that there are several endophenotypes, subgroups of the disease where an endothelial vascular phenotype is predominant," Dr. Douglas explained. "And as we understand more about the fundamental biology of the disease, I suspect that many of these things that have been shown in unselected populations not to have efficacy – you didn't hear me say negative, but not to have efficacy – may well be revisited within the context of a more well defined phenotype for the disease.

"I think it's imperative that we don't just call the balls and strikes here," Dr. Douglas added. "The idea is to move the science forward and to do it in a really thoughtful and rigorous way."

LIPS-A enrolled adult patients from 16 U.S. academic hospitals who were at risk for ARDS, defined as having a Lung Injury Prediction Score of 4 or greater (corresponding to a risk of about 18%), in the emergency department and were planned to be hospitalized.

They were randomized to receive aspirin (a 325-mg loading dose, followed by 81 mg/day) or placebo within 24 hours of emergency department presentation, with continuation out to hospital day 7, discharge, or death.

On average, patients received their first dose of the study drug slightly less than 13 hours after randomization, Dr. Kor reported.

Incident ARDS by day 7 was seen in 10.3% of the aspirin group and 8.7% of the placebo group, a nonsignificant difference. Findings were similar for each study site individually.

The groups were also statistically indistinguishable with respect to mean number of ventilator-free days out to day 28 (24.9 vs. 25.2), mean intensive care unit length of stay (5.2 vs. 5.4 days), and the 28-day rate of survival (90% vs. 90%), among other secondary outcomes.

In terms of safety, the incidence of bleeding-related adverse events was not significantly greater with aspirin than with placebo (5.6% vs. 2.6%). Measures of renal function were also essentially the same.

Analyses of a host of biomarkers associated with injury, inflammation, and thrombosis generally showed no differences in levels between groups. The possible exception was a trend toward a higher level of interleukin-2 in the aspirin group.

Dr. Kor disclosed that he receives personal fees from UpToDate.

Symptomatic, elevated CAT scores

COPD *from page 1*

11;[19]374:1811-21.).

Patients were classified as not having COPD if the ratios of their forced expiratory volume in 1 second to forced vital capacity (FVC) was 0.70 or more after bronchodilator use and if their FVC was above the lower limit of the normal range. During a stable phase of disease, which was defined as greater than six weeks after a respiratory exacerbation, patients participated in the eight-question COPD Assessment Test (CAT). Patients with a CAT score of greater than or equal to 10 were considered to be symptomatic for COPD, and those with a lower CAT score were considered to be asymptomatic for COPD.

While 963 of the 1,812 study participants who were current or former smokers were classified as having Global Initiative for Chronic Obstructive Lung Disease stage 1 or 2 COPD, half of the current or former smokers who were not classified as having COPD were still symptomatic for COPD. Among the 199 study participants who had never smoked, 16% had COPD symptoms. Current or former smokers, who were symptomatic for but not classified as having COPD, had elevations in all components of the CAT score, compared with the asymptomatic patients with preserved pulmonary function. These patients also were more likely to be current smokers, report symptoms of chronic bronchitis, report a history of wheezing and asthma, and report a previous diagnosis of COPD. The authors had no relevant financial disclosures.

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VIEW ON THE NEWS

Dr. Vera De Palo, FCCP, comments: It is often symptoms that bring patients to seek hospital care. This study points out a split between smoking-related respiratory symptoms and the preserved spirometry that was found in a portion of the study group. Further research may better characterize this population of symptomatic current and former smokers. With identification of effective treatments and improved symptom management, we may be able to promote better respiratory health, thereby reducing hospital utilization.

Medical histories of study participants

	Patients who never smoked	Current or former smokers	Current or former smokers	Current or former smokers	Current or former smokers
		Preserved pulmonary function	Preserved pulmonary function	Mild to moderate COPD	Mild to moderate COPD
		Asymptomatic for COPD	Symptomatic for COPD	Asymptomatic for COPD	Symptomatic for COPD
Characterisitic	Group A	Group B	Group C	Group D	Group E
Symptoms of chronic bronchitis	4/196	23/417	133/408	27/326	191/604
Wheezing	27/198	137/422	291/421	152/334	476/623
History of COPD	0/197	45/412	173/399	168/320	485/603
Any diagnosis of asthma	10/195	30/420	114/419	50/330	161/611
Childhood diagnosis of asthma	4/197	15/423	41/417	25/331	69/619

Note: The multicenter, observational study involved 2,736 individuals aged 40-80 years.

Source: N Engl J Med. 2016 May 11;374(19):1811-21

Ultrasound improves early diagnosis of VAP

BY WILLIAM PERLMAN
Frontline Medical News

FROM CHEST

The use of lung ultrasound, both alone and in combination with clinical and microbiologic data, can improve the early diagnosis of ventilator-associated pneumonia (VAP), according to the results of a study published in *Chest*.

The early diagnosis of VAP is challenging, and leaves intensivists with two options. The first is waiting for positive results from patients' specimens, which delays treatment and increases mortality risk. The other is to administer antibiotics to all patients suspected of having VAP, which may be inappropriate and can lead to the development of multiresistant bacteria.

"A pressing need therefore exists for reliable diagnostic tools to diagnose VAP early so that antibiotics can be promptly initiated, avoiding two extreme approaches," wrote Dr. Silvia Mongodi of the Fondazione IRCCS Policlinico San Matteo in Pavia, Italy, and her colleagues.

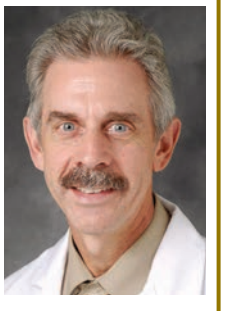
Based on the results of previous research, the investigators hypothesized that lung ultrasound (LUS) could be used to diagnose VAP early and help to avoid treatment delays or mistakes. To test this hypothesis, the diagnostic performance of LUS alone and in combination with clinical and microbiologic data was evaluated prospectively in 99 patients with suspected VAP in ICUs at Saint Joseph Hospital (Paris), Fondazione IRCCS Policlinico San Matteo, and Centre Hospitalier de l'Université de Montréal (Chest. 2016 Apr;149[4]:969-80. doi: 10.1016/j.chest.2015.12.012).

The study results showed that subpleural consolidations and dynamic linear/arborescent air bronchograms were the principal LUS signs of VAP, and that the presence of both in the same individual made the diagnosis highly specific (88%), with a high positive predictive value (86%) and a positive likelihood ratio of 2.9. Furthermore, the addition of data from either of two different endotracheal aspirate assessment techniques (EAgram [direct Gram stain examination] or EAquant [direct Gram stain culture]) to the data from the principal LUS signs showed 97% specificity with each technique and positive likelihood ratios of 6.6 and 7.1, respectively, Dr. Mongodi and her associates reported.

Dr. Mongodi and her colleagues said that their results were encouraging but would need to be validated in larger clinical trials and that the specificity of the examination for VAP diagnosis could be increased by daily monitoring of ICU patients.

No funding was received for this study. The authors reported no conflicts of interest.

VIEW ON THE NEWS



Dr. Daniel Ouellette, FCCP comments: Ultrasound techniques are increasingly being used in the intensive care unit to direct physician decisions. A report by Mongodi and colleagues suggests that ultrasound may be employed to diagnose ventilator-associated pneumonia in critically ill patients. While promising, this study is limited by small patient numbers and by the fact that reliable criteria to diagnose VAP are lacking. Further research is needed before this technique can be used reliably in the ICU.

Varenicline, bupropion don't increase events in smokers

BY SHANNON AYMES
Frontline Medical News

Neuropsychiatric adverse events do not increase significantly in smokers treated with either varenicline or bupropion, a large cohort study shows.

Both bupropion and varenicline have been tied to long-term smoking cessation in observational studies and randomized trials. However, concerns about adverse neuropsychiatric events, including aggression and suicidality, have been raised. Furthermore, data are limited on the safety of the medications in smokers with known psychiatric conditions.

At the request of the Food and Drug Administration, Dr. Robert M. Anthenelli and his colleagues conducted a randomized, double-blind, triple-dummy, placebo- and active-controlled trial to assess bupropion and varenicline in motivated smokers with and without psychiatric diagnoses for 12 weeks. The efficacy endpoint in the multinational trial, called the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES), was abstinence for 9-12 weeks. The primary endpoint was adverse neuropsychiatric events, reported Dr. Anthenelli of the psychiatry department at the University of California, San Diego.

In total, 8,144 participants were randomized to either a nonpsychiatric (n = 4,028) or a psychiatric (n = 4,116) cohort. Men made up 44% of the study population, and the average age was 46.5 years. Most participants were white (82%) and American (52%). The psychiatric cohort included participants with diagnoses of primary mood disorders, anxiety and psychotic disorders, and borderline personality disorders, and 49% reported treatment with a psychotropic medication (Lancet. 2016 Apr 22. doi: 10.1016/S0140-6736).

Overall, the incidence of neuropsychiatric adverse events was similar in the bupropion (4.5%), varenicline (4.0%), nicotine patch (3.9%), and the placebo (3.7%) groups. However, more neuropsychiatric events were reported in the psychiatric cohort than the nonpsychiatric cohort (5.8% versus 2.1%, *P* less than .0001). Likewise, the psychiatric cohort reported moderate and severe neuropsychiatric adverse events more often in the bupropion group (6.7% versus 2.2%), varenicline (6.5% versus 1.3%), nicotine patch (5.2% versus 2.5%), and placebo groups (4.9% versus 2.4%) than the nonpsychiatric cohort.

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In the nonpsychiatric cohort, the risk differences for moderate and severe neuropsychiatric adverse events were –1.28 (95% confidence interval, –2.40 to –0.15) for varenicline vs. placebo and –0.08 (95% CI, –1.37 to 1.21) for bupropion vs. placebo. In the psychiatric cohort, the risk differences for moderate and severe neuropsychiatric adverse events were 1.59 (95% CI, -0.42 to 3.59) for varenicline-placebo and 1.78 (95% CI, -0.24 to 3.81) for bupropion-placebo.

Rates of abstinence were higher in the participants who received varenicline, compared with placebo (OR, 3.61; 95% CI, 3.07-4.24), bupropion (OR, 1.75; 95% CI, 1.52-2.01), and the nicotine patch (OR, 1.68; 95% CI, 1.46-1.93).

The most common adverse events reported included abnormal dreams, headache, insomnia, and nausea.

Dr. Anthenelli and his associates noted several limitations. For example, participants in the psychiatric cohort were stable or in remission; they were restricted to particular psychiatric diagnoses; and participants with current substance abuse or risk for suicide were excluded.

However, they said the EAGLES trial results provide "further evidence that varenicline and bupropion can be used safely by psychiatrically stable smokers," they wrote. "Although varenicline appears to be the most effective single pharmacotherapy available, all of the first-line medications – varenicline, bupropion, and nicotine patch – are efficacious, compared with placebo."

The authors report relationships with several pharmaceutical companies, including Pfizer, GlaxoSmithKline, Arena Pharmaceuticals, Alkermes, Cerecor, Johnson & Johnson, and Forum Pharmaceuticals.

The study was funded by Pfizer and GlaxoSmithKline.

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Endobronchial coils boost exercise tolerance

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Compressing damaged lung tissue with endobronchial coils improves exercise tolerance in patients with severe emphysema, albeit with the tradeoff of more adverse events, concludes the phase 3 RENEW trial.

After a year of treatment, the 6-minute walk distance had improved in patients given coils, whereas it had worsened in patients managed with usual care, with a difference of nearly 15 meters between groups, investigators reported at an international conference of the American Thoracic Society and simultaneously published (JAMA. doi:10.1001/jama.2016.6261. Published online May 15, 2016).

However, the median gain with coils fell short of the study's predefined minimal clinically important difference of 25 meters. Additionally, major complications, mainly lower respiratory tract infections, were more common with the coils, although they resolved with time.

"Participants in the RENEW trial had advanced disease; 77% had homogeneous emphysema. This is a group that has very few therapeutic options," commented lead investigator Dr. Frank C. Sciurba, director of both the Emphysema Research Center and the Pulmonary Function Exercise Physiology Laboratory at the University of Pittsburgh. "The response rates of endobronchial coils to improve quality of life and exercise tolerance in these severely symptomatic patients balanced against peri-procedural adverse events in this population provides an evidence-based choice for symptomatic patients and treating physicians when there are few other options."

RENEW (Lung Volume Reduction Coil Treatment in Patients With Emphysema) was conducted among 315 patients from the United States, Canada, the United Kingdom, Germany, the Netherlands, and France who had emphysema with severe air trapping.

This was a very inclusive study. We randomized nearly half of those screened.

DR. SCIURBA

"This was a very inclusive study. In contrast to the surgical and valvular studies, we randomized nearly half of those screened because we allowed patients with homogeneous disease and of course didn't select based on fissure integrity, which is a selection criterion for other studies," Dr. Sciurba commented.

The patients received either guideline-based usual care alone (including pulmonary rehabilitation and bronchodilators) or with the addition of bilateral, bronchoscopically placed coils (RePneu Lung Volume Reduction Coil System, currently investigational in the United States).

At 12 months, the median 6-minute walk distance had improved by 10.3 meters with coil treatment but worsened by 7.6 meters with usual care ($P = .02$). The proportion of patients attaining an improvement of at least 25 meters was higher in the coil group (40.0% vs. 26.9%; $P = .01$).

In exploratory analyses, patients having more nonpulmonary comorbidities at baseline derived lesser benefit in walk distance from coil treatment, Dr. Sciurba noted.

The coils also netted greater improvement in the median change in forced exploratory volume in 1 second (FEV1) (difference between groups, 7.0%; $P < .001$) and in scores on the St. George's Respiratory Questionnaire (difference between groups, −8.9 points).

At the same time, patients in the coil group had higher rates of major complications such as pneumonia requiring hospitalization and other potentially life-threatening or fatal events (34.8% vs. 19.1%, $P = .002$) and of other serious adverse events such as pneumonia (20% vs. 4.5%) and pneumothorax (9.7% vs. 0.6%).

"All of these adverse events returned to baseline at 9 to 12 months," Dr. Sciurba reported. Also, there was no significant difference between groups in mortality rate.

Of note, 35% of the 40 cases of coil-associated opacities initially thought to be pneumonia were likely a noninfectious inflammatory reaction to the coils. "These adjudicated noninfectious coil-associated opacities were associated with a better response," he noted.

Finally, patients with greater air trapping at baseline had better-than-average improvements in outcomes with the coils, regardless of whether they had homogeneous or heterogeneous disease. Among patients with lesser air trapping, those with homogeneous disease derived less benefit from coils.

Dr. Sciurba disclosed that he receives institutional support from PneumRx and Pulmonx. The study was sponsored by PneumRx.

VIEW ON THE NEWS

Dr. Vera De Palo, FCCP, comments: When patients are functionally limited, as physicians we like to be able to offer options. The results of this trial indicate that another option may exist to improve functionality. As with all treatment decisions, matching the patient to the best therapeutic option and weighing the risks and benefits of the choice will be important.

PAH often linked to connective tissue disease in aged

BY KATIE WAGNER LENNON
Frontline Medical News

FROM CHEST

Patient age contributes to significant differences in the characteristics and etiology of pulmonary arterial hypertension seen in randomized, controlled trials, including more frequent connective tissue disease–associated disease in older patients, according to a post-hoc analysis of trials.

Additionally, older age was associated with worse baseline functional status, worse outcomes in the 6-minute walk distance, and an overall reduced response to treatment, while hemodynamic severity was higher in younger patients.

"Although registry data have shown that idiopathic PAH [pulmonary arterial hypertension] is increasingly recognized in older populations, our analysis shows that idiopathic etiology was less frequent in the older group. In contrast, CTD [connective tissue disease]–associated PAH accounted for a higher proportion of PAH etiology in the oldest age group," wrote Jonathan A. Rose of Case Western Reserve University, Cleveland, and colleagues (Chest. 2016;149[5]:1234-44. doi: 10.1016/j.chest.2015.11.008).

The researchers analyzed seven multicenter, randomized, double-blind, placebo-controlled treatment trials for PAH conducted by United Therapeutics and one open-label extension study that involved following patients being treated with subcutaneous treprostinil for 4 additional years. The researchers categorized the 2,627 patients included in the trials in the following three age groups: 50 years or younger, 51-64 years, and 65 years or older.

Between 53% and 74% of patients in all trials across all age groups had idiopathic PAH, but older patients comprised a significantly smaller proportion of the patients with idiopathic PAH in three of the trials ($P = .004$) and a significantly higher percentage of the patients with CTD-associated PAH in all of the trials (P less than .001). Across the trials, CTD-associated PAH occurred in 15%-21% of patients 50 years or younger, 25%-40% of those aged 51-64 years, and 27%-49% of those aged 65 years or older.

From baseline to the end in three of the studies, a smaller change in the 6-minute walk distance was seen in older patients and a higher proportion of older patients had an overall decrease in total 6-minute walk distance. Additionally, a lower proportion of patients in the oldest age group were classified as being of the World Health Organization functional classes I and II, with 9%-32% of patients aged 65 years or older, 10%-33% in those aged 51-64 years, and 16%-43% of those aged 50 years or younger. Hemodynamic severity was among the areas in which older patients performed better than younger patients, with the oldest age group having lower baseline mean pulmonary artery pressure and pulmonary vascular resistance in the two trials that measured hemodynamics. Mortality was generally small in these studies.

Two of the authors, Jody M. Cleveland and Youlan Rao, Ph.D., reported being employees of United Therapeutics, while Dr. Omar A. Minai, another author of the report, serves on the scientific advisory board of United Therapeutics. The other authors declared no conflicts.

klennon@frontlinemedcom.com

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.

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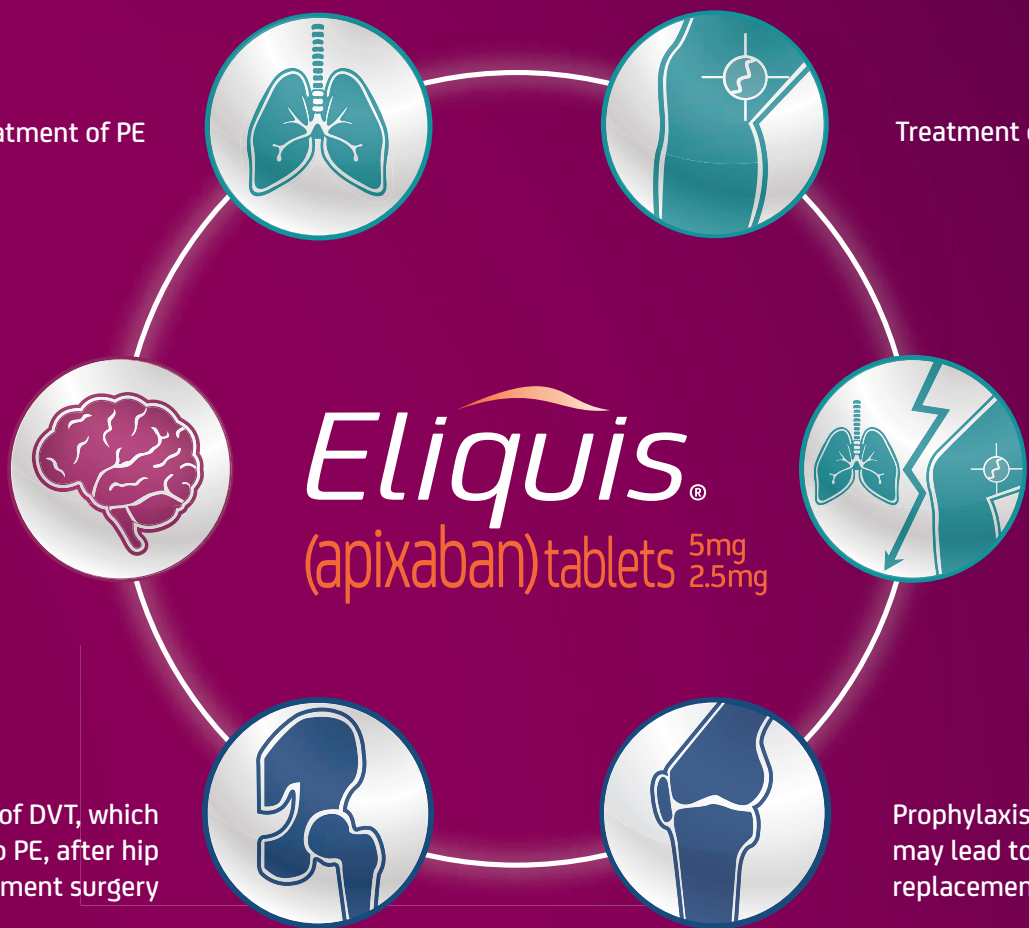

Learn more about ELIQUIS for the treatment of DVT/PE and access reprints of our clinical studies.

hcp.eliquis.com

NVAF=nonvalvular atrial fibrillation; DVT=deep vein thrombosis; PE=pulmonary embolism.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

DRUG INTERACTIONS (CONT'D)

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS
(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery—ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS (apixaban). The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions]*
- Bleeding *[see Warnings and Precautions]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions]*

Clinical Trials Experience

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

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

¶ GI bleed includes upper GI, lower GI, and rectal bleeding.

** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Strong Dual Inhibitors of CYP3A4 and P-gp

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except nonvalvular atrial fibrillation patients who meet the criteria for dosage adjustment *[see Dosage and Administration (2.1) in full Prescribing Information]*. Patients with ESRD (CrCl <15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2) in full Prescribing Information]*.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction *[see Warnings and Precautions]*. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

1356615A0 / 1356514A0 Rev September 2015

432US1501679-06-01

PULMONARY PERSPECTIVES® Building critical care in northern Haiti

BY NATALIE NAPOLITANO, MPH, RRT-NPS; AND DANIEL D. ROWLEY, MSC, RRT-ACCS, NPS

Background

Milot is located in northern Haiti, 12 miles south of Cap-Haitian. It is the site of two national historical landmarks: The Palace of Sans-Souci and the Citadelle Laferrière. Both were commissioned by the former slave, King Henri Christophe, a leader during the Haitian revolution who became the country's first ruler.

In the heart of Milot is Hôpital Sacré Coeur (HSC). CRUDEM Foundation (CRUDEM Foundation, http://crudem.org/about-crudem/, Accessed January 10, 2016) was founded by the Sacred Heart brothers from Montréal, Canada, and originally included a clinic, as well as other capital improvements to the town of Milot.

In 1986, CRUDEM Foundation took over the management of the hospital until 2 years ago when The Holy Name Foundation assumed control of both the CRUDEM Foundation and the management of the hospital, providing some much needed capital for structural improvements to the hospital campus.

HSC is a full-service, tertiary care hospital serving as a referral center for surgical and advanced specialty treatment center for all of Haiti.

Before the 2010 earthquake, HSC was a 73-inpatient bed facility with limited radiographic services and reliable basic laboratory services. It provided numerous outpatient services as well, such as obstetrics and gynecology, pediatrics, internal medicine, and an HIV clinic.

Specialty clinics, such as ENT, dermatology, cardiology, and orthopedic, were supported by volunteer medical and surgical teams from the United States.

After the earthquake, HSC served as an evacuation center, treating over 1,000 severely injured Haitians transported to Milot by the US Navy and Coast Guard. HSC's medical volunteers from the United States flocked to Milot to assist the Haitian staff in the aftermath.

In 2 weeks, the hospital ramped up to a 420 beds and performed over 180 surgeries, many of these amputations.

The hospital has been transformed since the earthquake. HSC now has 122 beds with a six-bed adult/pediatric ICU, neonatal ICU, and three operating rooms. The hospital operates an oxygen-generating unit that produces oxygen for the hospital, as well as bottled oxygen available to other hospitals and clinics.

Among the other services provided to the community are one of the few prosthetic laboratories in Haiti, a blood bank, and community programs providing vaccinations; prenatal care; and HIV/AIDS, TB, malaria, and filariasis treatment.

MS. NAPOLITANO

MR. ROWLEY

The community health department also distributes food provided by World Food Program. In addition, the hospital currently employs 247 people, making it one of the largest employers paying a fair, living wage in the region. Some salary support is provided by outside aid organizations, such as USAID and the Red Cross.

Working alongside the Haitian medical staff are teams of US medical volunteers who usually visit for 1 week and assist with running key specialty programs, including a pediatric diabetes program, a pediatric congenital cardiac program, an adult cardiology program, an intensive care medicine program, as well as specialty surgical clinics. Some of these teams fundraise to provide salary support for the long-term existence of these programs.

Respiratory Training Program

The respiratory care training program began in 2011 when Dr. Peter Kelly, then-President of the CRUDEM Foundation, and Dr. Harold Previl, Medical Director for Hôpital Sacré Coeur (HSC), made a request to the American Association for Respiratory Care (AARC) through CEO Sam Giordano to assess the ability of HSC staff to utilize the ventilators (invasive and noninvasive) donated by Philips/Respironics.

We traveled to Milot in December of 2011 as independent volunteers to perform an educational, equipment, and infrastructural respiratory care needs assessment at HSC with a goal of assisting the Haitian staff in independently performing advanced level respiratory—in essence critical care—for patients of all ages.

The traditional practice had been to avoid endotracheal intubation and, if necessary, to wean and extubate prior to the departure of the US team.

This situation created the potential for de facto terminal weans/extubations. In response to this, the HSC administration and medical staff were interested in acquiring the training necessary to enable them to initiate and maintain this level of care while working within their available resources to assist patients in a functional recovery.

After the completion of this formal needs assessment and identification of intrastructural equipment and educational needs, we determined that with advanced training, the Haitian staff could begin to provide advanced level care at HSC. This team developed and delivered a training program for doctors and nurses that included didactic and lab courses, with a progressive curriculum over 10 months administered by volunteer registered respiratory therapists from the United States.

Reinforcement of the program continues by including respiratory therapists with the pediatric medical and adult surgical teams to work alongside Haitian staff, providing clinical instruction, as well as assistance in maintaining the respiratory support devices.

The respiratory care program has been responsible for the following improvements in clinical care:

- Development of and routine deployment of simple bubble CPAP in the neonatal ICU and pediatric ward with a treatment protocol
- Invasive and noninvasive ventilation protocols for all ages
- Oxygen delivery protocols for all ages
- Development of standardized charting/recording of trend data from respiratory support devices
- Continued infusion of disposable respiratory care equipment needed and maintenance of all mechanical support devices.

The administration of HSC has made a commitment to critical care medicine in a number of areas. The physical plant has been updated to ensure electricity 24 hours a day and a steady supply of oxygen.

Recently, they appointed a Haitian internal medicine physician as head of the ICU. A number of steps will be taken to support him and the ICU team, including visits from ICU physicians and nurses and travel to the United States to work with critical care physicians and build partnerships. As part of this initiative, the respiratory therapy team has made a commitment to send specialty trained respiratory therapists to the HSC to work with the ICU team, as well as providing physician resources for assistance.

In addition, Natalie Napolitano and Dr. Michael Canarie, pediatric intensivist at Yale-New Haven Children's Hospital, and others, are working with the administration to lay the groundwork for advancing current neonatal ICU care and developing formalized pediatric critical care with the building of the new pediatric unit that will have four beds equipped for ICU level care.

The HSC team recognizes that respiratory support is only one aspect of critical care. In addition to the essential staff training, many other material and structural challenges remain.

Among material needs are the readily availability and standardization of medications, such as sedatives and long-acting anticonvulsants and IV pumps needed to more accurately deliver these medications.

Consistent means need to be ensured by which to provide adequate nutrition for critically ill, intubated patients.

Biomedical support is important for the smooth and consistent function of the unit. Also, options for rehab to assist with recovery from the predictable muscle deterioration common in critical illness will promote a quicker return to functional recovery.

The continued success of this program relies on the partnership between the Haitian administration and staff; current volunteer leaders; and additional respiratory therapists, critical care physicians, and nurses who travel to Milot to provide clinical instruction and material support (e.g., oxygen delivery devices, disposable noninvasive and invasive ventilation circuits, blood gas analyzer with electrolyte panel, airway equipment, etc).

More Information: The CRUDEM Foundation. http://crudem.org/about-crudem/. Accessed January 10, 2016.

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Minimizing LVAD pump thrombosis poses challenges

BY MITCHEL L. ZOLER
Frontline Medical News

PHOENIX – Cardiothoracic surgeons who implant left ventricular assist devices in patients with failing hearts remain at a loss to fully explain why they started seeing a sharp increase in thrombus clogging in these devices in 2012, but nevertheless they are gaining a better sense of how to minimize the risk.

Three key principles for minimizing thrombosis risk are selecting the right patients to receive left ventricular assist devices (LVAD), applying optimal management strategies once patients receive a LVAD, and maintaining adequate flow of blood through the pump, Dr. Francis D. Pagani said in a talk at a session devoted to pump thrombosis at the annual meeting of the Society of Thoracic Surgeons.

Other critical aspects include optimal implantation technique, quick work-up of patients to rule out reversible LVAD inflow or outflow problems once pump thrombosis is suspected, and ceasing medical therapy of the thrombosis if it proves ineffective and instead progress to surgical pump exchange, pump explantation, or heart transplant when necessary, said Dr. Ahmet Kilic, a cardiothoracic surgeon at the Ohio State University, Columbus.


DR. KILIC

Another key issue is that, now that the pump thrombosis incidence is averaging about 10% of LVAD recipients, with an incidence rate during 2-year follow-up as high as 24% reported from one series, surgeons and physicians who care for LVAD patients must have a high index of suspicion and routinely screen LVAD recipients for early signs of pump thrombosis. The best way to catch pump thrombosis early seems to be by regularly measuring patients' serum level of lactate dehydrogenase (LDH), said Dr. Robert L. Kormos, professor of surgery and director of the artificial heart program at the University of Pittsburgh.

"We measure LDH on most clinic visits, whether or not the patient has an indication of pump thrombosis. We need to screen [LDH levels] much more routinely than we used to," he said during the session.

"Elevated LDH is probably the first and most reliable early sign, but you need to also assess LDH isoenzymes because we've had patients with an elevation but no sign of pump thrombosis, and their isoenzymes showed that the increased LDH was coming from their liver," Dr. Kormos said in an interview.

Although serial measurements and isoenzyme analysis can establish a sharp rise in heart-specific LDH in an individual patient, a report at the meeting documented that in a series of 53 patients with pump thrombosis treated at either of two U.S. centers, an LDH level of at least 1,155 IU/L flagged pump thrombosis with a fairly high sensitivity and specificity.

This LDH level is roughly five times the upper limit of normal, noted Dr. Pagani, professor of surgery and surgical director of adult heart transplantation at the University of Michigan, Ann Arbor, and a senior author on this report.

But prior to this report Dr. Kormos said that he regarded a LDH level of 600-800 IU/L as enough of an elevation above normal to prompt concern and investigation. And he criticized some LVAD programs that allow LDH levels to rise much higher.

"I know of clinicians who see a LDH of 1,500-2,000 IU/L but the patient seems okay and they wonder if they should change out the pump. For me, it's a no brainer. Others try to list a patient like this for a heart transplant so they can avoid doing a pump exchange. I think that's dangerous; it risks liver failure or renal failure. I would not sit on any LVAD that is starting to produce signs of hemolysis syndrome, but some places do this," Dr. Kormos said in an interview.


DR. KORMOS

"Pump thrombosis probably did not get addressed in as timely a fashion as it should have been" when it was first seen on the rise in 2012, noted Dr. James K. Kirklin, professor of surgery and director of cardiothoracic surgery at the University of Alabama, Birmingham. "It is now being addressed, and we realize that this is not just a pump problem but also involves patient factors and management factors that we need to learn more about. We are quite ignorant of the patient factors and understanding their contributions to bleeding and thrombosis," said Dr. Kirklin. He also acknowledged that whatever role the current generation of LVAD pumps play in causing thrombosis will not quickly resolve.

"I'm looking forward to a new generation of pumps, but the pumps we have today will probably remain for another 3-5 years."


DR. SMEDIRA

The issue of LVAD pump thrombosis first came into clear focus with publication at the start of 2014 of a report that tracked its incidence from 2004 to mid-2013 at three U.S. centers that had placed a total of 895 LVADs in 837 patients. The annual rate of new episodes of pump thrombosis jumped from about 1%-2% of LVAD recipients throughout the first part of the study period through the end of 2011, to an annual rate of about 10% by mid 2013 (N Engl J Med. 2014 Jan 2;370[1]:33-40).

"The inflection occurred in about 2012," noted Dr. Nicholas G. Smedira, a cardiothoracic surgeon at the Cleveland Clinic. "No one has figured out why" the incidence suddenly spiked starting in 2012 and intensified in 2013, he said. This epidemic of pump thrombosis has produced "devastating complications" that have led to multiple readmissions and reduced cost-effectiveness of LVADs and has affected how the heart transplant community allocates hearts, Dr. Smedira said during his talk at the session. He noted that once the surge in pump thrombosis started, the timing of the appearance of significant thrombus shifted earlier, often occurring within 2-3 months after LVAD placement. There now is "increasing device-related pessimism" and increasing demoralization among clinicians because of this recurring complication, he said.

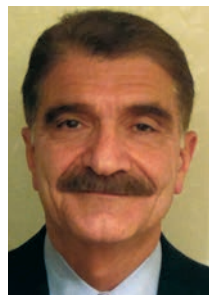
More recent data show the trend toward increasingly higher rates of pump thrombosis continuing through the end of 2013, with the situation during 2014 a bit less clear. Late last year, data from 9,808 U.S. patients who received an LVAD and entered the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) showed that the incidence of pump thrombosis during the first 6 months following an implant rose from 1% in 2008 to 2% in 2009 and in 2010, 4% in 2011, 7% in 2012, 8% in 2013, and then eased back to 5% in the first half of 2014 (J Heart Lung Transplant. 2015 Dec;34[12]:1515-26). The annual rate rose from 2% in 2008 to a peak of 11% in 2013, with 12-month data from 2014 not yet available at the time of this report.

"The modest reduction of observed pump thrombosis at 6 months during 2014 has occurred in a milieu of heightened intensity of anti-co-

Continued on page 23

VIEW ON THE NEWS

Dr. Hossein Almassi, FCCP, comments: With improvements in technology and development of rotary pumps, there has been a significant growth in the use of mechanical circulatory support (MCS) for treatment of end stage heart failure with a parallel improvement in patients' survival and the quality of life.



The authors of this report presented at the 2016 annual meeting of the STS, are authorities in the field of MCS outlining the observed increase in pump thrombosis noted in 2012. The sharp increase in the thrombosis rate is different from the lower incidence seen in the preapproval stage of the pump trial.

It should be noted that the report is related mainly to the HeartMate II left ventricular assist device (LVAD) and not the more recently implanted HeartWare device.

The diagnostic algorithm outlined in the accompanying reference (J Heart Lung Transplant. 2013 July;32[7]:667-70) regarding the diagnosis and management of suspected pump thrombosis is worth reading with the main criteria heralding a potential pump thrombosis being 1)sustained pump power elevation, 2) elevation of cardiac LDH or plasma-free hemoglobin, 3) hemolysis, and 4) symptoms of heart failure.

With further refinements in technology, the field of MCS is awaiting the development of newer LVAD devices that would mitigate the serious problem of pump thrombosis.

NUCALA
THE FIRST TARGETED ANTI-INTERLEUKIN 5 THERAPY FOR SEVERE ASTHMA WITH AN EOSINOPHILIC PHENOTYPE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype.

- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

Important Safety Information

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Hypersensitivity reactions (eg, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration but in some instances can have a delayed onset (ie, days). In the event of a hypersensitivity reaction, NUCALA should be discontinued.

Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster
In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared to none in placebo. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection
It is unknown if NUCALA will influence a patient's response against parasites. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasm, 3% (<1%).

NUCALA IS PROVEN TO:

- **Reduce exacerbations* by 53%** (NUCALA: 0.83/year; placebo: 1.74/year, *P*<0.001)[1]
- **Reduce daily OCS dose while maintaining asthma control** (*P*=0.008)[1]
- **Improve quality of life (SGRQ) with a responder rate of 71% for NUCALA compared with 55% for placebo** (odds ratio of 2.1; 95% CI: 1.3, 3.2)†
  - Statistical hierarchy was not met, endpoint is exploratory, and results are descriptive only[1]

In a 32-week study of patients with severe asthma with an eosinophilic phenotype, NUCALA (n=194) and placebo (n=191), each added to high-dose ICS and at least 1 other controller with or without OCS and dosed once every 4 weeks, were compared to evaluate the frequency of exacerbations. In a 24-week study of 135 patients with severe asthma with an eosinophilic phenotype, NUCALA and placebo were each added to high-dose ICS and at least 1 other controller and dosed once every 4 weeks to compare the percent reduction in daily OCS dose (weeks 20 to 24) while maintaining asthma control.[1]

ICS=inhaled corticosteroids; OCS=oral corticosteroids; SGRQ=St. George's Respiratory Questionnaire.

*Defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients requiring maintenance oral/systemic corticosteroids, exacerbations were defined as at least double the existing maintenance dose for at least 3 days.[1]

†The SGRQ is a validated measure of health impairment for chronic respiratory diseases and is able to address the impact asthma has on a patient's quality of life. Response is defined as a change in score of 4 or more as threshold.[1]

Visit **NUCALAhcp.com** for more information, including patient access programs.

Important Safety Information (cont'd)

ADVERSE REACTIONS (cont'd)

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, 10% of subjects who received NUCALA experienced systemic (allergic and nonallergic) and local site reactions compared to 7% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of subjects who received NUCALA compared to 2% of subjects in the placebo group. Manifestations included rash, pruritus, headache, and myalgia. Systemic nonallergic reactions were reported by 2% of subjects who received NUCALA and 3% of subjects in the placebo group. Manifestations included rash, flushing, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection Site Reactions: Injection site reactions (eg, pain, erythema, swelling, itching, and burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

The data on pregnancy exposures from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are progressively transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy.

Reference: 1. Data on file, GSK.

Please see Brief Summary of Prescribing Information for NUCALA on the following pages.

Nucala®
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

NUCALA®
(mepolizumab) for injection, for subcutaneous use

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. *[See Clinical Studies of full Prescribing Information.]*

Limitations of Use

- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications]*.

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo [*see Adverse Reactions]*. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS

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

- Hypersensitivity reactions *[see Warnings and Precautions]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions]*

Clinical Trials Experience

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

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies of full Prescribing Information]*. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial

Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) and local site reactions was 7% in the placebo group and 10% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-Term Safety

Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

Immunogenicity

Overall, 15/260 (6%) subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was

no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryo-fetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryo-fetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies of full Prescribing Information.]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies *[see Adverse Reactions]*.

Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

OVERDOSAGE

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks (approximately 70 times the MRHD on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients varicella vaccination should be considered before starting treatment with NUCALA.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations]*.

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Manufactured by
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U.S. License Number 1727

Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 11/2015 NCL:1BRS

Cardiothoracic surgeon shortage requires action

BY RICHARD PIZZI
Frontline Medical News

BALTIMORE – By 2035, U.S. cardiothoracic surgeons will see a 61% increase in the national caseload, and potentially a 121% increase in cases for each surgeon, according to a data analysis presented at the annual meeting of the American Association for Thoracic Surgery.

Using data from the American Board of Thoracic Surgery, a research team at Ohio State University performed case load calculations for 2035 based on cases per surgeon per year in 2010. The researchers estimated that the average caseload per surgeon in 2035 will be 299 cases, compared with a 2010 caseload of

Continued on following page

FRONTLINE MEDICAL NEWS

Ripple effect of complications in lung transplant

BY RICHARD MARK KIRKNER
Frontline Medical News

As the frequency of lung transplants rises, so too has the strain on resources to manage in-hospital complications after those operations. Researchers from the University of Pittsburgh have identified independent predictors of short-term complications that can compromise long-term survival in these patients in what they said is the first study to systematically evaluate and profile such complications.

"These results may identify important targets for best practice guidelines and quality-of-care measures after lung transplantation," reported Dr. Ernest G. Chan and colleagues (J Thorac Cardiovasc Surg 2016 April;151:1171-80).

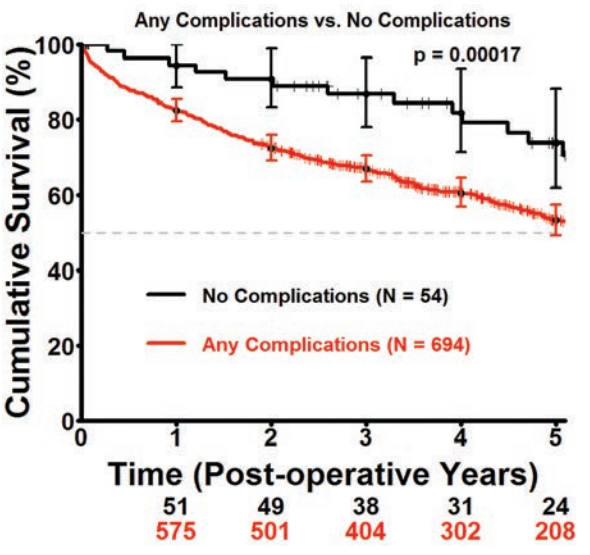
The study involved 748 patients in the University of Pittsburgh Medical Center Transplant Patient Management System database who had in-hospital complications after single- or double-lung transplant from January 2007 to October 2013. The researchers analyzed 3,381 such complications in 92.78% of these patients, grading the complications via the extended Accordion Severity Grading System (ASGS). The median follow-up of the cohort was 5.4 years.

The researchers also classified complications that carried significant decrease in 5-year survival into three categories: renal complications, with a hazard ratio (HR) of 2.58; hepatic, with an HR of 4.08; and cardiac, with an HR of 1.95.

"Multivariate analysis identified a weighted ASGS sum of greater than 10 and renal, cardiac, and vascular complications as predictors of decreased long-term survival," Dr. Chan and colleagues noted.

These findings highlight the need for further analysis into an intriguing aspect of surgical management of complications after high-risk procedures.

In-hospital complications are important predictors of long-term survival, Dr. Chan and coauthors wrote, citing studies from Memorial Sloan-Kettering Cancer Center in New York and the University of Minnesota. (N Engl J Med. 2001;345:181-8; Ann Surg. 2011;254:368-74). They also noted variable findings of several studies with regard to the impact center volume can have on long-term survival, particularly because high-volume centers may be better prepared to manage those complications.



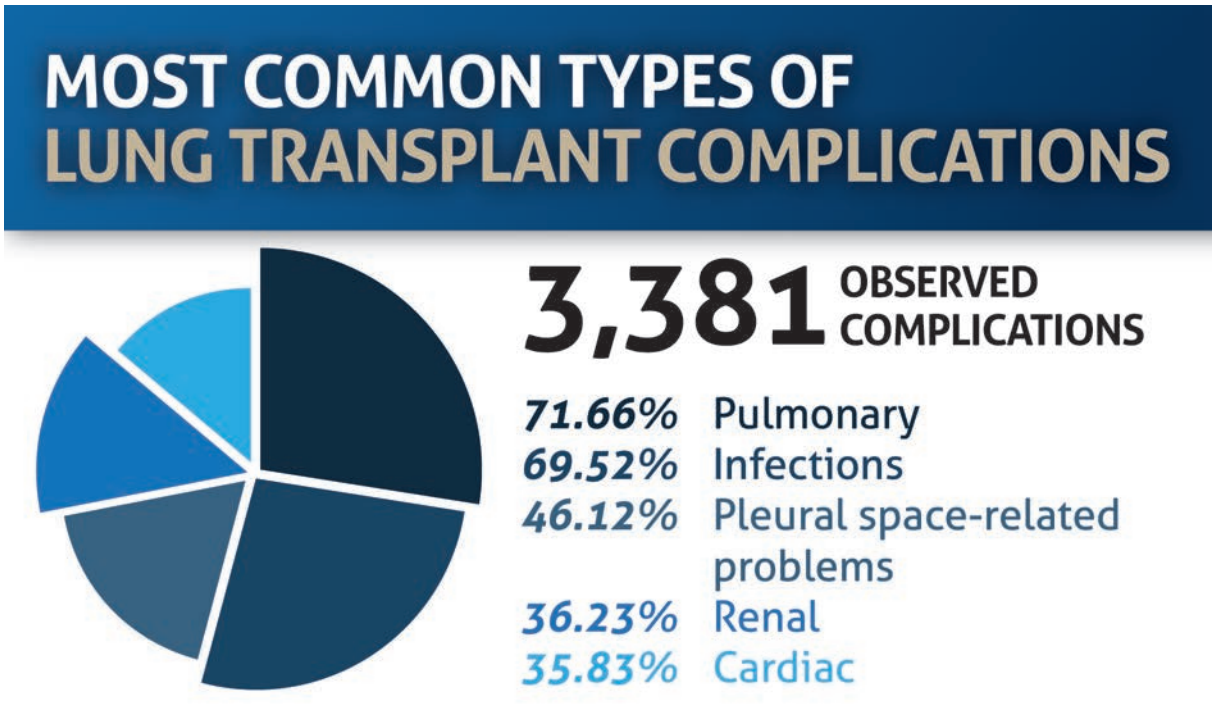
"These important findings highlight the need for further in-depth analysis into an intriguing aspect of surgical management of complications after high-risk procedures," the researchers wrote. Their goal was to create a postoperative complication profile for lung transplant patients.

Of the 748 patients in the study, 7.22% (54) had an uneventful postoperative course. The noncomplication group had a cumulative 5-year survival of around 73.8% vs. 53.3% for the complications group. On average, each patient in the complication group had almost five different complications. The most common were pulmonary in nature (71.66%), followed by infections (69.52%), pleural space–related problems (46.12%), renal complications (36.23%), and cardiac (35.83%). Renal complications accounted for the greatest decrease in 5-year survival at 35.4% vs. 64.4% in patients who did not have renal complications.

Survival rates for other categories of complications vs. the absence of those complications were: hepatic, 18.1% vs. 57.3%; cardiac, 39.5% vs. 62.3%; vascular, 29.4% vs. 58.5%; neurologic, 32.6% vs. 57.1%; musculoskeletal, 27.4% vs. 56.8%; and pleural-space complications, 48.7% vs. 60.3%.

The multivariate analysis assigned hazard ratios to these predictors: age older than 65 years, 1.01; renal events, 1.70; cardiac events, 1.29; vascular events, 1.33; and weighted ASGS sum, 1.08.

The researchers had no financial relationships to disclose.



Continued from page 17

agulation management, greater surgical awareness of optimal pump implantation and positioning and pump speed management. Thus, one may speculate that current thrombosis risk-mitigation strategies have contributed to reducing but not eliminating the increased thrombosis risk observed since 2011," concluded the authors of the report.


DR. PAGANI

Surgeons and cardiologists must now have a high index of suspicion for pump thrombosis in LVAD recipients, and be especially on the lookout for four key flags of a problem, said Dr. Kormos. The first is a rising LDH level, but additional flags include an isolated power elevation that doesn't correlate with anything else, evidence of hemolysis, and new-onset heart failure symptoms. These can occur individually or in some combination. He recommended following a diagnostic algorithm first presented in 2013 that remains very valid today (J Heart Lung Transplant. 2013 July;32[7]:667-70).

Dr. Kormos also highlighted that the presentation of pump thrombosis can differ between the two LVADs most commonly used in U.S. practice, the HeartMate II and the HeartWare devices. A LDH elevation is primarily an indicator for HeartMate II, while both that model and the HeartWare device show sustained, isolated power elevations when thrombosis occurs.

Dr. Pagani, Dr. Kirklin, and Dr. Smedira had no disclosures. Dr. Kormos has received travel support from HeartWare. Dr. Kilic has been a consultant to Thoratec and a speaker on behalf of Baxter International.

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Continued from previous page

135 per surgeon. This increase is not matched by the number of surgeons currently trained and certified annually.

Dr. John Ikonomidis, chief of the division of cardiothoracic surgery at the Medical University of South Carolina in Charleston, and a discussant on the presentation, said surgeon retirements and an increase in the population needing treatment have put the specialty in a bind.

"We have a bit of a crisis now, honestly, but this particular paper puts it in even further perspective," Dr. Ikonomidis said in a video interview. "By 2035 we're looking at a 3,000-surgeon shortage, relative to what would be available." He noted that approximately 90 medical residents per year are certified as cardiothoracic surgeons, a rate which will not produce enough CT surgeons to meet the projected shortage.

"We need to continue to have this conversation," he concluded. "It is a reminder that the predictions we made 15 years ago appear to be true, and we probably need to do something about it, at least in the short term."

Dr. Ikonomidis reported no relevant financial disclosures.

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Paperwork snarls limit at-school access to asthma meds

BY KARI OAKES
Frontline Medical News

BALTIMORE – Four out of five children with asthma didn't have access to their medication at school because the proper paperwork was missing, according to a survey of 10 inner-city Milwaukee elementary schools.

The number of students who had the required physician-signed authorization forms remained low throughout the school year, said Dr. Santiago Encalada, a pulmonary fellow at the Medical College of Wisconsin, Milwaukee.

Dr. Encalada cited administrative hurdles, lack of standardization, and challenges in school-physician-family communication as barriers to children's access to asthma medication at school. Although school nurses in Milwaukee have standing orders for emergency albuterol administration, they otherwise need physician signatures on school-generated forms to administer both rescue and prophylactic asthma administration.

Access to even basic asthma care necessities were lagging in the 10 inner-city Milwaukee elementary schools surveyed and a significant disparity existed even within this population.

In a study whose purpose was to assess the percentage of children with asthma who had appropriate orders on file in a sample of 10 Milwaukee inner-city schools, the schools had orders on file for just 11% of students, on average, at the beginning of the 2014-2015 school year. At the second assessment in January 2015, the average number of students with orders on file at each school had risen to 22%, with schools that had performed better earlier also showing greater gains at mid-year. However, the June 2015 assessment showed that the gains did not continue, with the schools' aggregate average of 21% of students with appropriate orders showing no improvement from mid-year.

The number of students with

VIEW ON THE NEWS

Dr. Susan Millard, FCCP: comments: The issues identified in this article are huge and not just an occurrence in the inner cities. The critical problem is that the children are even more at risk when living in the inner cities and for sudden death due to asthma. Having one form for the whole state would help tremendously because we could print out an asthma action plan and the form for the school and then fax it directly!

asthma in schools varied from about 40 to nearly 200. Numbers varied through the school year as enrollments shifted in these high-need schools, said Dr. Encalada, who presented his findings during a poster session at the annual meeting of the Pediatric Academic Societies. In general, the schools with lower enrollments tended to do better with having orders on file, although statistical analysis was not performed for this variable.

"On average, 80% of asthmatic students in the inner city schools we studied did not have school forms or orders available for life-saving asthma rescue medications, with significant variation between schools. Our findings show that access to even basic asthma care necessities are lagging for this vulnerable population, and a significant disparity exists even within this population," said senior author Nicholas Antos, associate director of the Cystic Fibrosis Center at Milwaukee's Children's Hospital of Wisconsin.

In interviews and discussion with school nurses and physicians' offices, Dr. Antos and Dr. Encalada found that there were often simple but fundamental misunderstandings that impeded the proper flow of paperwork. For example, schools in

Continued on following page

Continued from previous page

Milwaukee do not have standardized forms that authorize administration of prescription medications at school, so forms may be confusing to providers and their staff. Privacy concerns sometimes impeded the ability of clinic staff to authorize treatment for students. Also, the inevitable shuffle of paperwork in school-aged families meant that the forms sometimes were simply lost on the way to school.

Understanding the barriers in the process both on the school side and in physician offices has helped Dr. Antos, Dr. Encalada, and their colleagues to start to build a better pathway.

For example, a module has been built into the EHR asthma visit template that allows easy generation of a school form and asks for patient consent for release of information to the schools.

KARI OAKES/FRONTLINE MEDICAL NEWS

"Privacy concerns can prevent students from receiving treatment." said Dr. Encalada.

"To help address these problems, we have devised interventions to improve the way school nurses can contact clinicians, and helped design innovative standardized Asthma Action Plans that can double as school orders," Dr. Antos said.

In addition to working with local providers and schools, Dr. Encalada and Dr. Antos have reached out to pediatric societies and the American Academy of Asthma, Allergy, and Immunology (AAAAI). Emphasizing the need for "education of stakeholders of all types," Dr. Antos said that change "may be difficult, but we hope with the support of pediatric organizations, the AAAAI, and school administrators, we can begin to break down the barriers preventing quality and timely communication with school nurses."

The authors had no financial disclosures.

The study was funded by the Centers for Disease Control and Prevention through the Wisconsin Asthma Coalition (WAC).

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Early caffeine did not help, may harm preemies

BY MITCHEL L. ZOLER
Frontline Medical News

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BALTIMORE – Early initiation of caffeine treatment in premature neonates on mechanical ventilation did not cut the time to when these babies could successfully wean off the ventilator, according to findings of a single-center, randomized controlled study of 83 children.

The results also showed an "unexpected" trend toward increased mortality among the neonates who received early caffeine treatment, Dr. Cynthia M. Amaro reported at the annual meeting of the Pediatric Academic Societies. This signal of elevated mortality with caffeine treatment prompted the study's data and safety monitoring board to prematurely stop the trial, limiting enrollment to just 75% of the number originally planned in the study's design, thereby raising questions about the reliability of the primary-endpoint finding that early caffeine treatment did not result in the benefit of a reduced time to extubation.

Dr. Amaro said that she and her associates ran the study to address what had emerged as a significant area of doubt in routine U.S. practice on how to best use caffeine treatment in this neonatal population following publication of findings from the landmark Caffeine for Apnea of Prematurity (CAP) Trial (N Engl J Med. 2006 May 18;354[20]:2112-21). Results from the CAP Trial had shown in nearly 2,000 randomized, premature infants that treatment with caffeine led to significantly fewer episodes of bronchopulmonary dysplasia as well as quicker time to extubation of mechanical ventilation. Caffeine or other methylxanthines stimulate an infant's respiratory center to allow faster extubation.

Ever since that publication a decade ago, "clinicians have been using caffeine earlier and more liberally, without really good data to support its early use in mechanically-ventilated preterm babies," explained Dr. Amaro, a neonatologist at the University of Miami and Holtz Children's Hospital in Miami.

Based on the new findings from the study she reported, "we are now not routinely initiating caffeine in mechanically ventilated preterm babies and just using caffeine immediately before extubation to treat apnea of prematurity. This returns caffeine treatment to the way it was used in the CAP Trial," she said. "Further studies are needed before we can say what is best for early treatment of these preterm babies," Dr. Amaro said in a video interview.

Her report led to a flurry of comments during the question period, with several pediatricians voicing concern about the reliability of results from a study that followed only 83 patients because of its premature termination.

"The data and safety monitoring board's decision is a big issue," said Dr. Carl E. Hunt, a pediatrician at the Uniformed Services University of the Health Sciences in Bethesda, Md. "There is a literature that shows results of studies can be very different when they stop early. It's unfortunate because we don't have other prospective data, and it may now be hard to do a large randomized, controlled trial" of early caffeine treatment, Dr. Hunt said.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

"Preterm infants require further study." said Dr. Amaro.

While Dr. Amaro conceded that premature termination limited her study's size, she also asserted that her analyses confirmed the validity of the finding of no benefit from early caffeine treatment. "We projected to full enrollment, and there still was no difference in the time to first successful extubation," she said.

Her study enrolled preterm infants during January 2013–December 2015 born at 23-30 weeks' gestation who required mechanical ventilation during their first 5 days. Randomization assigned 41 infants to receive a 20-mg/kg bolus of caffeine, followed by a maintenance dosage of 5 mg/kg that continued until extubation, while 42 patients received placebo and did not get caffeine until just before attempted extubation. The bolus and maintenance caffeine dosages tested were identical to those used in the CAP Trial.

The researchers defined successful extubation as keeping a child off restart of mechanical ventilation for more than 24 hours. The average gestational age of the enrolled neonates was 26 weeks, their average weight was 700 g, and intubation started an average of 3 hours after delivery.

The study's primary endpoint, age at first successful extubation, was an average of 24 days among the neonates treated with caffeine and 20 days in those on placebo, Dr. Amaro reported. Mortality occurred at an average of 30 days after delivery in the caffeine recipients and after an average of 10 days in the controls. The incidence of death was 22% in those on early caffeine and 12% among those in the placebo group, an excess of four deaths in the intervention arm that was not statically significant.

A recent review of more than 29,000 matched very-low-birth-weight infants managed in routine practice showed that neonates who received early caffeine had an adjusted mortality risk that was 23% higher than that of matched infants not receiving early caffeine, Dr. Amaro noted (J Pediatrics. 2014 May;164[5]:992-8).

The incidence of bronchopulmonary dysplasia also did not show a statistically significant difference between the two study arms, 46% among those on early caffeine and 53% in the placebo group. Patients on early caffeine also had higher rates of necrotizing enterocolitis, more episodes of necrotizing enterocolitis requiring surgery, and more intraventricular hemorrhages, but none of these differences reached statistical significance.

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VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: Apnea of prematurity is a very common occurrence. We are excited to have new data but I am in agreement that a larger multicenter study is extremely important before instituting a protocol change.

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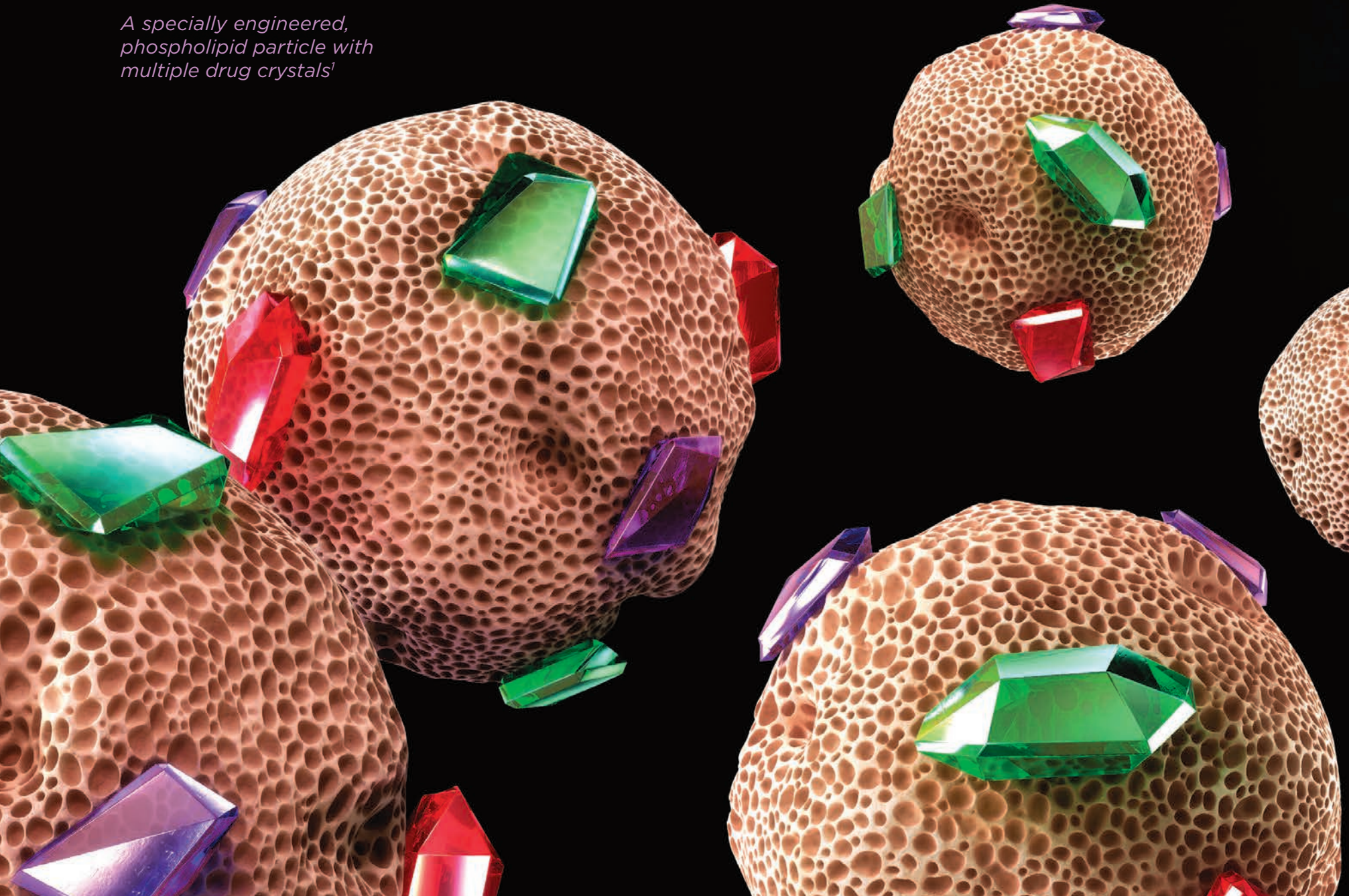

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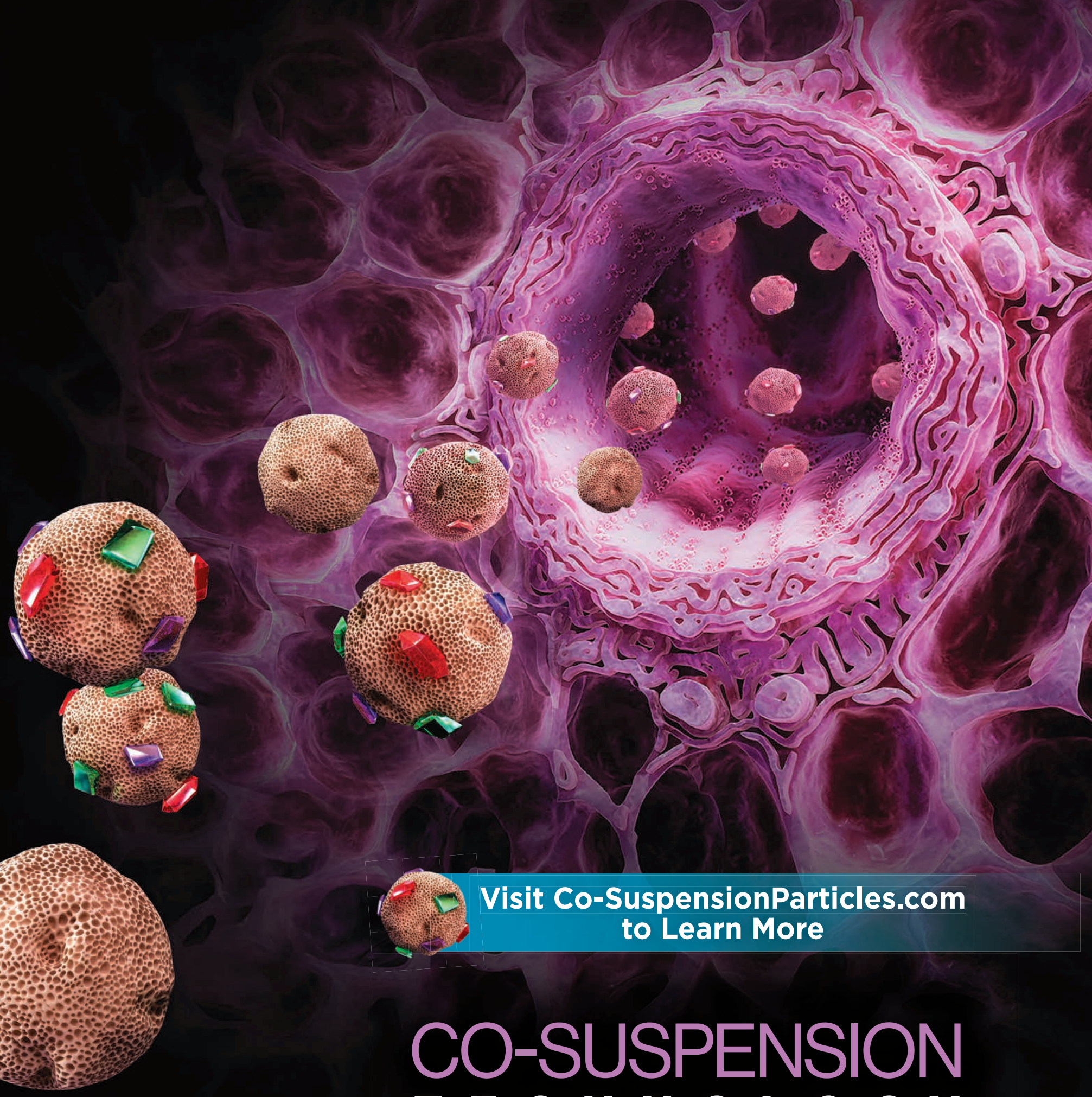

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FDG-PET/CT leads pack for pretreatment staging

BY HEIDI SPLETE
Frontline Medical News

For pretreatment staging of small-cell lung cancer (SCLC) the use of positron-emission tomography combined with CT was more sensitive compared with several other alternative modalities, according to a new report based on a review of studies.

Overall, positron emission tomography using [F]-fluorodeoxyglucose as a radiotracer combined with CT (FDG-PET/CT) had greater sensitivity for the detection of osseous metastases than did either bone scintigraphy or CT alone, according to Dr. Jonathan R. Treadwell, Ph.D., of ECRI Institute–Penn Medicine's Evidence-based Practice Center in Plymouth Meeting, Pa., and his colleagues.

In addition, the researchers concluded that adding FDG-PET/CT to the protocol for patients who have undergone standard staging increased the sensitivity for detecting additional metastases. Data on endobronchial ultrasound were insufficient to draw any conclusions about its relative value.

The findings generally line up with those that are found in recent guidelines from the American College of Radiology (ACR) and American College of Chest Physicians (ACCP).

In 2014, the ACR gave the highest rating of "usually appropriate" (with regard to staging SCLC) to FDG-PET/CT from skull base to mid-thigh, while bone scintigraphy was rated as "may be appropriate" and not necessary if PET/CT had been done, the researchers wrote.

The 2013 ACCP guideline "suggested" FDG PET instead of bone scintigraphy for patients with limited disease, they added.

The researchers reviewed data from seven studies to assess the accuracy and effectiveness of several imaging modalities for the pretreatment staging of SCLC.

The report was generated for the Agency for Healthcare Research and Quality (AHRQ) as part of its Comparative Effectiveness Review series, and is not an official AHRQ position, the researchers noted.

Combining FDG-PET with CT scanning has demonstrated even greater effectiveness at identifying malignant tumors and metabolically active metastases than has PET alone, because the CT allows for more localized anatomic detail, the researchers explained.

"False negative scans usually result from non–metabolically active sites of tumor or from suboptimal quality studies," they said, while false positives using FDG-PET are usually attributed to inflammation or metabolically active infection.

The meta-analysis included data on endobronchial ultrasound, which involves ultrasound to view structures inside and adjacent to the airway; bone scintigraphy, a less expensive planar molecular imaging technique; and CT alone.

Comparative evidence on pretreatment staging for SCLC is limited, according to the researchers. The data did not allow them to determine how FDG-PET/CT compared to other imaging in terms of specificity, and any type of imaging can yield false positives, they said.

However, higher sensitivity alone can benefit patients in terms of improving patient selection for optimal therapy, sparing patients chemotherapy if not needed, and improving the prediction value of ongoing research, they noted.

"Although high-quality evidence may not be voluminous, I think most physicians would agree with the conclusion that a bone scan is not mandatory in the work-up of possible SCLC, if a PET/CT has been done," Dr. W. Michael Alberts of the Moffitt Cancer Center in Tampa, Fla., said in an interview.

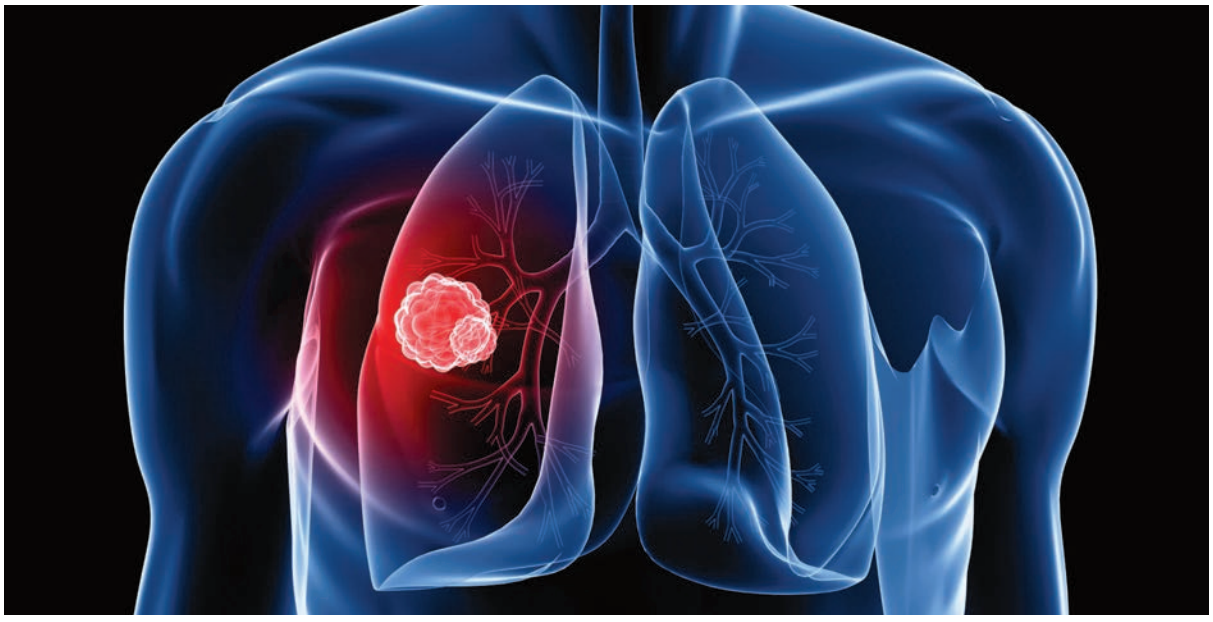
Cost might play a role in why the guidelines are being issued at this time, he noted, because "the initial work-up of the patient with suspected SCLC may prove to be quite expensive, and the elimination of a superfluous test may be a fiscal winner." However, more research is needed in this area, particularly in the areas of including the order of pretreatment testing and the incorporation of new procedures and imaging modalities, he added.

"Perhaps more intellectually challenging, however, might be the question of why SCLC is becoming less common, or why has improvement in treatment been so slow compared to NSCLC," he added.

The researchers had no financial conflicts to disclose.

BMI, smoking affect mutation pattern in NSCLC

BY JENNIFER SHEPPHIRD
Frontline Medical News



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The prevalence of mutations in oncogenic driver genes is correlated to smoking dose and body mass index, according to a prospective epidemiology study of environmental factors and mutation frequencies in non–small-cell lung cancer that was published online.

In the Japan Molecular Epidemiology for Lung Cancer study, Dr. Tomoya Kawaguchi and colleagues found that increased mutation frequencies in TP53, KRAS, and NFE2L2 correlated with smoking dose ($P < .001$ for all), whereas decreased mutation frequencies were observed in EGFR ($P < .001$) and CTNNB1 ($P = .030$).

The number of KRAS mutations in smokers increased in proportion to body-mass index (BMI) increases ($P = .026$).

Simultaneous mutations in EGFR and CTNNB1 suggested possible biological relevance; 88% of CTNNB1 mutations (15/17) occurred with EGFR mutations.

TP53 and NFE2L2 mutations were more frequent in advanced-stage disease, wrote Dr. Kawaguchi of the department of respiratory medicine at Osaka (Japan) City University and colleagues (J Clin Oncol. 2016 May 9. doi: 10.1200/JCO.2015.64.2322).

Although smoking is the most studied cause of lung cancer, about one-quarter of lung cancers worldwide occur in never-smokers.

"It remains elusive which environmental factors contribute to the EGFR mutations that are frequently observed in never-smokers," the investigators wrote. "In this study, the prevalence of EGFR mutations was higher in those who had more [environmental tobacco smoke], although this difference did not reach the level of statistical significance in the sample size.

More detailed methods to detect the mutations (e.g., digital polymerase chain reaction) might yield more precise information."

Levels of sex hormones were not significant factors in mutation frequencies, but the investigators found that estrogen receptor was more highly expressed in never-smokers than smokers, and the presence of estrogen receptor was associated with EGFR mutations in younger patients.

The investigators studied environmental influences on lung cancer by collecting information by questionnaire and by detecting mutations in 72 candidate genes from 876 patients with stage I to IIIB non–small-cell lung cancer (441 ever- and 435 never-smokers).

In total, 622 patients had at least one mutation, and 860 mutations were observed.

Dr. Kawaguchi and colleagues also examined patterns of estrogen-receptor expression by immunohistochemical staining and evidence of human papillomavirus (HPV) infection by a polymerase chain reaction–based microarray system.

Contrary to retrospective analyses that had pointed to a link between HPV and NSCLC, this prospective study showed little evidence for HPV in early NSCLC.

Dr. Kawaguchi and several coauthors reported having financial ties to Chugai Pharmaceutical and Eli Lilly. Nippon Boehringer Ingelheim, Daiichi Sankyo, and Novartis were among the other funding sources for some of the authors.

Demographics linked with NSCLC surgery

BY WILLIAM PERLMAN
Frontline Medical News

The demographic characteristics of neighborhoods are associated with the odds of receiving surgical treatment for early non–small-cell lung cancer (NSCLC), according to a study published in Cancer Epidemiology, Biomarkers & Prevention.

Living in areas with higher economic deprivation was associated with lower odds of receiving surgery for both black and white patients, in a retrospective study of 8,322 patients with early-stage NSCLC.

"The results of this study are intended to bring importance to segregation and other characteristics as determinants of lung cancer outcomes. As a result, what is learned from these epidemiologic findings can be applied to interventions and public policies to improve patient outcomes and contribute to the difficult and complex task of reducing racial health disparities," wrote Dr. Asal M. Johnson of Stetson University and her associates (Cancer Epidemiol Biomarkers Prev; 25[5];750-8).

The early-stage NSCLC patients were identified in the Georgia Comprehensive Cancer Registry from 2000 to 2009 to determine the effects of residential segregation and other neighborhood characteristics on the odds of receiving surgical treatment and the risk of death based on 5-year survival.

Three separate multilevel models were employed: A, economic deprivation; B, segregation; and C, segregation and economic deprivation. Individual-level variables (age, sex, and tumor grade) and area-level variables (place of residence, educational attainment, and elderly concentration) were controlled for in all models.

Regarding odds of surgical intervention, model A showed that living in areas with higher economic deprivation was associated with lower odds of receiving surgery for both black and white patients.

Model B demonstrated that living in highly segregated areas was associated with lower odds of receiving surgery among black patients only.

Living in areas with higher economic deprivation was associated with lower odds of receiving surgery for both black and white patients.

For white patients, no significant associations were observed between living in areas with combined segregation-deprivation and receipt of surgery using model C; however, living in segregated areas, regardless of the level of economic deprivation, was associated with decreased odds of receiving surgery for black patients.

As for 5-year survival, all three models indicated no effects of economic deprivation, segregation, or the combination of segregation and deprivation on survival among white patients. Models A and B showed no effects of economic deprivation or segregation on survival in black patients. In model C, however, the combination of high residential segregation and high economic deprivation was associated with a 31% higher risk of death in these patients, even after surgery. A limitation of this study was that individual demographic variables only included race, gender, and age, according to the authors.

Funding was provided by Stetson University. The authors reported no conflicts of interest.

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Repeat SICU admissions trigger palliative consult

BY THERESE BORDEN
Frontline Medical News

ICU readmission was most predictive of the need for palliative care among patients in the surgical intensive care unit, based on a study of six potential trigger criteria associated with in-hospital death or discharge to hospice.

To facilitate proactive case findings of patients who would benefit from a palliative care consult, a team of surgical ICU and palliative care clinicians at the Icahn School of Medicine at Mount Sinai, N.Y., developed and tested a system of palliative care triggers. The study was published online in the Journal of Critical Care (http://dx.doi.org/10.1016/j.jcrc.2016.04.010).

Based on a literature review, the researchers created a six-item list of potential triggers for palliative care:

length of stay over 10 days, ICU readmission, intensivist referral, status post cardiac arrest, metastatic cancer, and a match of two or more on a set of secondary criteria.

Data were collected for the period from Sept. 4, 2013, through May 30, 2014, at the surgical ICU of a 1,170-bed tertiary medical center. Patients who received a palliative care consultation were compared with those who did not, and the trigger list was tested for accuracy in predicting patient outcomes.

The primary outcomes were hospital death, hospice discharge, and a combined endpoint of these two outcomes. Patients who died in the hospital or were released to hospice care were assumed to be those most in need of a palliative care consult.

Bivariate analysis was done to calculate the unadjusted odds ratios of individual triggers to each of these outcomes. Then, the team used logistic regression analysis to calculate the adjusted odds ratios of triggers to outcomes.

Of the 512 patients admitted to the SICU in the study period, those not discharged by the end of the study were excluded, leaving 492 patients in the study.

Bivariate analysis found that all of the triggers were significantly associated with in-hospital death.

With the multivariate analysis and adjusted odds ratios, SICU readmission, status post cardiac arrest, metastatic cancer, and secondary triggers were significantly associated with hospital death.

For the combined outcome of hospital death or release to hospice care, the relationships were stronger. In particular, repeat SICU readmissions and metastatic cancer triggers were

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strongly associated with the combined outcome (odds ratio, 19.41, CI 5.81-54.86 and OR, 16.40, CI 4.69-57.36, respectively).

The secondary triggers did not show the same strength of association, although they were associated significantly with the combined outcome (OR, 4.41, CI 2.05-9.53).

The most prominent finding is the strength of repeat SICU admissions with the hospital death or release to hospice.

The strong relationship between repeat SICU admission and outcomes led the researchers to conclude "that one might consider adapting this clinical criterion as a standalone criterion. This would require all patients who are readmitted to the SICU to be seen by palliative care to assess their overall goals of care and understanding of their serious illness. This approach may be particularly useful for smaller palliative care teams that do not have the resources to screen daily with a series of triggers."

The American Federation of Aging Research and the National Institute on Aging funded the study.

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CRITICAL CARE COMMENTARY: "Personalizing" ICU nutrition

BY DR. PAUL E. WISCHMEYER

We in the ICU community are proud that over the last 10 years we have finally begun to reduce mortality following severe sepsis. But, a fundamental question that must be asked is, "Are we winning many battles in our ICUs, but ultimately losing the war?" The same data showing we have reduced in-hospital mortality from sepsis by half in the last 10 years also reveals we have tripled the number of patients going to rehabilitation settings (Kaukonen et al. *JAMA*. 2014;311[13]:1308). Moreover, how many of these 'ICU-survivors' even survived a year? Troubling data reveals 40% to 50% of the mortality within 12 months of ICU admission occurs after patient leaves the ICU (Wischmeyer et al. *Crit Care*. 2015;19(suppl 3):S6. Commonly, patients placed in nursing homes or rehabilitation settings never return home to their loved ones or regain a meaningful quality of life (QoL). Thus, authorities from leading ICU trials groups have stated that given low ICU mortality and the many patients sent to rehabilitation, QoL should become the primary endpoint of future ICU trials.

Can We Do Better for Our ICU Patients? The Role of 'Personalized' Nutrition Delivery

Recent research indicates ICU patients lose as much as a kilogram of lean body mass (LBM) and/or weight per day (Wischmeyer et al. *Crit Care*. 2015;19(suppl 3):S6. Patients may gain weight post-ICU, but much of this is fat mass, not functional LBM. This is not surprising, as data from burn patients demonstrate the catabolic/hypermetabolic state can persist for up to 2 years posthospital discharge and may markedly hinder recovery of LBM and QoL (Wischmeyer et al. *Crit Care*. 2015;19(suppl 3:S6).

The key question then becomes, "Can we change our practice and begin to create survivors instead of victims?" One component of improving post-ICU QoL may be personalized or targeted nutrition delivery. Targeted nutrition delivery emphasizes utilization of long-standing basic metabolism data showing nutritional needs change significantly over the course of critical illness. In the early acute phase of critical illness, massive mobilization of the body's calorie reserves occurs as muscle and lipid stores are broken down to drive glucose production (Gillis et al. *Anesthesiology*. 2015;123:1455). This evolutionarily conserved response provides energy to escape an attacker and recover from initial injury. This metabolic stress response can generate 50% to 75% of a patient's glucose needs, and this glucose generation is not suppressed by feeding (Oshima et al. *Clin Nutr*. 2015 Nov 7. pii: S0261-5614(15)00270-8. doi: [Epub ahead of print]). Further, the acute phase of sepsis/trauma does not lead to hypermetabolism but rather a total energy expenditures (TEE) to resting energy expenditure (REE) ratio of ~1.0 (Uehara et al. *Crit Care Med*. 1999;27[7]:1295). Thus, caloric need does not increase in acute phase (the first few days post-ICU admission). In fact, more severe shock lowers measured REE as the body appears to hibernate. During later chronic/recovery phases, massive increases in metabolic needs occur, with TEE increasing up to ~1.7-fold above REE (Uehara et al. *Crit Care Med*. 1999;27[7]:1295). These data hypothesize we should feed less nonprotein calories early post-ICU admission to prevent risk of "overfeeding" and markedly increase calorie delivery during recovery. We also know protein losses increase fourfold in first 24 hours of critical illness (Wischmeyer et al. *Crit Care*. 2015;19(suppl 3):S6. Unfortunately, large international surveys indicate we deliver ~0.6 g/kg/day of protein for the first 2 weeks post-ICU admission. This is less than half of the latest SCCM/ASPEN ICU guideline recommended protein delivery (1.2 to 2.0 g/kg/d) (McClave et al. *JPEN*. 2016;40[2]:159). Thus, an ideal targeted strategy may be ~15 kcal/kg/day of total energy during the acute phase, while ensuring patients receive optimal protein delivery (1.2 to 2.0 g/kg/d) immediately post-ICU admission. Reduced calorie delivery during the acute phase is not ideal in malnourished patents (NUTRIC Score (w/o Il-6) >5) who are unlikely to have metabolic reserves sufficient to generate endogenous energy supply. Ironically, our most recent SCCM/ASPEN guidelines emphasize these points by suggesting hypocaloric parenteral nutrition (PN) (≤ 20 kcal/kg/d) with adequate protein (≥1.2 g/kg/d) in patients requiring PN over first ICU week. Further, new guidelines suggest provision of trophic feeds for the initial phase of sepsis, advancing after 24 to 48 hours to >80% of target energy *with early delivery of 1.2 to 2.0 g protein/kg/d*. Given limited commercially available high-protein, low-kcal enteral feeding options, total parenteral nutrition (TPN) or enteral protein supplements will be required to achieve this. TPN is now a significantly safer route to achieve this as three recent large trials of TPN vs enteral nutrition (EN) in the ICU have shown TPN use is no longer associated with increased infection risk (Wischmeyer et al. *Crit Care*. 2015;19(suppl 3):S6). In support of early TPN use, the new SCCM/ASPEN guidelines indicate in any patient at high nutrition risk, when EN is not feasible, exclusive PN should be initiated as soon as possible post-ICU admit.


DR. WISCHMEYER

Targeted Nutrition in Recovery Phase? Significantly Increased Protein/Calorie Needs!

Data from the landmark "Minnesota Starvation Study" performed at the end of World War II demonstrate a healthy 70-kg human, following significant weight loss, requires an average of 5,000 kcal/day for 6 months to 2 years to fully regain lost LBM and weight (Kalm et al, *J Nutr*. 2005;135[6]:1347). As many ICU patients suffer similar marked weight/LBM loss, we must consider that significant calorie/protein delivery will be required to restore this lost LBM and QoL post-acute phase. This is supported by metabolism data showing the average TEE in the second week of ICU care was 47 kcal/kg/d in sepsis and 59 kcal/kg/d in trauma (Uehara et al. *Crit Care Med*.1999;27[7]:1295). Although this is well beyond what most providers deliver to recovering ICU patients, these are actual measured metabolic requirements of our patients as they recover – and with early ICU mobility programs, this delivery may be vital.

This demands that we ask, "Is it possible our patients have been unable to recover their QoL post-ICU for months to years due to our lack of understanding of their fundamental metabolic needs in different phases of illness?" This concept of adequate protein/calorie delivery improving QoL is exemplified in recent data showing ICU patients mechanically ventilated >8 days who received low nutritional adequacy over first ICU week (<50% calorie/protein needs) had an increased mortality vs patients receiving higher nutritional adequacy (>80% calorie/protein needs) (Wei et al. *Crit Care Med*. 2015;43[8]:1569). These data also demonstrate that every 25% increase in calorie/protein delivery in the first ICU week results in an improvement in 3-month post-ICU physical QOL scores (via SF-36), with medical ICU patients showing significant improvements in both 3- and 6-month SF-36 scores.

Finally, we must ask if patients leaving our ICUs can consume ade-

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©Andrei Malov/Thinkstock

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quate calories/protein to optimally recover. Recovering patients are challenged by loss of appetite and lack of education around diet optimization. To address this, a large body of data demonstrates oral nutrition supplement (ONS) must become fundamental in our post-ICU/hospital discharge care. Numerous meta-analyses in a range of hospitalized patients demonstrate ONS reduces mortality, reduces hospital complications, reduces hospital readmissions, shortens length of stay, and reduces hospital costs (Cawood et al. *Ageing Res Rev*. 2012;11[2]:278). Finally, a recent 78-center randomized trial in 652 patients demonstrated high-protein ONS with beta-hydroxy beta-methylbutyrate (an anabolic amino acid-derivative) (HP-HMB) could reduce 90-day mortality by 50% in malnourished elderly patients posthospitalization (Deutz et al. *Clin Nutr*. 2016;35[1]:18).

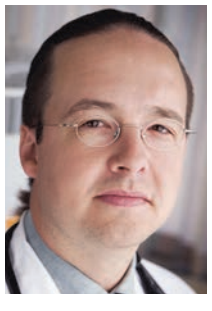
In conclusion, we need to consider basic metabolism and historic understanding of starvation and recovery to deliver 'personalized' nutrition to our ICU patients. If we are to optimize patient outcomes, we must realize patients' nutritional needs change over time. Further, we must learn to target and incorporate nutritional therapies, such as vitamin D, probiotics, and anabolic/anticatabolic agents, to optimize our patients' chance to survive and thrive against all evolutionary odds. If we are to begin winning this war on long-term ICU outcomes and start creating survivors…and not victims, we must ensure every patient gets the right nutrition at the right time!

Dr. Wischmeyer is Professor of Anesthesiology and Pediatrics (Nutrition section), University of Colorado School of Medicine, Denver.

Disclosures/ Conflicts of Interest: Dr. Wischmeyer has received grant funding related to this work from the NIH NHLBI **R34 HL109369**, Canadian Institutes of Health Research, Baxter, Fresenius, Lyric Pharmaceuticals, and Medtronics. Dr. Wischmeyer has served as a consultant to Nestle, Abbott, Fresenius, Baxter, Medtronics, Nutricia, and Lyric Pharmaceuticals for research related to this work. Dr. Wischmeyer has received honoraria or travel expenses for lectures on improving nutrition care in illness from Abbott, Fresenius, and Medtronics.

VIEW ON THE NEWS

Dr. Lee Morrow, FCCP, comments: This installment of Critical Care Commentary ponders a fundamental ICU dilemma – one that is common to ALL critically ill patients – nutrition. Despite decades of randomized trials, ICU practitioners misinterpret and/or erroneously apply such data regarding how and when our patients should be fed. Dr. Wischmeyer's observations regarding the evolving standards for ICU nutrition, based on the recently updated ASPEN Guidelines, highlight the differences in outcomes based on whether we 'try' or whether we 'succeed' in providing the right calories and protein at the appropriate stage of each patient's illness.



ECLS May Save Mother and Fetus

BY RICHARD MARK KIRKNER
Frontline Medical News

In pregnant women with acute respiratory distress syndrome, extracorporeal life support can be effective and safe for both the mother and fetus, according to a meta-analysis of 332 articles published in the April issue of the Journal of Thoracic and Cardiovascular Surgery (2016;151:1154-60).

Dr. Sarah A. Moore and her coauthors at the University of New Mexico, Albuquerque, reported that their literature search yielded a total of 45 patients treated with extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO).

The reports were published from 1991-2015.

Dr. Moore and her colleagues also reported on the first successful use

of ECLS in a pregnant patient at their own institution with life-threatening hantavirus cardiopulmonary syndrome.

The researchers extrapolated from the literature, which consisted primarily of case reports and small case series.

In the 45-patient study cohort, the survival rate was 77.8% after ECLS for mothers and 65.1% for the fetuses.

In the 45-patient study cohort, the survival rate was 77.8% after ECLS for mothers and 65.1% for the fetuses.

The average gestational age was 26.5 weeks, ranging from 28 to 43 weeks, and the patients were on ECLS for an average of 12.2 days, with a range of one to 57 days.

The most common reason for ECLS in this cohort was severe H1N1 influenza, otherwise known as swine flu, complicated with acute respiratory distress syndrome (ARDS).

The largest series, from France, involved 11 pregnant women treated

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with ECMO for severe ARDS secondary to severe H1N1 influenza (PLoS One. 2010;5:e13112).

Unlike other reports, the New Mexico meta-analysis did not include postpartum patients.

The mitigating case for the study was a previously healthy 25-year-old pregnant woman who was in respiratory failure with hantavirus cardiopulmonary syndrome (HCPS) when she arrived at University of New Mexico Health Sciences Center.

ECLS in pregnant women is not without its complications; the most common was major bleeding.

Despite mechanical ventilation, the patient remained severely hypoxic and developed worsening hypertension.

"The patient was placed on venoarterial ECMO for 72 hours, recovered without complications, and delivered a healthy infant," Dr. Moore and her colleagues said. "The mother and son remain asymptom-

atic 6 years later."

Dr. Moore and her colleagues said strategies used in the nonpregnant population with ARDS might not be appropriate in pregnant mothers for two reasons: permissive hypercapnia may harm the fetus; and prone positioning can be difficult for women in late-term pregnancy.

Also, corticosteroids for H1N1 influenza have been controversial.

That doesn't mean ECLS in pregnant women is not without its complications; the most common was major bleeding, reported in seven of the reviewed articles.

Other complications included

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OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see package insert for full Prescribing Information, including Patient Information

INDICATIONS AND USAGE: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSAGE AND ADMINISTRATION: Testing Prior to OFEV Administration: Conduct liver function tests prior to initiating treatment with OFEV *[see Warnings and Precautions]*. **Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. **Dosage Modification due to Adverse Reactions:** In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV *[see Warnings and Precautions and Adverse Reactions]*. Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) *[see Warnings and Precautions and Adverse Reactions]*. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Elevated Liver Enzymes: The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment *[see Use in Specific Populations]*. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN *[see Use in Specific Populations]*. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations. **Gastrointestinal Disorders:** Diarrhea: Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV (nintedanib). Nausea and Vomiting: Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **Embryofetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryofetocidal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV *[see Use in Specific Populations]*. **Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Liver Enzyme and Bilirubin Elevations *[see Warnings and Precautions];* Gastrointestinal Disorders *[see Warnings and Precautions];* Embryofetal Toxicity *[see Warnings and Precautions];* Arterial Thromboembolic Events *[see Warnings and Precautions];* Risk of Bleeding *[see Warnings and Precautions];* Gastrointestinal Perforation *[see Warnings and Precautions].* **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV (nintedanib), more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous systemic disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

DRUG INTERACTIONS: P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exp sure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **Anticoagulants:** Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust

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hemolysis, cannula dislodgement, uterine compression causing ineffective flow rate that improved after emergency cesarean section, and nosocomial infections, including urinary tract and line-related infections.

The study also took a closer look at the use of ECMO in pregnant women during the 2009 H1N1 pandemic; 8 of 33 pregnant women placed on ECMO died, compared with two maternal deaths among the 12 pregnant women placed on ECLS for other reasons.

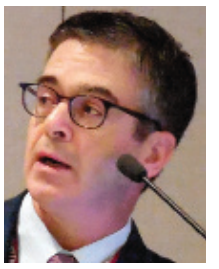
Dr. Moore and her coauthors acknowledged several limitations of their study, namely the likelihood of selection bias, "given that centers are less inclined to publish their bad outcomes."

Other study limits the researchers noted are: the small cohort obviated a proper statistical analysis; there was no control group; and the survival rate in pregnant women with ARDS who do not have ECLS is unknown.

Dr. Moore and her coauthors had no relationships to disclose.

VIEW ON THE NEWS

An Option for ARDS in Pregnancy



The meta-analysis performed by Dr. Moore and her colleagues provides strong support for the use of ECMO in pregnant women with ARDS. What is lacking, but was not the authors' focus, is how to maximize survival.

When managing pregnant women with severe cardiopulmonary dysfunction, the decision matrix for extracorporeal support requires rapid assessment of cardiopulmonary function and involves multidisciplinary collaboration, including critical care teams, maternal-fetal medicine physicians, perfusion services, and cardiothoracic surgery.

Initially, a pulmonary artery catheter and transthoracic echocardiography are needed to determine cardiac output to direct the decision-making on whether venoarterial or venovenous support is indicated.

An experienced perfusionist should be brought in to assess the ECMO cannula and circuit capabilities.

Lower-extremity venoarterial ECMO can cause cerebral and cardiac hypoxia in patients with mild cardiac dysfunction, usually of the right ventricle, secondary to hypoxia, acidosis, and hypercarbia.

In the cohort that Dr. Moore and her colleagues included in their study, venovenous ECMO was the safest and most effective approach.

With the successful use of ECMO during pregnancy, the rewards can be spectacular: How often can we save two lives with one operation?

Dr. Nicholas G. Smedira is with the Cleveland Clinic. He made his remarks in an invited commentary (J Thorac Cardiovasc Surg. 2016;151:1161-2). Dr. Smedira had no disclosures.

MACRA's impact on small practices downsized

BY GREGORY TWACHTMAN
Frontline Medical News

MACRA will not be as hard on small and solo practices as it first appeared when draft implementing regulations were published, according to Andy Slavitt, administrator of the Centers for Medicare & Medicaid Services.

Mr. Slavitt testified May 11 before the House Ways & Means Health Subcommittee to address legislators' concerns about how the government intends to implement the Medicare Access and CHIP Reauthorization Act of 2015.

Rep. Sam Johnson (R-Tex.) expressed concern that the draft regulations project would have "the greatest negative impact on payments to practices with nine or fewer doctors and the least harm to large systems with 100 or more docs."

The calculations in the draft regulation were based on data from 2014, a year in which few small and solo practices reported quality data.

"In 2015 and subsequent years, the reporting went up," Mr. Slavitt testified. "So at best, this table would be very, very conservative. ... Reporting is going to be far easier going forward."

Mr. Slavitt said that the CMS will do all it can to help ensure that small and solo practices have every opportunity to participate in the both the Merit-Based Incentive Payment System (MIPS) and in advanced alternative payment models.

"The question of making sure that small groups and solo practitioners can be successful is of utmost importance. Our data show that physicians who are in small and solo practices ... do just as well as physicians that are in practices that are larger than that," he said, adding that technical assistance specific to solo and small practices is being developed to help them transition to these value-based payment models.

Other federal officials have been spreading the same message to physicians. Speaking May 7 at the annual meeting of the American College of Physicians, Dr. Thomas A. Mason, chief medical officer in the Office of the National Coordinator for Health Information Technology, pointed out that the MACRA legislation put aside $20 million a year for 5 years beginning in 2016 to help solo and small practices transition to MIPS and APMs.

The CMS considers helping small groups and solo practitioners to participate in the new programs to be a priority.

MR. SLAVITT

"It is specifically to help with the shift and transforming practices to measuring quality and improving quality performance," he said in an interview. "The MACRA statute specifically calls out what the dollars need to be used for and the two points are for assisting MIPS-eligible professionals and improving their MIPS composite score as well as the transition to advanced alternative payment models."

The U.S. Department of Health & Human Services already has begun soliciting contractors to support small and solo practices, he added.

"Direct technical assistance through this program will target eligible clinicians in individual or small group practices of 15 or fewer, focusing on those practicing in historically under resourced areas," according to a request for proposals. "Technical assistance is defined as provider outreach and education, practice readiness, practice facilitation, health information technology (HIT) optimization, practice workflow redesign, change management, strategic planning, assisting clinicians in fully transitioning to Alternative Payment Models, and enabling partnerships."

The federal health IT office plans to provide more information on the availability of transition assistance soon, Dr. Mason said.

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VIEW ON THE NEWS

Dr. Michael E. Nelson, FCCP, comments: If you are unfamiliar with MACRA, or alternatively don't feel concerned about it, you will very likely notice a reduction in your income over the next few years. As a punishment for advocating the demise of the Sustainable Growth Rate formula (SGR), the Federal Government has come up with the Quality Payment Program (QPP), which includes the Merit-Based Incentive Payment System (MIPS) and Alternative Payment Models (APM). The Physician Quality Reporting System (PQRS), Value-Based Payment Modifier (VM) and Medicare Electronic Health Record (EHR Meaningful Use) are being morphed into the Merit-based Incentive Payment System (MIPS). If you don't like this, you may choose an Alternative Payment Model (APM). You may use either of these as an Eligible Professional (EP). These programs are being phased in between 2015 and 2021. If all of these eponyms have looked like gibberish to you, I would encourage you to go to the CMS website, Google, Facebook, or whatever information source you use and self-educate.

ABIM announces shorter MOC assessment

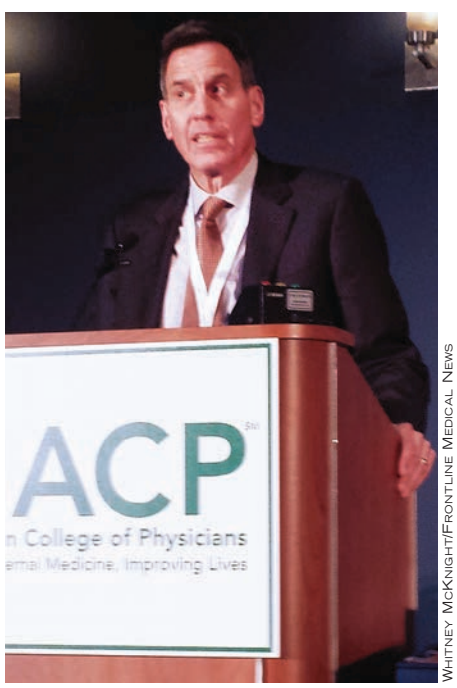
BY WHITNEY MCKNIGHT
Frontline Medical News

WASHINGTON – Shorter, more frequent MOC assessments are coming to an office or home computer near you under a new American Board of Internal Medicine certification option announced May 5 at the annual meeting of the American College of Physicians.

The new option comes in response to outrage expressed in meetings and online by physicians affected by ABIM recertification protocols that many said were redundant and impractical.

"We know there has been a lot of frustration, and anger and concern," said Dr. Yul Ejnes, who serves on the ABIM's internal medicine specialty board.

"Already more than 9,000 ABIM board-certified physicians have shared their opinions with us through a survey and hundreds more are helping ABIM by participating in our [maintenance of certification] blueprint review and open book study," said Dr. Richard J. Baron, president and CEO of ABIM.



WHITNEY MCKNIGHT/FRONTLINE MEDICAL NEWS

Physicians' assessments can be based on their practice experience.

Starting January 2018, the new option will mean that physicians who take shorter assessments on their personal or office computer – with properly authenticated security measures – can do so more frequently than every 10 years, but no more than annually.

Physicians also will be able to participate in crafting assessments based on their actual practice experience, and eventually, if they perform well, test out of the longer assessments currently mandated every 10 years.

"By offering shorter assessments, that [can be taken] at home or at the office, we hope to lower the stress and burden that many physicians have told us the current 10-year exam generates," Dr. Baron said. However, since 20% of diplomates surveyed said they preferred the 10-year exam, it will continue to be an option.

The shorter assessment may be available to some internal medicine subspecialties in 2018, Dr. Baron said.

Physicians maintaining certification in internal medicine whose certification expires before January 2018 will need to pass the current exam, although they will not need to assess again for 10 years.

A blueprint for a new exam has been created based on feedback from dozens of internal medicine professional organizations. The blueprint focuses on the most important things

Continued on page 48

24-hour BREO—Approved for Asthma

For adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA. BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**
- **When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.**

CONTRAINDICATIONS

- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required.
- BREO is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.

WARNINGS AND PRECAUTIONS (cont'd)

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO immediately and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS

- In a 12-week trial, adverse reactions (≥2% incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis, 10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% (<1%); and cough, 1% (2%).
- In addition to the adverse reactions reported in the two 12-week trials, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 once daily in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia, and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.
- In a 24- to 76-week trial of subjects with a history of 1 or more asthma exacerbations within the previous 12 months, asthma-related hospitalizations occurred in 1% of subjects treated with BREO 100/25. There were no asthma-related deaths or asthma-related intubations observed in this trial.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.

BREO ELLIPTA was developed in collaboration with Theravance

Reach for BREO

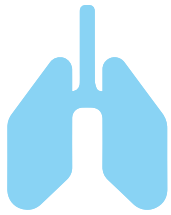
Reach With Confidence

In patients uncontrolled on an ICS alone, BREO has been proven to:

Deliver 24-hour lung function improvement

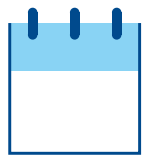
with one inhalation, once daily*

Reduce asthma exacerbations



in patients with a history of exacerbations†

Increase days without asthma symptoms



and increase days without use of rescue medication‡

Important Safety Information (cont'd)

DRUG INTERACTIONS (cont'd)

- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

- BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.
- Use BREO with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the following pages.

Supporting Clinical Study Information

*In a randomized, double-blind (RDB) study of 1039 patients§ symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=312) demonstrated a 108 mL improvement from baseline in weighted mean (wm) FEV_1 (0-24 hours) at the end of the 12-week treatment period vs fluticasone furoate (FF) 100 mcg once daily (n=288) ($P<0.001$).[1] (In an RDB, placebo-controlled study of 609 patients§ symptomatic on a low- to mid-dose ICS, in a subset of patients, BREO 100/25 once daily [n=108] demonstrated a change from baseline in wm FEV_1 [0-24 hours] at the end of the 12-week treatment period vs FF 100 mcg once daily [n=106] of 116 mL [95% CI: –5, 236; $P=0.06$].[2])

†In a 24- to 76-week RDB study of 2019 patients§ with ≥1 exacerbations in the prior year, BREO 100/25 once daily (n=1009) reduced the risk of experiencing an exacerbation by 20% (Hazard Ratio=0.795, $P=0.036$) vs FF 100 mcg once daily (n=1010).[3] An exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids (SCS) for ≥3 days or an in-patient hospitalization or emergency department visit due to asthma that required SCS.

‡In an RDB study of 1039 patients§ symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=345) provided an increase from baseline in the % of rescue-free and the % of symptom-free 24-hour periods during the 12-week treatment period of 12.2% and 7.8%, respectively ($P\leq0.002$), vs FF 100 mcg once daily (n=346).[1]

§Studies included patients with asthma ≥12 years of age; BREO is only approved for use in patients ≥18 years of age.

References: 1. Bernstein DI et al. *J Asthma.* 2015. doi:10.3109/02770903.2015.1056350. **2.** Bleecker ER et al. *J Allergy Clin Immunol Pract.* 2014;2(5):553-561. **3.** Bateman ED et al. *Thorax.* 2014;69(4):312-319.

Visit BREOhcp.com for more information, including Patient Assistance Programs.

BREO® ELLIPTA®
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

BREO® ELLIPTA® 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

The following is a brief summary only and is focused on the asthma indication. See full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.2 Treatment of Asthma BREO is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 18 years and older. LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1), Adverse Reactions (6.2), Use in Specific Populations (8.4)]*. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.
Important Limitation of Use: BREO is NOT indicated for the relief of acute bronchospasm.

4 CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions: Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*; Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS. A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted.

5.2 Deterioration of Disease and Acute Episodes BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate. Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO. BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta$_2$-Agonists BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of ICS In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.6 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients from Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*. Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.10 Paradoxical Bronchospasm As with other inhaled medicines, BREO can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO should be discontinued immediately; and alternative therapy should be instituted.

5.11 Hypersensitivity Reactions, Including Anaphylaxis Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO *[see Contraindications (4)]*.

5.12 Cardiovascular Effects Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of ICS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.15 Coexisting Conditions BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.16 Hypokalemia and Hyperglycemia Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In clinical trials evaluating BREO in subjects with COPD or asthma, there was no evidence of a treatment effect on serum glucose or potassium.

5.17 Effect on Growth Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. *[See Use in Specific Populations (8.4) of full prescribing information.]*

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. *[See Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: *Candida albicans* infection *[see Warnings and Precautions (5.4)]*; Immunosuppression *[see Warnings and Precautions (5.6)]*; Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*; Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Clinical Trials Experience in Asthma BREO for the treatment of asthma was studied in 18 double-blind, parallel-group, controlled trials (11 with placebo) of 4 to 76 weeks' duration, which enrolled 9,969 subjects with asthma. BREO 100/25 was studied in 2,369 subjects and BREO 200/25 was studied in 956 subjects. While subjects aged 12 to 17 years were included in these trials, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. The safety data described below are based on two 12-week efficacy trials, one 24-week efficacy trial, and two long-term trials.

12-Week Trials Trial 1 was a 12-week trial that evaluated the efficacy of BREO 100/25 in adolescent and adult subjects with asthma compared with fluticasone furoate 100 mcg and placebo. Of the 609 subjects, 58% were female and 84% were white; the mean age was 40 years.

In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis,

10% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dysphonia, 2% (1%, 0%). Oral candidiasis includes oral candidiasis and oropharyngeal candidiasis.
Trial 2 was a 12-week trial that evaluated the efficacy of BREO 100/25, BREO 200/25, and fluticasone furoate 100 mcg in adolescent and adult subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years.
In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/25 (n=346) (BREO 100/25 [n=346] or fluticasone furoate 100 mcg [n=347]) were: headache, 8% (8%, 9%); nasopharyngitis, 7% (6%, 7%); influenza, 3% (3%, 1%); upper respiratory tract infection, 2% (2%, 3%); oropharyngeal pain, 2% (2%, 1%); sinusitis, 2% (1%, <1%); bronchitis, 2% (<1%, 2%); and cough, 1% (2%, 1%).
24-Week Trial Trial 3 was a 24-week trial that evaluated the efficacy of BREO 200/25 once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in adolescent and adult subjects with asthma. Of the 586 subjects, 59% were female and 84% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO 200/25 included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.
12-Month Trial Long-term safety data is based on a 12-month trial that evaluated the safety of BREO 100/25 once daily (n = 201), BREO 200/25 once daily (n = 202), and fluticasone propionate 500 mcg twice daily (n = 100) in adolescent and adult subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO 100/25 or BREO 200/25 for 12 months included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.
Exacerbation Trial In a 24- to 76-week trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010) (Trial 5). Subjects participating in this trial had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. Asthma-related hospitalizations occurred in 10 subjects (1%) treated with BREO 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 (n = 151) compared with 0 subjects treated with fluticasone furoate 100 mcg (n = 130). There were no asthma-related deaths or asthma-related intubations observed in this trial.
6.3 Postmarketing Experience In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.
Cardiac Disorders Palpitations, tachycardia.
Immune System Disorders Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.
Musculoskeletal and Connective Tissue Disorders Muscle spasms.
Nervous System Disorders Tremor.
Psychiatric Disorders Nervousness.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.
7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants Vilanterol, like 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 QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.
7.3 Beta-Adrenergic Receptor Blocking Agents Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.
7.4 Non–Potassium-Sparing Diuretics The electrocardiographic 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 coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects Pregnancy Category C. There are no adequate and well-controlled trials with BREO in pregnant women. Corticosteroids and beta$_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO. *Fluticasone Furoate and Vilanterol:* There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day). *Fluticasone Furoate:* There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day). *Vilanterol:* There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).
Nonteratogenic Effects Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.
8.2 Labor and Delivery There are no adequate and well-controlled human trials that have investigated the effects of BREO during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO should be used during labor only if the potential benefit justifies the potential risk.
8.3 Nursing Mothers It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and beta$_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.
8.4 Pediatric Use BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established. In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. *[See Clinical Studies (14.2) of full prescribing information.]* Adolescents aged 12 to 17 years made up 14% of the study population (n = 281), with a mean exposure of 352 days for subjects in this age-group treated with BREO 100/25 (n = 151) and 355 days for subjects in this age-group treated with fluticasone furoate 100 mcg (n = 130). In this age-group, 10% of subjects treated with BREO 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age-group.
Effects on Growth Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of children and adolescents with ICS, including fluticasone furoate, on final adult height are not known. *[See Warnings and Precautions (5.17); Use in Special Populations (8.4) of full prescribing information.]*
8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.
8.6 Hepatic Impairment Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.
8.7 Renal Impairment There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No human overdosage data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.
10.1 Fluticasone Furoate Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.
10.2 Vilanterol The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).
Asthma-Related Death **Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Also inform them that currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.**
Not for Acute Symptoms Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used. Instruct patients to seek medical attention immediately if they experience any of the following: Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists; Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists; Significant decrease in lung function as outlined by the physician. Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.
Do Not Use Additional Long-Acting Beta$_2$-Agonists Instruct patients not to use other LABA for COPD and asthma.
Local Effects Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.
Immunosuppression Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
Hypercorticism and Adrenal Suppression Advise patients that BREO may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO.
Reduction in Bone Mineral Density Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.
Ocular Effects Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.
Risks Associated with Beta-Agonist Therapy Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
Hypersensitivity Reactions, Including Anaphylaxis Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

BREO was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 9/2015 BRE:6BRS

Pulmonologists' hospital revenue up almost 18%

BY RICHARD FRANKI
Frontline Medical News

Pulmonologists generated 17.9% more revenue for hospitals in 2015 than they did in 2012, according to a survey by physician recruitment firm Merritt Hawkins.

In 2015, pulmonologists generated $1.19 million in average net revenue for their affiliated hospitals, compared with $1.01 million in 2012, when Merritt Hawkins last conducted its survey of hospital chief financial officers.

Net revenue generated by physicians in all 18 specialties included in the survey averaged $1.56 million in 2015, which was up 7.7% over the $1.45 million generated in 2012. Average revenue for specialists was up 12.8% – going from $1.42 million in 2012 to $1.61 million in 2015 – while revenue generated by primary care physicians dropped 10.5% from $1.56 million in 2012 to $1.4 million in 2015, the survey showed.

Since specialists' net revenue is at least partly influenced by patient demographics, those who see more patients over age 65 years, including pulmonologists, may "generate a disproportionate number of medical procedures and tests," and with "over 10,000 Baby Boomers turning 65 every day," the demand for those specialists is likely to increase, the report noted.

The survey was completed by 74 hospital chief financial officers. Despite the small number, Merritt Hawkins said that the "results are reliable and accurate, in large part because the overall number for average annual revenue generated by all physician specialties for their affiliated hospitals has remained virtually unchanged" over the course of six surveys spanning 14 years.

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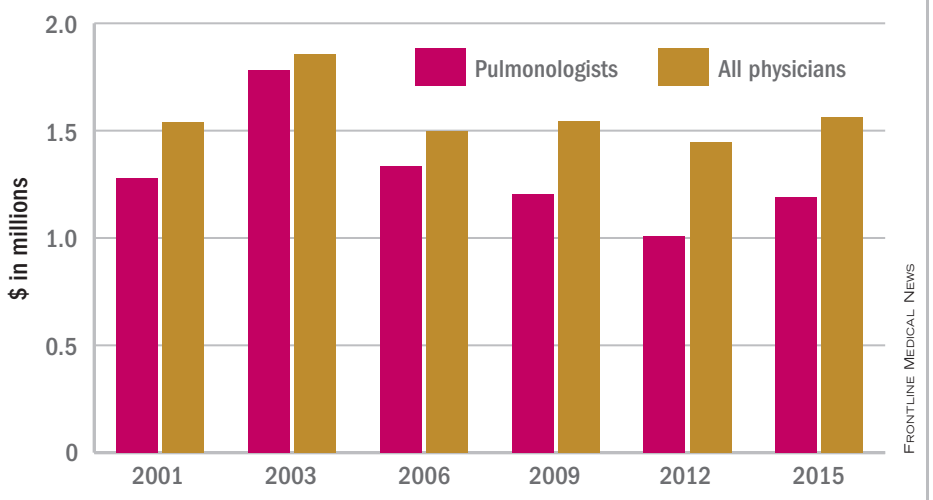
Revenue generated for hospitals: Pulmonologists vs. all physicians



FRONTLINE MEDICAL NEWS

Note: 2015 figures based on a survey of 74 hospital chief financial officers.
Source: Merritt Hawkins

Continued from page 43

to know in daily practice, as well as the important things to know that aren't encountered in daily practice, according to ABIM officials.

"The feedback we have so far on the new blueprint is that it is more relevant," said Dr. Patricia M. Conolly, ABIM chair-elect.

We know it isn't perfect, and we know we'll never get it exactly right, but we will have an ongoing process to ensure the exam reflects what internists are doing."

The ABIM is currently accepting comments on the proposed assessment, and expects to announce more specific details before the end of 2016.

Dr. Baron said ABIM is testing an "open book" assessment as well as ways to provide secure assessments at a physician's home or office. ABIM also seeks to determine how to provide immediate feedback on assessments and learning activities and will work with societies to expand the number of continuing medical education activities available for MOC credit.

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EPG_EUROPHOTOGRAPHICS/THINKSTOCK

Many 'nonurgent' ED cases actually are urgent

BY MARY ANN MOON
Frontline Medical News

Many emergency department cases deemed "nonurgent" by triage personnel actually are indistinguishable from those deemed "urgent," according to a Research Letter to the Editor published in JAMA Internal Medicine.

To examine whether a triage determination of nonurgent status really rules out the possibility of serious pathology, researchers analyzed data from the National Hospital Ambulatory Medical Care Survey, a representative annual probability sample survey of ED visits categorized by level of urgency. They focused on 59,293 ED visits by patients aged 18-64 years during a 3-year period, which were representative of 240 million ED visits across the country. An estimated total of 218.5 million of these visits (92.5%) were categorized as urgent and 17.8 million (7.5%) as nonurgent by triage personnel, said Dr. Renee Y. Hsia of the department of emergency medicine and the Philip R. Lee Institute for Health Policy Studies, University of California San Francisco, and her associates.

Patients required diagnostic services such as blood tests, electrocardiograms, or imaging in 8.45 million "nonurgent" visits (48%), and patients required procedures such as intravenous fluids, casting, or splinting in 5.76 million "nonurgent" visits (32%).

More than 775,000 "nonurgent" visits (4%) resulted in hospital admission, including 126,000 admissions to critical care units. And in 1.19 million "nonurgent" visits (7%), patients arrived by ambulance.

In addition, half of the top 10 diagnoses from "nonurgent" visits were identical to those from urgent visits, the investigators said (JAMA Int Med. 2016 April 18. doi: 10.1001/jamainternmed.2016.0878).

"Certainly, not all of these data necessarily indicate that these services were required, and they could signal overuse or a lack of availability of primary care physicians. However, to some degree, our findings indicate that either patients or health care professionals do entertain a degree of uncertainty that requires further evaluation before diagnosis," Dr. Hsia and her associates said.

To some degree, our findings indicate that either patients or health care professionals do entertain a degree of uncertainty that requires further evaluation before diagnosis.

Triage was never intended to completely rule out the possibility of severe illness in patients considered nonurgent, but was meant to predict the amount of time a patient could safely wait to be seen in the ED. However, over time, "the term 'nonurgent' has been often politicized to mean 'inappropriate,' which has implications for both the patient and health care system, when these 2 terms are conflated," they noted.

"Our findings highlight the lack of certainty of nonurgent status even when it is determined prospectively by a provider at triage, and suggest that caution must be taken when using triage scores beyond their intended purpose," the investigators said.

The authors had no conflicts.

Judge says feds overstepped on ACA cost-sharing

BY ALICIA GALLEGOS
Frontline Medical News

The Obama administration suffered another legal judgment against the Affordable Care Act when a district court judge ruled that the government has wrongly spent billions of dollars to repay insurers for health insurance provided to certain low-income patients.

Congress never appropriated the money for those payments and "no public money can be spent without [an appropriation]," Judge Rosemary M. Collyer of the U.S. District Court for the District of Columbia wrote in her May 12 opinion.

If the ruling stands, the reimbursements could end, making health insurance too expensive for the millions of low-income patients who benefit from the ACA's cost-sharing subsides, according to Jay Mark Waxman, a Boston-based health law attorney.

"If premiums become too expensive, you have people pulling out, then you have the so-called death spiral," Mr. Waxman said in an interview. "The law could remain intact, but you could end up with not having very many people taking advantage of the marketplace, particularly the Silver Plan."

The case in question, *U.S. House of Representatives v. Burwell*, revolves around two sections of the ACA. Section 1401 provides tax credits to certain patients in order to make insurance premiums more affordable, while Section 1402 requires insurers to reduce copayments, deductibles, and other out-of-pocket costs for certain low-income patients. The health law requires the federal government to reimburse insurers for the cost of these two sections.

While the first section received funding through the congressional appropriations process, the second section did not. In January 2014, HHS started repaying cost-sharing subsidies to insurers using federal funds. The House sued, claiming that HHS is illegally spending monies that Congress never appropriated. HHS has argued that other statutory provisions of the ACA authorize expenditures for cost-sharing reimbursements.

Judge Collyer ruled in the House's favor, writing that paying out reimbursements without an appropriation violates the Constitution.

House members praised the court decision, calling it a victory for "the rule of law and the American taxpayer."

"We received vindication of what we have known for quite some time – that the administration does not have the authority to spend over $150 billion for payments to insurance companies without an appropriation from Congress," House Energy and Commerce Committee Chairman Fred Upton (R-Mich.) said in a statement. "The court's message was clear: Complying with Article I of the Constitution is not optional for President Obama."

It's too early to predict how the legal case might be resolved, said Katherine Hempstead, who directs health

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insurance coverage for the Robert Wood Johnson Foundation. "There's a lot of potential endings that don't lead to people losing their cost-sharing reductions . . . the probability of people losing their reductions is remote."

The House could lose the case on appeal, she said. Whether the House has standing to sue HHS has been questioned as well, she noted. HHS continues to argue that the House has not established a concrete or imminent injury and therefore, the suit should be thrown out. In addition, some have suggested that the federal ruling could be interpreted as requiring Congress to appropriate money to pay for the cost-sharing reductions, she said.

The ultimate resolution could come from the U.S. Supreme Court, Mr. Waxman added. Another possibility is that the next administration will decline to pursue the case.

"Depending on the timing, it could just stop in the court of appeals," he said. "The next administration could say, 'We're happy with where it is and not take it up. You don't know what's going to happen."

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Ruling may expand liability under False Claims Act

BY ALICIA GALLEGOS
Frontline Medical News

A case before the U.S. Supreme Court could expand physicians' liability under the False Claims Act (FCA).

The case of *Escobar v. Universal Health Services* centers on the theory of implied certification and how that legal test should be used to determine whether a claim for payment is fraudulent.

The case "is an opportunity for the Supreme Court to figure out how far the False Claims Act is going to stretch," said Lawrence M. Kraus, a Boston health law attorney who attended the April 19 oral arguments. "On the practical level, it may have an impact as to whether [such] cases get dismissed at an early stage or whether they go into the discovery phase, which can be quite long, unpleasant, and expensive."

The *Escobar* case arises from the death of a patient who was treated at a Lawrence, Mass., mental health clinic operated by Universal Health Services. The patient died from an alleged adverse reaction to medication prescribed for her by clinic staff, according to allegations by her family. The patient's father, Julio Escobar, later learned counselors and psychologists involved in his daughter's treatment were not licensed, were not properly supervised by a physician, and had lied about their medical credentials, according to court documents.

The Massachusetts Department of Public Health found the clinic had violated 14 distinct regulations, including those relating to staff licensure and supervision. As a result of the investigation, the clinic entered into a correction plan with the agency and paid a civil fine.

Mr. Escobar and his wife then filed suit under the FCA and the Massachusetts False Claims Act, claiming that Universal had presented false claims to Medicaid by seeking payments for services provided by unlicensed, unsupervised health care providers. Although the reimbursement claims submitted to the government accurately described the services provided and cited the correct charges, the plaintiffs alleged that because the clinic's operations violated state requirements to participate in Medicaid, Universal had also violated the FCA. The federal government intervened in the case on behalf of the Escobars.

Universal countered that the FCA suit was invalid because a reimbursement claim cannot be false unless its details are untrue or inaccurate.

The plaintiffs, however, contend that a claim does not have to include explicit false statements to be fraudulent. Rather, their complaint relies on "implied certification," a theory holding that any submission for government payment includes an implicit certification that the health provider has complied with all applicable contract requirements, laws, and regulations that could be a condition of payment. Universal falsely claimed entitlement when it submitted reimbursement requests that did not conform to applicable laws, the plaintiffs argued.

The 1st U.S. Circuit Court of Appeals ruled in favor of Escobar, and Universal appealed to the Supreme Court.

This case may impact whether these kinds of cases get dismissed early or go to discovery.

MR. KRAUS

Circuit courts across the country have split on the issue, Mr. Kraus noted.

"There have been a number of different approaches from appeals courts in the country," he said. "This is not a new issue, but one that the Supreme Court found important enough to decide."

Why should doctors care about this case?

A ruling for the plaintiff could increase the chances that physicians are accused of an FCA violation after submitting a claim for payment, said William W. Horton, a Birmingham, Ala., health law attorney and chair of the American Bar Association Health Law Section.

"The problem that this raises for health care providers is: There is an enormous web of laws and regulations out there, many of which don't have anything to do with whether a particular service was rendered or not," Mr. Horton said in an interview "If you adopt the implied certification theory and take a broad view, than you significantly enhance the scope of claims that could be pursued under the False Claims Act."

Mr. Horton provides this example: Take a physician group that has an in-office lab, and assume that for some technical reason, the group doesn't satisfy the Stark Law exception for in-office ancillary services. If a physician in the group refers a Medicare patient to the lab and the group bills Medicare, that's a Stark Law violation because the group didn't meet the Stark exception, even if there's no dispute over whether the patient needed the test or whether the test was done correctly, or whether the Medicare claim accurately reflected the charges, he said. By broadly applying the implied certification theory to this scenario, a case could be made that the practice violated the FCA in submitting the claim because the group was implicitly certifying that the claim did not result from a referral that violated the Stark Law.

"The group could be found liable for the enormous penalties available under the False Claims Act even though the services rendered were medically necessary and appropriate, and even though the group did not expressly certify, in so many words, that the claim did not result from a referral that violated the Stark Law," Mr. Horton said.

The group could be found liable for the enormous penalties available under the False Claims Act.

MR. HORTON

Medical associations, including the American Medical Association and American Hospital Association have weighed in on the case in favor of Universal Health Services. In its brief, the AMA said there is a "sharp distinction" between statutory, regulatory, or contractual violations and false or fraudulent claims.

"Implied certification claims find no support in the statute and do not resemble claims Congress had in mind when enacting or amending the FCA," according to the brief. "They deprive contractors of their constitutional rights to have notice that they are engaging in conduct subject to heightened sanctions."

How might the Supreme Court rule?

During oral arguments on April 19, some justices appeared to indicate which way they are leaning, Mr. Kraus said.

Chief Justice John Roberts seemed concerned about the reach of the FCA under the implied certification theory. He raised questions about how people conducting business with the government would know about each and every regulation that could apply as a condition of payment.

Associate Justice Sonia Sotomayor and Associate Justice Elena Kagan appeared in favor of implied certification, while Associate Justice Samuel Alito Jr., Associate Justice Clarence Thomas, and Associate Justice Ruth Bader-Ginsberg did not display a strong opinion either way, Mr. Kraus said. Associate Justice Stephen Breyer appeared to be conflicted, asking for guidance from Roy T. Englert, an attorney for Universal Health Services.

"I'm asking for advice from you, from your point of view," Justice Breyer said to Mr. Englert. "What the sentence in the opinion should say that describes the circumstances under which the person who submits a form saying, 'I want a thousand dollars. I just supplied the guns or the medical care.' ... When has that person committed fraud? – Or that's what I want. What is the sentence you want me to write?"

Justices could rule a number of ways. They could uphold the appeals court decision, which would affirm a broad interpretation of implied certification theory. They could rule that the implied certification theory is valid, but it cannot be stretched as far as the appeals court expanded it. Justices could choose to reject the implied certification theory altogether and decide that the government must expressly identify every condition of payment in which a health provider is certifying compliance when they submit a claim, either on the claim form or by regulation. The high court could also split on the issue four to four, leaving intact the range of circuit court interpretations on implied certification across the country.

"There's a very real question as to whether they're going to be able to get a majority on any of those decisions because this is not an easy question," Mr. Horton said. "The court has a pretty wide range of potential rulings available to it, but I don't know *what* they're going to be able to get a majority around, *if* they're going to be able get a majority around any result at all."

A decision in the case is expected by June.

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Los Angeles: Fun for the Whole Family

When you travel to Los Angeles for CHEST 2016, October 22 - 26, your intentions will be clear. You'll want to connect with your colleagues from around the globe, earn CME and MOC, and learn in an innovative, hands-on environment. We've got that covered with cutting-edge sessions and a community of innovative problem-solvers. But why travel by yourself when your destination is known for beautiful weather, sandy beaches, amusement parks, and entertainment for the whole family? In LA, your whole family can enjoy a vacation, and you can join in some fun in the sun during your free time or before or after the meeting.

SEAN PAVONE/THINKSTOCK

Disney

If you haven't taken your kids to Disneyland, this may be a great opportunity to visit "the happiest place on earth." Anaheim, home to Disneyland, is about an hour drive from the Los Angeles Convention Center. Take flight with Dumbo the Elephant, visit the Haunted Mansion, spin around in tea cups, ride Mickey's Fun Wheel, and much more.

Universal Studios

Located in Hollywood, Universal Studios is only about a half-hour's drive from the convention center. You'll enjoy theme park rides and shows, a real working movie studio, and lots of lovable characters. Plus, you can explore a new offering, the mysteries of Hogwarts castle at the Wizarding World of Harry Potter.

Knott's Berry Farm

This theme park and amusement park is about 50 minutes from the convention center. The park has roller coasters, children's rides, water rides, and plenty of fun and scary activities to try out during the weeks leading up to Halloween.

Los Angeles Zoo and Botanical Gardens

About 25 minutes from the convention center, the Los Angeles Zoo and Botanical Gardens is home to more than 1,100 mammals, birds, amphibians, and reptiles representing more than 250 different species, of which 29 are endangered. Learn about animals from around the world and their habitats.

California Science Center

Just a 10-minute drive from the convention center, the California Science Center is fun for all ages. The center includes four major exhibits that focus on air and space, technology, commonalities of living organisms, and ecosystems. There is also an educationally focused IMAX theater with a seven-story screen.

CHEST 2016

Los Angeles will energize you with its family-friendly entertainment, and CHEST 2016 will keep you current with the latest developments in chest medicine. Don't miss out on the opportunity to inspire your patient care. Learn more and register today at chestmeeting.chestnet.org.

NAMDRC Signals Concern Over CMS Proposed Changes in Payment Methodology

BY PHIL PORTE
Executive Director, NAMDRC

CMS has proposed a dramatic change in the methodology used to determine payment to physician offices that provide drugs covered under the Part B Medicare benefit. Under current policy, physician offices are reimbursed at a rate of the average sales price (ASP) +6%. While not exactly a "moneymaker" in the pulmonary space, this policy has been particularly attractive to oncologists who have the opportunity to select expensive medicines that, according to CMS, may overlook very similar, less expensive drugs.

The proposal, in effect a nationwide pilot, reduces the payment to ASP + 3%, plus a $16 administrative fee. The response from the oncology community has been vociferous opposition, and it has garnered significant support on Capitol Hill. But the impact on the pulmonary community has, for the most part, been muted, thanks to uncertainty about the impact such a policy change may trigger. NAMDRC submitted detailed comments to CMS, highlighting concerns that this initiative, which is mandatory and nationwide in scope, could adversely impact the medical care of seniors who suffer from COPD and other related pulmonary diseases. NAMDRC is also concerned about the precedent this policy sets by using limited demonstration authority to change statutory payment policy nationwide.

While NAMDRC supports the goals of developing new health-care delivery methods to increase quality and provide more efficient patient care, it is nevertheless troubled by the Part B drug reimbursement policy proposed by CMS, as it appears to have been created in a vacuum without any input from stakeholders involved, particularly beneficiaries and their physicians. Forcing vulnerable Medicare beneficiaries, many with potentially life-threatening conditions, including COPD, the third leading cause of death in the United States, and asthma, to be exposed to a new mandatory payment initiative that runs the notable risk of impeding access to life-saving therapies runs counter to the initiatives that Congress has put forth.


MR. PORTE

While NAMDRC understands the need to look seriously at cost issues within our core health programs, we must not subject beneficiaries and their physicians to the problematic choice between practice economics and prescribing the most medically appropriate treatment for each individual patient. As CMS knows, biologic medications for treatment of asthma are likely to take an important role in treatment protocols in the immediate future; one new biologic for asthma was approved recently, and two new biologics in the pipeline are likely to be approved by the end of the year. Beyond asthma, the development of new biologics in the pulmonary field is likely to expand in the foreseeable future.

As noted above, in the proposed rule, CMS expresses concern that the current 6% ASP add-on payment "may encourage the use of more expensive drugs because the 6% add-on generates more revenue for more expensive drugs." In addition to lacking any data to support this premise, the reimbursement changes contemplated under this model may actually increase overall health-care spending by causing patients to receive care in more expensive settings.

Most importantly, there is no evidence indicating that the payment changes contemplated by the model will improve quality of care and may adversely impact those patients who lose access to their most appropriate treatments. Instead, NAMDRC believes that Medicare beneficiaries would be best served by a more patient-centric approach with appropriate safeguards, while also fostering physician-patient collaboration and ensuring that the unique needs of seniors are met. Therefore, NAMDRC strongly requested that CMS withdraw the proposed rule and obtain meaningful stakeholder input, including from patients and providers, before proceeding with Phase 2 of the proposed pilot.

2017 Educational Conference planning underway: NAMDRC's 2017 Program Committee is targeting the middle of July for completion of the primary program for the 2017 conference to be held at the Meritage Resort, Napa, CA, March 23-25, 2017. For information on the program, visit www.namdrc.org or call the Executive Office at 703/752-4359.

This Month in *CHEST*: Editor's Picks

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

Associations Between Different Sedatives and Ventilator-Associated Events, Length of Stay, and Mortality in Patients Who Were Mechanically Ventilated.
By Dr. M. Klompas et al.

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Lung Function Trajectories in World Trade Center-Exposed New York City Firefighters Over 13 Years: The Roles of Smoking and Smoking Cessation.
By Dr. T. K. Aldrich et al.

Alert - Edit Errors on EBUS

BY DR. MICHAEL E. NELSON, FCCP
CHEST Physician Editorial Advisory Board

Beginning this year, the CPT® code for endobronchial ultrasound (EBUS) **31620** was replaced by three new codes that more accurately describe the procedure as it is currently performed. Codes **31652** and **31653** are reported when EBUS is used for sampling proximal lesions (mediastinal or hilar). Code **31654** is used in identifying more distal lesions. As with other bronchoscopy procedures, the diagnostic code, **31622**, is included with these three new codes and the multiple endoscopy rule applies.

CPT code **31652** is utilized when one samples two or fewer proximal locations. CPT code **31653** is utilized when one samples three or more proximal locations. **31652** and **31653** may not be used together; use the code that best describes the work that was done. These two codes include the sampling procedures and, therefore, one does not use CPT codes for sampling, e.g., **31628** or **31629**, with either **31652** or **31653**. However, if additional procedures are performed on structures distal to the hila, then it is appropriate to use other bronchoscopy codes with **31652** and **31653**.

CPT code **31654** is an "add-on" code that is used to identify more peripheral lesions for sampling. As such, it may be used with all of the other bronchoscopy codes.

Unfortunately, when CMS originally published the National Correct Coding Initiative (NCCI) edits for these new codes, there were errors present. NCCI edits are used to instruct CMS payers and clinicians

Continued on following page

CHEST Foundation Margaret Pfrommer: The Impact of the Highly Motivated

In 1956, Margaret Pfrommer, a healthy teenager, became a quadriplegic with limited head control, no use of her upper extremities, no vital capacity. She used a wheelchair the rest of her 42 years.

When she was forced into a nursing home more than a decade later, Margaret's frustration with her circumstances compelled her to become an advocate for herself and for all those with significant disabilities. She was one of the first to pilot a motorized wheelchair with a "sip-and-puff" mechanism. Her consultation and feedback were instrumental in developing the prototype and other technologies that allowed Margaret and many others with severe disabilities to live independently.

As a champion for improving patient care, Margaret served as president of the Coalition of the Physically Handicapped (COPH), chair of the Citizen's Council, chair of the Illinois Delegation to the National White House Conference on Handicapped Individuals, chair of the board of directors of Access Living of Metropolitan Chicago, and was a member of the board of directors of the Rehabilitation Engineering and Assistive Technology Society of North America (RESNA).

Margaret also made it her mission to highlight the importance of the clinician and patient relationship. She emphasized understanding the patient and family perspective and respecting their knowledge. Her insistence that patients and clinicians collaborate to determine a most effective care management plan has proven invaluable to many chest medicine professionals.

Margaret died in 1998. Less than a year following her death, Dr. Allen I. Goldberg, MBA, Master FCCP,

Continued from previous page

when two distinct CPT codes may or may not be used together. The NCCI edits for **31652** and **31653** published on January 1, 2016, had a value of "0" for all other bronchoscopy codes; this instructed payers to reject any claims for **31652** or **31653** if any other bronchoscopy code was appended. The societies alerted CMS to these problems, and the NCCI edits were corrected. However, these corrections did not take effect until April 1, 2016. It is, therefore, quite possible that some claims will have been rejected by CMS and other carriers from January 1 until March 31. All claims for EBUS procedures during this time should be reviewed and resubmitted if rejected. You have 1 year to resubmit these claims to avoid nonpayment for untimely filing.

and Dr. Eveline A. M. Faure, FCCP, helped create the Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation. The memorial lecture is partially supported by generous gifts from CHEST and the CHEST Foundation, Post-Polio Health International, and numerous friends of the foundation.

Understanding the patient's perspective was Margaret's passion, and through these lectures, we are able to ensure that her legacy lives on for those who champion her effort and admire her dedication. To support the Margaret Pfrommer Memorial Lecture, go to chestnet.org/donate or call 224/521-9517.

CHEST® FOUNDATION

Flu vaccination cut hospitalizations for heart failure

BY MITCHEL L. ZOLER
Frontline Medical News

FLORENCE, ITALY – Influenza vaccination of heart failure patients cut their rate of hospitalization for cardiovascular disease by nearly a third during the year following vaccination in a study of more than 59,000 British heart failure patients.

Influenza vaccination of heart failure patients also cut their rate of hospitalization for respiratory infections by a statistically significant 16% during the year following vaccination, Dr. Kazem Rahimi said at a meeting held by the Heart Failure Association of the ESC.

"In the absence of randomized trials, this [observational] study of 59,202 heart failure patients provides the most compelling evidence to date for the protective effect of influenza vaccination on hospital admissions,"

said Dr. Rahimi, a cardiologist and epidemiologist who is deputy director of the George Institute for Global Health at the University of Oxford (England).

The analysis also showed that influenza vaccination of heart failure patients had no significant effect on all-cause hospitalizations.

Dr. Rahimi and his associates analyzed electronic health records from primary and secondary care settings in England during 1990-2013, from which they identified 59,202 heart failure patients with records for at least 1 year of influenza vaccination and at least 1 year without vaccination. The patients averaged 75 years old and were divided equally among women and men.

To control for potential confounding factors, they used a self-control model in which hospitalizations for each heart failure patient during the year following an influenza vaccination were compared with an adjacent year for that same patient when no vaccination occurred.

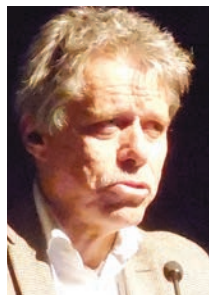
The results showed that the incidence of hospitalizations for cardiovascular diseases fell by a statistically significant 30% in the year following an influenza vaccination, compared with one or more adjacent years without vaccination. The protection against hospitalization

Continued on following page

VIEW ON THE NEWS

Results highlight vaccination need in heart failure

The main problem with observational studies is confounding, and the observational studies done until now that had looked at the protective role of influenza vaccination in heart failure patients had not been very convincing. Dr. Rahimi and his associates performed a high-quality study that adds to the evidence and underlines recommendations for influenza vaccination of heart failure patients. Their study was very large, and it used a self-control approach to adjust for potential confounding. I think they did their best to eliminate confounding.



The newly released, updated guidelines from the European Society of Cardiology for the diagnosis and treatment of acute and chronic heart failure recommend annual vaccination of heart failure patients against influenza and pneumococcal disease. The data reported by Dr. Rahimi also document that only about half of heart failure patients in England currently receive an annual influenza vaccine. That percentage needs to increase.

Dr. Arno W. Hoes is professor of clinical epidemiology at the University Medical Center in Utrecht, the Netherlands. He made these comments as designated discussant for the study. He had no disclosures.

Continued from previous page

was strongest during the second month following vaccination and then gradually waned over the ensuing year; by about 10 months following vaccination the protection effect had disappeared.

The study also looked at influenza vaccine uptake by heart failure patients through the 24-year period examined. During that time, the vaccination uptake rate rose from a low of less than 10% in 1990 to a peak rate of just over 60% in 2006, after which the rate gradually declined to a rate of just under 50% in 2013. Dr. Rahimi attributed the rise in uptake during the period from 1990 to 2006 in part to incentives that primary care physicians in England began receiving to administer influenza vaccine to their patients. "Higher uptake of annual vaccination in heart failure patients may help alleviate the burden of influenza-related hospital admissions," he said.

Dr. Rahimi had no disclosures

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Nitroxyl helped heart failure patients

BY MITCHEL L. ZOLER
Frontline Medical News

FLORENCE, ITALY – A novel intravenous prodrug that results in formation of nitroxyl once inside the body showed several potentially beneficial hemodynamic effects during a single, 6-hour infusion in a controlled proof-of-concept study with 46 patients hospitalized with advanced heart failure with reduced ejection fraction.

While receiving the drug, patients showed "statistically significant and clinically meaningful" reductions in pulmonary capillary wedge pressure and in pulmonary artery diastolic pressure, two of the three primary endpoints of the study, Dr. Veselin Mitrovic said at a meeting held by the Heart Failure Association of the ESC.

For the study's third primary endpoint, a change in cardiac index, treatment with the drug led to increased cardiac output using noninvasive measures, especially at the highest tested dose, as well as in all of the subset of treated patients in whom cardiac index was measured by thermodilution.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

"This is the first demonstration of safety and preliminary efficacy in patients with advanced heart failure," said Dr. Veselin Mitrovic.

On the safety side, the drug appeared safe and well tolerated at all four tested doses, while causing no episodes of symptomatic hypotension and no increase in heart rate. Transient, asymptomatic reductions in blood pressure were similar in the treated and control patients.

"This is a very interesting and exciting drug that went in the right direction," summed up Dr. Mitrovic, professor of cardiology at Goethe University in Frankfurt, Germany, and head of the department of cardiovascular research at the Kerckhoff Clinic in Bad Nauheim, Germany.

"This is the first demonstration of safety and preliminary efficacy in patients with advanced heart failure," he said in an interview. "We had a very good clinical signal in a relatively small study. We now need a larger study."

The drug "improved myocardial function in several ways: inotropy,

Continued on following page

VIEW ON THE NEWS

Interesting drug shows multiple benefits

Nitroxyl is a very promising and interesting drug. It had an effect on both contractility and inotropy, and also affected diastolic function and reduced afterload. The study's inclusion criteria enrolled patients who are typical for acute heart failure. It is very important to conduct these sorts of hemodynamic studies of a drug's effect in this setting.

This drug is obviously very powerful in reducing pulmonary capillary wedge pressure; only about 20% of patients did not respond. It also reduced both systolic and diastolic pulmonary artery pressure and right artery pressure, suggesting that it has a powerful effect on contractility in a way that not only affects the periphery by reducing systolic and diastolic pressures, but also produced little change in heart rate. What is important is that this drug acts at multiple points in the cardiovascular system.

The drug's safety and tolerability looked very good, but it needs to undergo further study.

Dr. Petar M. Seferovic is a professor of cardiology at Belgrade University, Serbia. He made these comments as designated discussant for the report. He has been a speaker for and consultant to Berlin-Chemie, Boehringer Ingelheim, Pfizer, and Gedeon Richter.

Continued from previous page

lusitropy, and unloading. It also causes arterial vasodilation and increased stroke volume," Dr. Mitrovic said. "Other drugs with a positive inotropic effect increase myocardial oxygen consumption; but with this drug, we see a neutral effect on mixed venous oxygen saturation. It balances myocardial oxygen consumption by its effect on unloading and reduced vascular resistance. This is a big advantage."

Each molecule of nitroxyl is made from single atoms of hydrogen, nitrogen, and oxygen, and its physiologic action is distinct from nitric monoxide. Nitroxyl improves calcium efficiency and recycling without producing intracellular calcium overload, and its effects are not mediated by cyclic AMP or cyclic GMP.

The dose-ranging study enrolled 34 patients with New York Heart Association class III heart failure and 11 with class IV. All patients had to have a left ventricular ejection fraction of 40% or less, and their actual ejection fractions averaged about 25%.

When measured after 2, 4, and 6 hours of infusion, pulmonary capillary wedge pressure (PCWP) fell by an average of about 5 mm Hg, compared with baseline, among patients who received the three highest-dose infusions of the nitroxyl prodrug, known as CXL-1427, and by an average of about 3 mm Hg in those who received the lowest dose.

That effect had disappeared when PCWP was remeasured 2 hours after the end of the 6-hour infusion, and the 11 patients randomized to placebo showed no change at any time point in PCWP. The average declines in PCWP in each of the four dose groups were statistically significant changes, compared with the control patients.

All the drug-treated patients showed an average drop in pulmonary artery systolic pressure of about 5 mm Hg, compared with baseline, and about 3-4 mm Hg in pulmonary artery diastolic pressure. The patients who received the highest dose of CXL-1427 had an average drop in their right artery pressure of about 4 mm Hg. All of those decreases were statistically significant, compared with the lack of any measurable changes in the control patients.

Total peripheral resistance also showed statistically significant declines relative to baseline in all the treated patients when these decreases were compared with the controls.

CXL-1427 was initially developed by Cardioxyl Pharmaceuticals. Bristol-Myers Squibb acquired the company in late 2015.

The study was sponsored by Cardioxyl.

Dr. Mitrovic has been a consultant to Bayer, Cardiorentis, and Novartis.

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Exercise training cuts heart failure mortality

BY MITCHEL L. ZOLER
Frontline Medical News

FLORENCE, ITALY – Exercise training boosts the longevity of patients with heart failure.

Although results from several prior randomized, controlled trials had already shown a mortality benefit from exercise training for heart failure patients, these findings have now been confirmed by a meta-analysis that used the original, individual patient raw data collected in 20 separate randomized, controlled trials that together involved more than 4,000 patients.

The results showed that an exercise-training intervention run for at least 3 weeks produced a statistically significant, relative reduction in all-cause mortality of 18%, compared with similar patients who had been randomized to usual care without an exercise program, Oriana Ciani, Ph.D., reported at a meeting held by the Heart Failure Association of the European Society of Cardiology.

The individual patient data meta-analysis using results from randomized, controlled trials also showed a statistically significant 11% relative reduction in the incidence of all-cause hospitalization in heart failure patients during at least 6 months' follow-up of exercise programs that lasted for at least 3 weeks, said Dr. Ciani, a health technology researcher at the University of Exeter (England).

Her analysis also showed no suggestion of heterogeneity for each of these two beneficial effects from exercise programs, regardless of patients' age, sex, or baseline levels of left ventricular ejection fraction, heart failure etiology, functional status, or exercise capacity. "No evidence was found to support a differential treatment effect from exercise-based intervention across patient subgroups," she said.

The Exercise Training for Chronic Heart Failure (ExTraMATCH II) meta-analysis used data collected in randomized trials published through 2014 that involved at least 50 patients, used an exercise intervention for at least 3 weeks, and had follow-up for at least 6 months. Dr. Ciani and her associates identified 20 studies that included a total of 4,043 heart failure patients who fulfilled these criteria and for whom the researchers from the studies were willing to share individual patient data.

The analysis also showed a median time to all-cause mortality of 605 days among patients who received exercise training and 615 days in the controls, and a median time to first all-cause hospitalization of 229 days with exercise training and 241 days in the controls. The percentage of patients who were hospitalized during follow-up was reduced by an absolute 3.8% for those in the exercise group, compared with the controls.

Although the type of exercise intervention used varied among the 20 studies, most involved aerobic training, and some also used resistance training, Dr. Ciani said. She said she plans additional analyses of the data she has collected to examine the impact of exercise in heart failure patients on cardiovascular mortality, heart failure hospitalization, and a combined endpoint of all-cause death and all-cause hospitalization.

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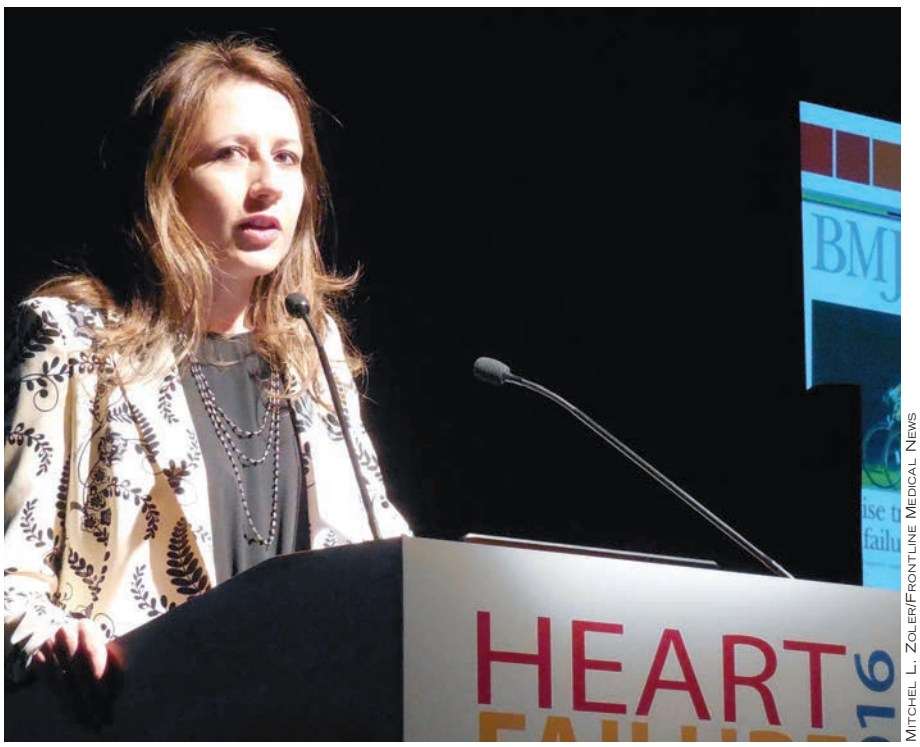

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

"No evidence was found to support a differential treatment effect from exercise-based intervention across patient subgroups," said Dr. Oriana Ciani.

VIEW ON THE NEWS

Exercise training underused in heart failure

These results are a step forward in confirming the safety and efficacy of exercise training for heart failure patients. It is a good addition to the literature. Its strength is its use of an analysis of individual patient data.
The findings deliver the important message that exercise rehabilitation is important for all heart failure patients. Currently, uptake of such programs is low, involving about 20% of heart failure patients.

The analysis showed a consistent effect from exercise training across all subgroups examined. The actual reductions in adverse outcomes were meaningful, with a 2% absolute reduction in all-cause mortality and a nearly 4% absolute reduction in all-cause hospitalization. However, the findings do not tell us which type of exercise prescription works best. Future research needs to especially focus on patients with heart failure with preserved ejection fraction to determine whether exercise benefits this particular type of heart failure patient.

Dr. Theresa A. McDonagh is a professor of heart failure at King's College, London. She made these comments as the designated discussant for the study. She had no relevant financial disclosures.

Guidelines add two new heart failure treatments

BY JENNIE SMITH
Frontline Medical News

Optimal use of two recently approved medications for heart failure has been detailed by the major heart societies in a guideline update.

The American College of Cardiology, the American Heart Association, and the Heart Failure Society of America issued joint recommendations May 20 on the two new medicines for stage C heart failure patients with a reduced ejection fraction.

Valsartan/sacubitril (Entresto, Novartis), is a combination angiotensin receptor–neprilysin inhibitor, the first in a novel class of drugs slugged ARNIs. Ivabradine (Corlanor, Amgen), is a sinoatrial node modulator. Both medicines were approved by the Food and Drug Administration in 2015, though ivabradine has been licensed for a decade in Europe.

Although a comprehensive update to ACC/AHA/HSFA heart failure guidelines is still being developed, the focused update is intended to coincide with the release of new European Society of Cardiology heart failure guidelines, "in order to minimize confusion and improve the care of patients with heart failure," the societies said in a statement May 20.

The recommendations were published online simultaneously in Circulation and the Journal of Cardiac Failure.

The guideline authors, led by Dr. Clyde W. Yancy of Northwestern University in Chicago, recommend that the ARNI replace an ACE inhibitor or an angiotensin II receptor blocker (ARB)

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Saint Agnes Hospital, a large community teaching hospital in Baltimore, Maryland is seeking a BE/BC pulmonary critical care physician to join a quickly growing pulmonary division. Sleep training is a plus. Scope of practice will include inpatient and outpatient consultation, fiberoptic bronchoscopy as well as resident teaching/mentorship. Not a J1 waiver opportunity. Please send CV, cover letter to Richard M. Pomerantz, MD, Chairman, Dept. of Medicine, St. Agnes Hospital, 900 S. Caton Ave, Baltimore, MD 21219 **scounsel@stagnes.org**

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Saint Joseph Hospital in Lexington, Kentucky is seeking a Pulmonary and Critical Care physician to join an established group in growing their comprehensive program. As part of KentuckyOne Health, this is an opportunity to work for the dominant health system in the state with over 600 employed providers.

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NEW JERSEY

Holy Name Medical Center (Teaneck, NJ – Bergen County) is currently seeking a board certified or eligible, full-time Interventional Pulmonologist for a hospital employed position to join a busy practice in Englewood, NJ. Those newly out of fellowship or graduating in 2016 or 2017 are encouraged to apply. Pulmonologists/Critical Care physicians should also apply. Our generous compensation package includes medical and dental insurance, life insurance, malpractice coverage, tuition reimbursement and 401K. If interested, please forward your CV to Jen Schachter at **schachter@holyname.org**

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MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

For heart failure, an angiotensin II receptor blocker and an angiotensin receptor–neprilysin inhibitor have not been compared, said Dr. Clyde W. Yancy.

Continued from page 60

for patients who have been tolerating these therapies alongside standard care with a beta-blocker and, for some patients, an aldosterone antagonist as well. The guidelines caution against combining an ARNI with an ACE inhibitor, and against using ARNIs in patients with a history of angioedema.

For patients not suited to treatment with an ARNI, continued use of an ACE inhibitor is recommended. In patients for whom an ACE inhibitor or an ARNI is inappropriate, use of an ARB remains advised.

The authors noted that head-to-head comparisons of an ARB versus an ARNI for heart failure do not exist; however, in a randomized, controlled trial in heart failure patients, treatment with valsartan/sacubitril plus standard care reduced cardiovascular death or heart failure hospitalization by 20%, compared with treatment with an ACE inhibitor plus standard care.

Ivabradine, meanwhile, has shown benefit in reducing heart failure hospitalizations in patients with symptomatic, stable, chronic heart failure with reduced ejection fraction who are receiving standard treatment including a beta-blocker, and who are in sinus rhythm with a heart rate of 70 beats per minute or greater at rest.

The new therapies, "when applied judiciously, complement established pharmacological and device-based therapies, representing milestones in the evolution of care for patients with heart failure," wrote Dr. Elliott M. Antman of Brigham and Women's Hospital and Harvard Medical School in Boston, Mass., in an editorial accompanying the guidelines.

About half of the guideline writing committee members and guideline reviewers disclosed financial relationships with pharmaceutical companies or device manufacturers, including Merck, Novartis, and Relypsa.

Dr. Yancy disclosed no conflicts of interest.

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PROFESSIONAL OPPORTUNITIES

CHEST MEDICINE ASSOCIATES
The Pulmonary • Critical Care • Sleep Medicine Specialists

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Web: **http://www.cmamaine.com**

EOE

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NETWORKS PCSK9 inhibitors, detecting RTIs, asthma therapies

Interprofessional Team

A degree advancement program in respiratory care: statement of program goal

A degree advancement program in respiratory care is an educational program designed specifically to meet the needs of practicing respiratory therapists with an RRT who, having already completed an accredited respiratory care program (AS degree) and are licensed in the State of California, wish to obtain advanced training in respiratory care in the areas of leadership, research, and education.

The degree advancement program is different from entry into the respiratory care professional practice program in purpose, design, and content.


MR. ROTH


DR. JAN

This degree advancement program expands the depth and breadth of both knowledge and critical thinking skills beyond that of an RRT.

Advanced educational experiences, designed to enhance a respiratory therapist's ability to function in clinical, teaching, administrative, or research environments, are essential components of the degree advancement program in respiratory care both to meet their current professional goals and to prepare them for practice as advanced degree respiratory care practitioners.

The program is innovative in the curricular offerings to encourage the next generation of leaders in the field of respiratory care.

What makes this new program unique is that the Baccalaureate program being offered is part of an expansion of services to students at the Community College level to earn an advanced degree at Modesto Junior College and Skyline College in California.

As the result of legislation, 15 different programs were selected as part of a 6-year pilot to meet the needs of students where no BS programs existed in California. The accredited program will focus on the three areas identified for advancement in the field.

This will be the first program of its kind (a community college offering a BS degree) in the United States.

Alan Roth, MS, RRT-NPS
Steering Committee Member

Cardiovascular Medicine and Surgery

PCSK9 inhibitors

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors are among a new class of lipid-lowering medications that are administered as monthly or bimonthly subcutaneous injections.

These include: (1) alirocumab (Praluent®) approved by the FDA on July 24, 2015; (2) evolocumab (Repatha™) approved by the FDA on August 27, 2015; and (3) bococizumab, which is in phase 3 trials. These medications are monoclonal antibodies, which target and inactivate hepatic PCSK9. The latter degrades LDL receptors (LDLR) in the liver. By blocking PCSK9, the monoclonal antibodies to PCSK9, prevent this LDLR degradation and make the LDLRs in the liver more available, thus, increasing the clearance of cholesterol-rich LDL (LDL-C) from the bloodstream and, thereby, lowering LDL-C levels.

These monoclonal antibodies were developed after the observation that naturally occurring loss-of-function polymorphisms that result in PCSK9 underexpression lead to lowering of LDL-C levels.

Although clinical trials have established the efficacy of the PCSK9 inhibitors in lowering LDL-C levels (ODYSSEY COMBO II trial, GAUSS-2 trial, ODYSSEY FH I and FH II trials, and the RUTHERFORD-2 trial), no definitive studies on hard cardiovascular end points (myocardial infarction, death, etc) are available yet.

The current FDA-approved indications for PCSK9 inhibitors are:

(1) Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

(2) Evolocumab is also approved as an adjunct in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

PCSK9 inhibitors are expensive and may cost more than $13,000 annually.

The costs are a potential concern for patients, insurance, and the public, given that the morbidity and mortality benefits have not been determined. However, this new class of potent LDL-C–lowering drugs offers promise to a group of patients who have genetic hyperlipidemia or are at very high risk for cardiovascular events and are not able to reduce their LDL-C level with existing therapies.

Dr. Fuad Jan, FCCP
Steering Committee Member

Chest Infections

New molecular biology-based tools for detection of RT infections

Identifying pathogens of respiratory tract infections (RTIs) and their antibiotic sensitivity by viral cultures may take up to 72 hours and delay appropriate antimicrobial use. In addition to viral isolation cell cultures, serologic antibody assay and direct fluorescent antibody (DFA) cell staining of nasopharyngeal (NP) swabs have been popular detection methods of viral RTIs, but most of those lacked sensitivity. Culture-independent molecular biology-based techniques like nucleic acid amplification tests (NAATs), multiplex PCR (polymerase chain reaction) and genomic- or proteomic- microarrays using silicon chips are proving to be the most efficient and sensitive diagnostic tools for viral RTIs. This new technology has increased the diagnostic yield for respiratory viruses by 30% to 50% over conventional methods. NAATs have shown greater sensitivity than DFA and culture (Mahony et al. *J Clin Microbiol.* 2007;45[9]:2965).

Several NAAT-based approaches like multiplex PCR, LAMP, and HDA, have been developed to detect a set of viruses, including conventional and emerging viruses, and are now being used routinely. Some multiplex assays detect up to 19 respiratory viruses and subtypes. Data from NAATs show new viruses (ie, SARS CoV, HMPV) transforming our understanding of the epidemiology of viral RTIs.


DR. KHAN

NP aspirates or swabs are preferred sample sources; however, flocked nasal mid-turbinate swabs may sample more cells and have sensitivity similar to NP swabs. Samples such as sputum, tracheal aspirates, and bronchoalveolar lavage require additional validation. The drawback of NAATs is their inability to determine specimen adequacy and quality.

Attempts to use NAATs to rapidly diagnose bacterial pathogen-causing RTIs and sepsis (Hazelton et al. *J Med Microbiol.* 2013;62(Pt2):223) show promise but, unlike viral pathogens, their effectiveness has not been proven yet.

Dr. Rumi Ahmed Khan, FCCP
Steering Committee Member

Clinical Pulmonary Medicine

Therapies for severe asthma: who, when, and why

Ten to twenty percent of patients have asthma that is not controlled with standard therapies and have reduced quality of life and productivity.

After key components of asthma care are addressed, including accurate diagnosis, asthma education, trigger avoidance, identification of asthma-aggravating conditions, and inhaler compliance/technique, how should we treat these patients?


DR. MASELLI


DR. PETERS

Four therapies are currently approved for uncontrolled asthma. Three of these are monoclonal antibodies: omalizumab (anti-IgE), mepolizumab (anti-IL5), and reslizumab (anti-IL5).

Bronchial thermoplasty uses radiofrequency delivered bronchoscopically to reduce airway smooth muscle mass and decrease bronchoconstriction.

How do we select the best therapy? Based on phenotypical characteristics, such as IgE levels and eosinophil counts, these therapies have been used successfully with improvements in various asthma outcomes. How should we treat the patient with allergic asthma, eosinophilia/high IgE levels, and frequent exacerbations (not an uncommon scenario)?

While head-to-head trials are needed to address which biologic should be used as "first-line" therapy, experts favor omalizumab because of long-term experience, safety data, and its ability to decrease symptoms and exacerbations.

To complicate matters more, multiple biological agents to treat severe asthma are under development.

Bronchial thermoplasty offers an alternative for patients who fail biologic therapy or patients unwilling to accept frequent injections.

In a relatively crowded field of therapies for severe asthma, it is important to take a step back to determine how we fit these therapies into clinical practice. Better treatment algorithms are needed to select the most cost-effective approach to these patients without neglecting the key components of asthma care.

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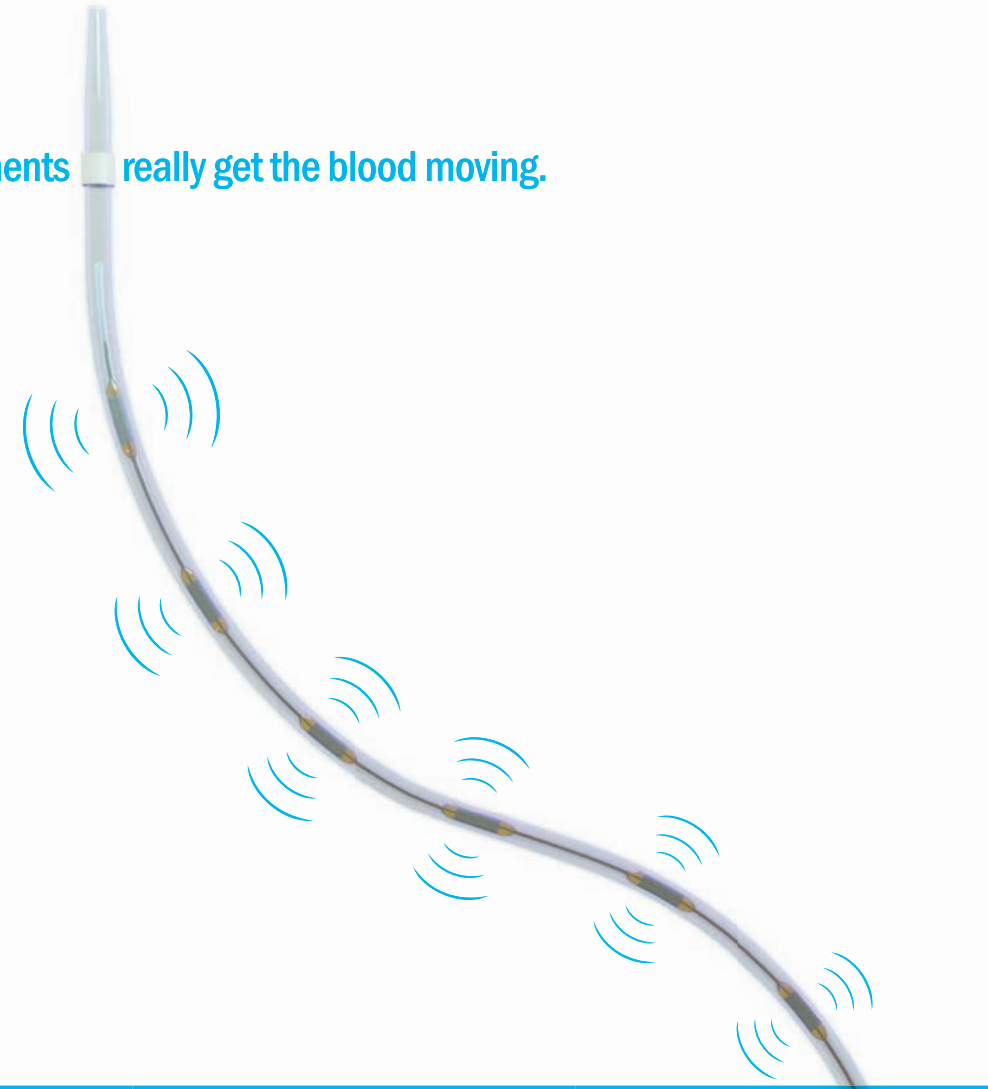

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