Celebrating 10 Years
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COURTESY DR. MIKE NELSON

Dr. Michael E. Nelson, FCCP, advises taking the reprieve as an opportunity to become familiar with the MIPS requirements.

MACRA flexibility is a win for most practices

BY GREGORY TWACHTMAN
Frontline Medical News

Federal flexibility in compliance with the first year of MACRA reforms is being perceived as a win for most physicians. Pressure from a number of physician organizations is credited in part for the Centers for Medicare & Medicaid Services' decision to reduce some of the reporting requirements for 2017 that will affect compensation in 2019.

Michael E. Nelson, MD, FCCP, who practices pulmonary, critical care and sleep medicine in Shawnee Mission, Kansas, said he suspects the change will be good news for most physicians participating in the Merit-Based Incentive Payment System (MIPS), but that "the devil will be in the details."

Hopefully, even the most unprepared of physicians will be able to avoid a reimbursement reduction by providing some QQP (Quality Payment Program) data," he said.

"Independent of whether Obamacare is supplanted by HilaryHealth or DonaldDocs, pun intended, the QPP program will continue until such time as a new mandate is received from Congress. So, unless you have MACRAphobia requir-

See **MACRA** • *page 20*

Post-hoc analyses strengthen FLAME's findings

LAMA/LABA benefited all subgroups

BY TED BOSWORTH
Frontline Medical News

LONDON – In chronic obstructive pulmonary disease (COPD), the advantage of a long-acting beta agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) over a LABA plus an inhaled corticosteroid (ICS) was observed in every subgroup in the FLAME trial evaluated, according to post hoc analyses presented at the annual congress of the European Respiratory Society.

"We thought that we might not see the difference in the COPD patients with more severe disease, but the advantage was consistent even among those who entered the trial on triple therapy," reported Jadwiga A. Wedzicha, MD, professor of respiratory medicine at the National Heart and Lung Institute, Imperial College, London.

FLAME, the recently published study that compared LABA/LAMA to LABA/ICS, was planned as a noninferiority study with the underlying hypothesis that LABA/LAMA would perform as well as LABA/ICS for the primary outcome of annual rate of COPD exacerbations (N Engl J Med. 2016;374:2222-34). Instead,

See **FLAME** • *page 7*

Macrolide okay in GOLD 1, 2

BY SARA FREEMAN
Frontline Medical News

LONDON – Maintenance azithromycin may be best reserved for patients with mild to moderate chronic obstructive pulmonary disease (COPD) who also have few symptoms, based on an analysis of the COLUMBUS randomized controlled trial.

Significantly fewer exacerbations (1.06 vs. 2.62; $P = .02$) occurred at 1 year in patients treated with the macrolide antibiotic rather than placebo if they were classified as having GOLD [Global Initiative for Chronic Obstructive Lung Disease] stage 1 or 2 versus stage 4.

Study participants who were classified as being part of GOLD group C (which includes patients with a high risk of COPD exacerbation but a low level of COPD symptoms) who were treated with maintenance azithromycin were also more likely to have fewer exacerbations at 1 year, compared with patients classified as being part of GOLD group

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INSIDE

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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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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.

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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

Characteristics predict response

Azithromycin *from page 1*

D (which includes patients with a high risk of COPD exacerbation and a high level of COPD symptoms), who took the same antibiotic (0.45 vs. 2.18; *P* less than .01).

A high serum eosinophil level (2% or higher) was a third factor found in COPD patients that was predictive of fewer exacerbations following azithromycin use (1.26 vs. 2.5; $P = .02$).

"Azithromycin maintenance therapy should not be given to every COPD patient," Remco Djamin, MD, of Amphia Hospital Breda in the Netherlands said in an interview at the annual congress of the European Respiratory Society. There is, of course, the concern over antibiotic resistance developing and macrolide antibiotic use has been linked with heart problems such as arrhythmia.

These data show, however, that there are certain predictors that might help clinicians decide if long-term antibiotic therapy might be beneficial for their patients who are experiencing frequent acute exacerbations of COPD.

Further research should look at the dosing and duration of azithromycin, Dr. Djamin suggested. Perhaps reducing the dose by half to 250 mg three times per week would be just as good; maybe 6 months' rather than 12 months' treatment would be sufficient, or perhaps it could be given intermittently. The aim is to ensure that patients are not being exposed unnecessarily, as there is concern over antibiotic resistance.

The use of azithromycin is not currently recommended in guidelines for COPD management to prevent exacerbations, but it is something that is likely to be added to the guidelines, as the evidence for its benefit mounts, Dr. Djamin said.

In addition to COLUMBUS, there have been at least two other studies looking at long-term antibiotic use to prevent exacerbations in patients with COPD.

One (Am J Respir Crit Care Med. 2008;178:1139-47) showed erythromycin could decrease the exacerbation rate at 1 year by 36%, compared with placebo, while the other (N Engl J Med. 2011;365:689-8) again showed a benefit for azithromycin, with a 27% decrease in the 1-year exacerbation rate.

In COLUMBUS, 92 patients who had experienced at least three or more acute COPD exacerbations in the previous year were randomized to treatment with azithromycin 500 mg or placebo, taken three times per week for 12 months.

This was a single-center, double-blind trial conducted in the Netherlands that showed a 42% reduction in the 1-year exacerbation rate could be achieved with the antibiotic treatment (Lancet Respir Med. 2014;2:361-8).

An additional benefit to using the antibiotic was seen in patients with GOLD stage 1-2 over patients with GOLD stage 4 and in patients with a higher percentage of serum eosinophils.

The GOLD stage 1-2 patients experienced fewer exacerbations leading to hospitalization, compared with patients with GOLD stage 4 (0.31 vs. 1.00; $P = .04$), while the patients with higher levels of eosinophils experienced fewer exacerbations requiring hospitalization than those patients with lower percentages of eosinophils (0.26 vs. 1.07; $P = 0.01$).

"[These patients'] exacerbations are often already being treated with antibiotics and so maintaining treatment has become one possible way of perhaps preventing exacerbations in the future," Dr. Djamin said, at the conference."

The study received no industry funding. Dr. Djamin had no competing interests to disclose.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: This study adds to the data supporting the use of thrice weekly macrolide in the prevention of COPD exacerbations in patients with frequent exacerbations. Importantly, it provides some guidance on which patients may benefit the most, given the concern for potential cardiac and antibiotic resistance complications. As suggested in the article, further study is needed to define the best treatment population and dosing strategy – especially since much of the effect of macrolide administration in chronic pulmonary diseases likely is immunomodulatory rather than one of pure antibiosis.

Asthma-COPD Overlap Syndrome definition under fire

BY TED BOSWORTH
Frontline Medical News

LONDON – A study comparing patient data with six definitions of the Asthma-COPD Overlap Syndrome (ACOS) found only one of the patients analyzed met all definitions. This provoked an animated discussion at the annual congress of the European Respiratory Society about the utility of ACOS as a clinical entity.

Of 864 patients diagnosed with COPD or asthma drawn from the Netherlands Epidemiology of Obesity cohort (a population-based study with 5,784 patients), 39.1% (338 patients) met at least one of the definitions of ACOS, while 0.1% (one patient) met the criteria for all six definitions.

When this finding was presented, the ERS audience first laughed and then applauded.

At the end of the presentation, long lines formed at the microphones. Every comment made was hostile to the concept of ACOS.

"Let us bring ACOS to an honorable death," said one audience member. His point, reiterated by all who commented subsequently, was that ACOS confuses efforts to treat the underlying respiratory symptoms. Even in those who have both asthma and COPD, the speaker, like other members of the audience, said he considered the diagnosis of ACOS unhelpful.

The six definitions in the study included the latest and just published consensus definition from the ERS (Eur Respir J. 2016;48[3]:664-73).

According to the ERS definition, the key features of ACOS are age greater than 40 years, long-term history of asthma (since childhood or early adulthood), and significant exposure to cigarette or biomass smoke.

The other definitions analyzed included a medical history of both asthma and COPD, a self-reported history of both asthma and COPD, and a record of the proportion of a person's vital capacity that he/she is able to expire in 1 second of forced expiration of less than 0.7 plus a record of fractionated nitric oxide concentration in exhaled breath of greater than or equal to 45 parts per billion.

Although attempted, a Venn diagram that would show overlapping subsets of patients that fell into these definitions "was not possible," according to Tobias Bonten, MD, University of Leiden, the Netherlands.

Asthma duration was just over 10 years in those identified as having ACOS by medical history alone (registry-based definitions), just over 20 years in those with a medical history and objective evidence of impaired lung function, but about 40 years in those with a self-report of both asthma and COPD.

One area that all groups created by the ACOS definitions did have in common was demographic variables, such as median age, proportion of patients defined as overweight or obese by body mass index, and proportion who were current smokers.

Members of the audience acknowledged the importance of considering the coexistence of asthma and COPD, but expressed skepticism about the value of ACOS as a separate entity in the clinic.

"ACOS is something like the emperor's new clothes," one audience member said during the discussion. "It is important to identify asthma patients with obstruction because they have reduced lung function that should be treated more actively, but I find the definition [of ACOS] unnecessary," he said.

A similar conclusion was drawn in a review article devoted to ACOS published last year (N Engl J Med. 2015;373[13]:1241-9). "It is premature to recommend the designation of ACOS as a disease entity," the authors wrote.

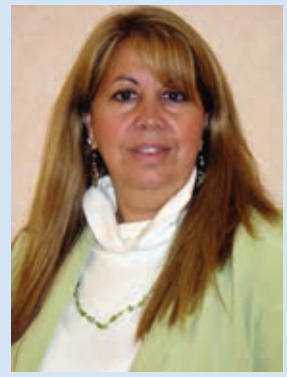
This is a position widely shared by clinicians, judging from audience comments provoked by this demonstration.

For the sake of time, the moderators were forced to end the discussion with significant lines of clinicians at the microphone.

"It is quite clear that ACOS should die," said one of the last speakers given a chance to voice an opinion. He suggested that the coexistence of asthma and COPD is something that "quite clearly can happen," but he objected to definitions he said are unhelpful for clinical care.

Dr. Bonten reported no relevant financial relationships.

IN THIS ISSUE



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Fluticasone furoate/vilanterol beats usual COPD care

BY AMY KARON
Frontline Medical News

A once-daily inhaled combination of fluticasone furoate and vilanterol was associated with an 8% lower rate of exacerbations in chronic obstructive pulmonary disease (COPD) than was usual care, with no increase in adverse effects, according to a multicenter trial designed to reflect real-world practice.

"Future effectiveness studies [like this one] are likely to influence clinical guidelines, not only for COPD but [also] for many other chronic diseases," said Jørgen Vestbo, MD, of University Hospital of South Manchester NHS Foundation Trust, Manchester, England, and his associates, for the Salford Lung Study investigators. The findings were presented at the annual congress of the European Respiratory Society and published simultaneously in the New England Journal of Medicine.

Current COPD guidelines are based on clinical trials of carefully selected and monitored patients, which substantially limits their usefulness in everyday practice, the researchers said. To help address that problem, their 12-month, prospective, open-label, parallel-group, randomized study enrolled 2,799 COPD patients in 75 general practices within a single urban area in the United Kingdom. Patients received 100 mcg of fluticasone furoate and 25 mcg of vilanterol or usual care. The primary outcome was the rate of moderate or severe exacerbations among patients who had experienced an exacerbation within 1 year before enrollment. Patients received all treatment from their usual providers and were monitored remotely for safety through electronic health records (N Engl J Med. 2016 Sep 4. doi: 10.1056/NEJMoa1608033).

Fluticasone furoate/vilanterol was associated with 1.74 moderate or severe exacerbations per year, compared with 1.9 events per year with usual-care group, for a statistically significant difference of 8.4% (95% confidence interval, 1.1%-15.2%; $P = .02$). The trial arms had similar rates of COPD-related health care visits and first moderate or severe exacerbations. They also did not notably differ in terms of serious adverse events of special interest, such as cardiovascular events (which affected 8% of patients in each group) or pneumonia (which affected 7% of fluticasone furoate/vilanterol patients and 6% of usual-care patients). Thirteen patients in each group developed fatal pneumonia, of which one case was considered related to usual care. The only other treatment-related death involved a deep-vein thrombosis and a pulmonary embolism in a patient receiving fluticasone furoate/vilanterol.

"Future effectiveness studies [like this one] are likely to influence clinical guidelines, not only for COPD but [also] for many other chronic diseases," said Dr. Vestbo and his associates.

Medication switches were about twice as common (22%) in the intervention group than in the usual care group (11%), perhaps because of the open-label nature of the trial, the researchers said. Only 4% of patients receiving fluticasone furoate/vilanterol needed better disease control, half the rate of the usual care group.

Dr. Vestbo reported personal fees from study funder GlaxoSmithKline.

All subgroups benefited

FLAME *from page 1*

the 11% lower rate of exacerbations for LABA/LAMA proved statistically significant ($P = .003$).

Six post hoc FLAME analyses were presented at the 2016 ERS Congress to further explore this result. All supported the main result. In addition to evaluating those who entered the trial on a LABA/LAMA/ICS triple-therapy combination, the analyses covered a broad array of subgroups defined by age, smoking history, and COPD severity as defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications.

In FLAME, 3,362 COPD patients who had at least one exacerbation in the preceding year were randomized to the LABA indacaterol (110 mcg) plus the LAMA glycopyrronium (50 mcg) once daily or the combination of the LABA salmeterol (50 mcg) and the ICS fluticasone (500 mcg) twice daily. In addition to the relative advantage on the primary outcome of any exacerbation, the LABA/LAMA combination also significantly reduced the rate of moderate to severe exacerbations (P less than .001), and it extended the times to the first moderate to severe exacerbation (P less than .001) and the first severe exacerbation ($P = .046$), according to the published data.

In the post hoc analyses, the advantage of LABA/LAMA relative to LAMA/ICS was remarkably consistent. For example, in stratifications made for age (less than 55 years, 55 to less than 65 years, 65-75 years, and greater than or equal to 75 years) at least a numerical advantage of LABA/LAMA was seen in all age groups for prevention of any exacerbation, and the difference reached statistical significance for those in the age group 55 to greater than 65 years. For prevention of moderate to severe exacerbations, the treatments were found to be equivalent for individuals younger than 55 years, but LABA/LAMA was statistically superior for the other three age categories.

We thought that we might not see the difference in the COPD patients with more severe disease. The advantage of LABA/LAMA relative to LAMA/ICS was consistent even among those who entered the trial on triple therapy, said Dr. Wedzicha.

For ex-smokers, unlike current smokers, the numerical advantage of LABA/LAMA over LABA/ICS for reduction in the rate ratio of all exacerbations did not reach statistical significance, but the LABA/LAMA combination did provide a statistically significant advantage for both ex-smokers and current smokers for moderate to severe exacerbations.

For patients with two or more exacerbations in the year prior to enrollment in FLAME, the relative degree of protection was of magnitude similar to that of patients with only one exacerbation even though the relative advantage in those with multiple prior exacerbations did not reach statistical significance. However, the lack of significance was likely due to the relatively small number of patients in this subpopulation, according to Dr. Wedzicha.

Similarly, the LABA/LAMA combination was at least numerically superior to LABA/ICS for all exacerbations and for moderate to severe exacerbations across GOLD classifications with one exception. When compared for relative protection against moderate to severe exacerbations, there was a slight and nonsignificant disadvantage for LABA/LAMA, but, again, Dr. Wedzicha reported, "the number of patients in this subgroup was quite small."

In another FLAME post hoc analysis, the odds ratio (OR) for exacerbations among the 1,893 patients (56.3%) who were on ICS at study entry was found to be almost identical to the OR among those who were not. Specifically, the ORs for all exacerbations and moderate to severe exacerbations were 0.88 ($P = .008$) and 0.86 ($P = .018$), respectively, for those previously treated with ICS and 0.88 ($P = .021$) and 0.78 ($P = .002$), respectively, for those who had not been treated with ICS.

The LABA/LAMA combination was also superior to LABA/ICS for improvements in quality of life, which was measured via the St. George's Respiratory Questionnaire. With an improvement of at least four units on the St. George's Respiratory Questionnaire defined as clinically meaningful, 49.5% of LABA/LAMA patients versus 43.8% of LABA/ICS patients (P less than .024) benefited on this measure.

Overall, the results from the FLAME post hoc analyses have demonstrated "remarkable consistency," and "imply that LABA/LAMA is the first choice of treatment for COPD patients at risk of exacerbation," Dr. Wedzicha reported.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: These additional post-hoc analyses of the FLAME trial presented at the ERS conference are helpful in a descriptive nature, but aside from the conclusions drawn from the peer-reviewed publication, one needs to take caution when addressing what conclusions can be drawn from such an analysis.

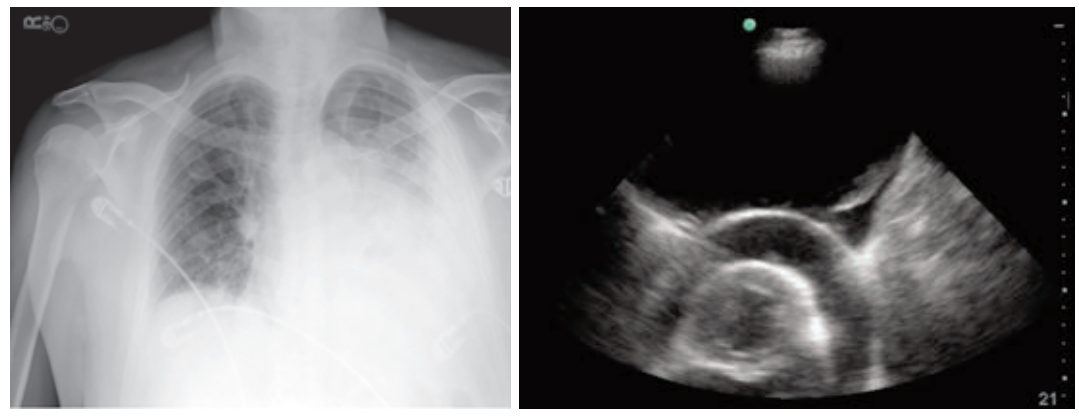
PULMONARY PERSPECTIVES® The sun should never set on an "un-ultrasound-ed" pleural effusion

BY RICARDO FRANCO-SADUD, MD; AND NILAM J. SONI, MD, MS

The adage, "the sun should never set on an untapped pleural effusion," was instilled in physicians for generations. However, anyone who practices medicine currently knows the sun often rises and sets several times before a pleural effusion is tapped. Why the change in mindset? Since the American Board of Internal Medicine removed the requirement for internal medicine residents to perform a minimum number of bedside procedures for certification, fewer graduating residents feel comfortable performing thoracentesis.

Additionally, the fear of litigation and institutional persecution from a postprocedure complication has caused many frontline clinicians to shy away from performing thoracentesis. Most important, we now appreciate that not all pleural effusions need to be tapped immediately, and the clinical decision making about the timing and technique to drain a pleural effusion is more complex than previously thought.

In recent years, the availability of portable ultrasound (US) for bedside diagnostics and procedural guidance has revolutionized the practice of medicine, including the management of pleural effusions. When confronted with an obscured lower lobe on chest radiograph, clinicians were previously relegated to primitive bedside maneuvers, such as percussion or auscultation, to make critical management decisions. Now, clinicians are able to look inside the body with point-of-care US and visually assess a pleural effusion before making any decisions. Point-of-care US has shifted the paradigm in the management of pleural effusions in several ways.



An obscured lower lobe on chest radiograph necessitated percussion or auscultation to make management decisions. Point-of-care ultrasound allows visual assessment of a pleural effusion.

US allows rapid detection and differentiation of pleural effusions from other pathologic findings.

Chest radiographs cannot accurately differentiate a pleural effusion from other common conditions, such as pneumonia, atelectasis, or an elevated hemidiaphragm. US is the only bedside diagnostic modality that can rapidly differentiate these conditions within seconds and may reveal unsuspected findings, such as a mass or pericardial effusion.

For example, the pleural US exam of a patient confirmed the presence of a large, left-sided pleural effusion (Figure, right) but also revealed an unsuspected large pericardial effusion (See dot.) that was causing hemodynamic compromise. Thus, management of this patient shifted focus from the pleural effusion to the pericardial effusion, and urgent pericardiocentesis was performed. The sensitivity of US to detect a pleural effusion is proportional to the volume of fluid, reaching 100% with as little as 100 mL of fluid (Kalokairinou-Motogna et al. *Med Ultra*. 2010;12[1]:12). The diagnostic accuracy of US for detection of pleural effusions is comparable to CT scans of the chest and superior to portable chest radiographs (Lichtenstein et al. *Anesthesiology*. 2004;100[1]:9).

US characterizes pleural effusions to determine the most appropriate management strategy.

Any clinician with basic ultrasonography skills can learn to evaluate pleural effusions and categorize them as simple or complex based on the sonographic appearance. Visualization of fibrinous stranding or loculations increases the probability of pleural fluid being exudative and often drives the decision to drain the fluid. The density and distribution of loculations can guide decisions about the most appropriate type of drainage procedure – thoracentesis versus tube thoracostomy versus surgical intervention. Use of color flow Doppler US allows clinicians to assess whether or not pleural fluid is free flowing and amenable to drainage, potentially saving the patient from an unnecessary attempt at drainage. US affords frontline clinicians the ability to streamline consultation with the most appropriate specialist based on the type of drainage procedure indicated and potentially prevent duplicate procedures on the same patient from different specialists.

US reduces the risk of postprocedure complications from thoracentesis.

The risk of postthoracentesis pneumothorax was reported to be as high as 20%-39% before the routine use of point-of-care US (Grogan et al. *Arch Int Med*. 1990;150:873). US guidance has been shown to increase procedural success rates and decrease the risk of postprocedure pneumothorax (2.7%), cost of hospitalization, and length of stay (Mercaldi et al. *Chest*. 2015;143[2]:532). Regardless of the chest radiograph or CT scan findings, if the US exam reveals a scant volume of pleural fluid, or densely loculated pleural fluid, clinicians can avoid unnecessary attempts at bedside drainage, which likely partly accounts for the reduction in postprocedure pneumothorax. Use of US for needle site selection may prevent up to 10% of potential accidental organ punctures and increases accurate site selection by 26%, compared with chest radiograph and physical examination findings combined (Diacon et al. *Chest*. 2003;123:436).

US facilitates patient-centered care.

Point-of-care US is the only new technology that has taken clinicians back to the bedside to spend more time with patients. Clinicians can simultaneously perform an US exam and converse with patients to gather a medical history. The US image serves as a tool to help patients understand their condition and facilitates shared decision making with clinicians at the bedside.

As more specialties have gained expertise in thoracic ultrasonography, the use of US guidance for thoracentesis has evolved to become the standard of care in many hospitals in the United States. Besides pulmonary specialists, several acute care specialists, including hospitalists, intensivists, and emergency medicine physicians, are routinely using point-of-care US to guide diagnostic decision making and procedures. Over the past 10 years, nearly a dozen procedure services led by internal medicine-trained hospitalists have been created at academic institutions that are routinely performing US-guided thoracenteses with low complication rates (Franco-Sadud et al. *SGIM Forum*. 2016;39[5]:13). More important, US is being used on the front lines to expeditiously evaluate pleural effusions and perform a diagnostic thoracentesis or consult with the appropriate subspecialist.

Even though demonstration of competency in bedside procedures is no longer required for board certification in internal medicine, many internal medicine residency programs have incorporated diagnostic and procedural point-of-care US training into their education curriculum (Schnobrich et al. *JGME*. 2013;5[3]:498). Further, approximately 62% of medical schools report integrating US education into their medical student curriculum, and in coming years, most medical students will likely graduate with a basic skill set in point-of-care ultrasonography (Bahner et al. *Academic Med*. 2014;89[12]:1681). As point-of-care US education becomes integrated in training of physicians and other health-care providers, use of US to guide management of pleural effusions could become universally practiced and accepted as the new standard of care. Thus, it is plausible that a day will come in the near future when the sun will not set on an "un-ultrasound-ed" pleural effusion.

Dr. Franco-Sadud is with the section of hospital medicine/division of general internal medicine, Medical College of Wisconsin, Milwaukee, Wisconsin; Dr. Soni is with the section of hospital medicine and the section of pulmonary and critical care medicine, South Texas Veterans Health Care System and University of Texas Health Science Center, San Antonio.

Turn the page to discover clinical data and formulary coverage for **BREO**

Reach with Confidence for **24-hour BREO**

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.

Please see additional Important Safety Information on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the pages following this advertisement.

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

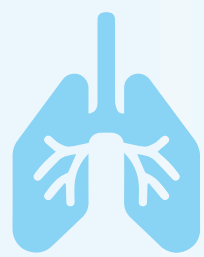
BREO offers patients proven efficacy with just one daily dose

In patients uncontrolled on an ICS,
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†

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 for ≥3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

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

Important Safety Information (cont'd)

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.

WARNINGS AND PRECAUTIONS (cont'd)

- 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.
- 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.

gsk

BREO ELLIPTA was developed in collaboration with Theravance

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Have confidence in access

Nationwide, BREO is now **covered without restriction**[§] on:

Individual patient access may vary by geography and plan benefit design.
SOURCE: Managed Markets Insight & Technology, LLC, database as of August 2016.

For local formulary information about BREO, please contact your GSK sales professional.

What you need to know about this formulary information:

[§]Covered without restriction means reimbursement from a health plan with no accompanying step edits or prior authorizations.

Formulary status may vary and is subject to change. Formulary coverage does not imply clinical efficacy or safety. Benefits designs offered by plans may vary. Actual benefits and out-of-pocket costs are determined by each plan administrator in accordance with its respective policy and procedures. Consumers may be responsible for some out-of-pocket costs based on an individual's plan.

The information provided is not a guarantee of coverage or payment (partial or full). Please verify coverage with and obtain most current information from plan sponsors. GSK does not endorse individual plans.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- 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.

ADVERSE REACTIONS (cont'd)

- 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.
- 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.

References: 1. Bernstein DI et al. *J Asthma.* 2015;52(10):1073-1083. **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.
Respiratory, Thoracic, and Mediastinal Disorders Paradoxical bronchospasm.

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 8/2016 BRE:7BRS

CHEST FOUNDATION 20TH ANNIVERSARY

CELEBRATING 20 YEARS

AS CHAMPIONS FOR LUNG HEALTH

1996

CHEST Foundation, founded by a strong group of motivated leaders, awards 30+ grants for clinical research, world health partnerships, lectures, and young investigators

1997—

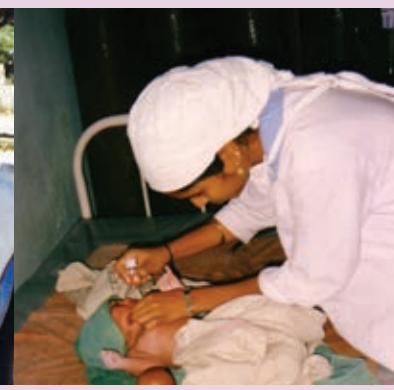
CHEST Foundation film *A Physicians Perspective*, highlighting end-of-life care, wins AMA Freddie Award

1998—

Women & Girls, Tobacco, & Lung Cancer Speaker's Kit developed to target women and children in an anti-tobacco use campaign

1999

CHEST Foundation recognizes 12 winning humanitarian programs with the new Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP



In 1935, Murray Kornfeld's vision of patients and clinicians working together to advance global lung health inspired the founding of the American College of Chest Physicians. We embraced that same vision 20 years ago when the CHEST Foundation was established as the charitable foundation of the American College of Chest Physicians. Through CHEST Foundation-supported programs, CHEST's 19,000+ members engage in clinical research, participate in community service, and deliver patient education, advancing the lung health of millions of patients in local communities around the world.

Today, as we celebrate our 20th anniversary as the CHEST Foundation, we'd like to say a huge thank you to all our volunteers, donors, and staff who have served as champions for lung health, making the successes of the last 20 years possible!

2006—

"Ant E Tobacco" program and "Make the Choice: Tobacco or Health?" toolkits evolved, allowing CHEST members to reach students in elementary schools

2007

CHEST Foundation Case Competition established to encourage teams of students from local universities to develop sustainable organizational models to improve asthma diagnosis and treatment

2008

CHEST Foundation supports AMA Alliance Screen-Out! Program, changing the Motion Picture Association of America's rating system so new movies showing smoking or tobacco use would be rated "R"

2009—

Physicians Speaking For Humanity (PS4H) campaign initiated to appeal to physicians who lecture and/or attend pharmaceutical focus groups to donate their honorariums to the CHEST Foundation

2000—
CHEST Foundation and Cultural Diversity in Medicine NetWork create Educational Guide on Lung Health for Elementary School Children

2001—
Ambassadors Group founded to serve as health advocates, participating in educational programs on tobacco addiction and asthma care

2001
CHEST Foundation established a 9/11 Emergency Response Fund, collecting $75,000 to support a free smoking cessation program for FDNY

2002—
First winner selected for new Distinguished Scholar program, developed to provide multiyear grants to CHEST members whose projects promise to impact clinical chest and critical care medicine

2002—
CHEST Foundation and Eli Lilly and Company Foundation partner to create Critical Care Family Assistance Program (CCFAP) to better engage family members during a loved one's ICU stay

2003—
Representatives from the American Association of Critical-Care Nurses (AACN) joined the CCFAP advisory team and assisted in the selection of additional program sites

2004
Following major tsumani in southeast Asia, CHEST Foundation set up a disaster relief fund, generating donations to care for victims and help rebuild a small fishing village in Sri Lanka

2005—
After hurricanes Katrina, Rita, and Wilma, CHEST Foundation created Hurricane Relief—Beyond the First Response Matching Gift Fund, to support CHEST members in efforts to serve their patients

2010
C. Sola Olopade, MBBS, MPH, FCCP, won his second Humanitarian Award for his work to protect women and children in rural Nigeria from the exposure to indoor pollution. Dr. Olopade continues his efforts in Africa, with funding from the NIH and United Nations Foundation

2011—
CHEST Foundation hosts "OneBreath Luau" raising funds to support the launch of OneBreath.org, part of a new public-facing campaign

2012—
"Beyond Our Walls" campaign launched, seeking support for CHEST's new Innovation, Simulation, and Training Center

2013
First DVT Disease Awareness Month campaign created, which inspired a greater effort in supporting similar campaigns delivering education on topics like COPD, asthma, lung cancer, and sarcoidosis

2014—
CHEST Foundation participated in the FDA's first youth tobacco prevention campaign, "The Real Cost," designed to educate at-risk youth about dangers and impacts of tobacco use

2015
Partnership with American Lung Association initiated to develop up-to-date online patient education guides featuring easy-to-access information on 40 lung health topics

2016
CHEST Foundation names "Champions Circle" Annual Fund giving club, "Founders Society" recognizing CHEST members for cumulative giving, and "Friends of the Foundation" for long-term industry partners

PRESIDENT'S REPORT The Six F's for our most important faculty volunteers

BY WILLIAM F. KELLY, MD, FCCP
CHAIR, EDUCATION

NICKI AUGUSTYN
SENIOR VICE PRESIDENT, EDUCATION

BARBARA PHILLIPS, MD, MSPH, FCCP
CHEST PRESIDENT 2015-2016

This has been an extraordinary year for CHEST, particularly in the core area of clinical education. In the past fiscal year, we exceeded our educational goals. We set out to reach 10,000 learners through educational programming including live courses and conferences, and online activities; in the end, we served 15,547.


DR. KELLY

Other goals accomplished include demonstrating a significant increase in average learner knowledge acquisition and procedural skills improvement; identifying top priorities for online offerings and delivering five stand-alone online modules that can serve as a point of entry to wider audiences; recording professional attendance at CHEST 2015 of 5,149 people; offering online training for guideline development and the panelists engaged in CHEST guidelines; achieving an attendance at CHEST World Congress in Shanghai of 2,089; and working with leading Chinese medical societies to see the China-CHEST Pulmonary and Critical Care Medicine Fellowship Program formally adopted by the government in China as one of the four first-ever subspecialty training programs to be implemented nationwide.


MS. AUGUSTYN


DR. PHILLIPS

This is a lot!

These accomplishments depend on intense work and collaboration between our incredibly talented faculty and volunteers from among CHEST membership and CHEST's amazing professional staff of 105 employees, of which 28 are dedicated full time to the development and delivery of education and best practices. Through this partnership, we continue to meet CHEST's mission: To champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

Without these dedicated women and men, CHEST would be utterly unable to complete its mission. Our faculty work in a vast array of opportunities, including writing questions for SEEK, serving as a content expert for guidelines, proposing and delivering sessions at CHEST, running Board Review courses, recording videos, facilitating hands-on simu-

lation sessions, and more. While intrinsically gratifying, there are many difficult elements to such work, requiring commitment that begins long before the delivery of an event or the launch of a new activity. Reviewing existing literature and knowledge on a topic to determine whether an activity will meet the needs of our membership; coming up with valid learning objectives; generating just the right multiple choice questions and other assessments to measure our success at helping learners reach those objectives; peer reviewing content to ensure we're teaching to the latest science and established best practices; and then measuring learner outcomes – these elements put the "state of the art" into CHEST's internationally recognized state-of-the-art educational program.

To achieve our mission, we have been asking CHEST's valiant and dedicated volunteers to do more than ever before, and some of what we have asked them to do has been frustrating, tedious, and less than rewarding, often due to imperfect technology platforms we've asked our volunteers to use; the disconnect between the educational goals we have set and the implementation of the clear processes, communication, and on-boarding of staff required to

Continued on following page

Continued from previous page

support them; and the lag of recognition proportionate to the nature of these new asks.

To acknowledge the priceless contributions made by our faculty volunteers, CHEST staff and volunteer leadership have developed a Faculty & Volunteer Treatment Action Plan, recently approved by the CHEST Board of Regents. This is part of our comprehensive "six F's" plan:

Formal recognition and rewards

Recognition and rewards: different meanings – but both important. Recognition is expressing gratitude for an expected job that was well done and includes a *formal* thank-you. Rewards are additional, tangible benefits for exceptional services. We now have enhanced guidelines for travel, honoraria, and amenities for our volunteer faculty. Also of note, two new awards will be bestowed annually beginning at CHEST 2016 Los Angeles – the Early Career Clinician Educator Award and the Master Clinician Educator Award. These are some additional ways we will more appropriately highlight the people who have helped make us CHEST, the leader in clinical education in chest medicine.

Feedback

In addition to learner satisfaction data, CHEST provides an unprecedented level of learner outcomes data to our faculty. We are even introducing a new peer-review of teaching (PRT) program, so faculty can get even more feedback from expert colleagues.

Faculty Development

As an education-focused organization, training and development play a foundational role. We are working to develop a comprehensive clinician educator program that will grow our bench of faculty. A newly launched database will more proactively track CHEST teaching opportunities and match interested members with these opportunities.

Face Time

Easy access to leadership and staff is important. We are implementing staff training that will better position all CHEST employees to more effectively facilitate and support the work we ask of our faculty. On another front, we are engaged in identifying new, user-friendly systems for session submission, conflict of interest disclosure, and review, as well as developing content.

Food

It is a simple but well-established fact that having a stocked lounge area for busy faculty on the run between teaching sessions enhances efficiency, communication, camaraderie, and overall morale.

Fun

The fun of discovering better ways to take care of our patients, be it from the teacher or learner perspective, in an engaging, effective learning environment is and always has been at the center of what we do.

CHEST's volunteer leaders, in service to their peers, the field, and the organization, have risen repeatedly to many challenges. We need to do a better job of rewarding and recognizing their irreplaceable contributions. The above initiatives, and others, we hope, will help demonstrate to our most precious resource, our member-faculty, that we truly value and appreciate their invaluable contributions on behalf of CHEST. Stay tuned and stay with us.

Subscribe to the new CHEST SEEK Library

The CHEST SEEK Library includes nearly 1,500 pulmonary, critical care, and sleep medicine questions in a 1-year subscription. Whether preparing for board exams or just wanting a solid review, sharpen your skills with this comprehensive collection for an introductory price of $149 ($199 for nonmembers). This is the best deal ever offered for SEEK, which can now be accessed via Apple, Android, and Web browser. Do not wait. The introductory price will only be offered for a limited time. Learn more at https://www.chestnet.org/Store.

This Month in *CHEST:* Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP
EDITOR IN CHIEF, *CHEST*

Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. By Dr. J. Corren, et al.

Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase III Study. By Dr. L. Bjermar, et al.

A Critical Review of the Quality of Cough Clinical Practice Guidelines. By Dr. M. Jiang, et al.

Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults With Community-Acquired Pneumonia. By Dr. W. H. Self, et al.

Evaluation of Pulmonary Nodules: Clinical Practice Consensus Guidelines for Asia. By Dr. C. Bai, et al.

Occupational and Environmental Contributions to Chronic Cough in Adults: Chest Expert Panel Report. By Dr. S. M. Tarlo, et al, on behalf of the CHEST Expert Cough Panel.

SUNRISE Program in India

Recently, CHEST completed the SUNRISE (Respiratory Initiative in Scientific Education) live learning program in India. More than 800 physicians attended and gained knowledge in asthma, COPD, ILD, and sleep over a 3-day period in three different cities – Bengaluru, Kolkata, and Delhi. According to the feedback report, more than half of the participants rated the program as highly above average, and approximately 70% will change something in their practice based on what they learned. Suggestions for next year's program, including content and speakers, are being considered.

Diego Maselli, MD, FCCP, addresses attendees in Bengaluru.

Attendees at the SUNRISE Program held in Delhi.

Three options for MIPS

MACRA *from page 1*

ing medication, you need to take this reprieve as an opportunity to familiarize yourself with the MIPS requirements as I expect this might not happen again. Most importantly, remember the final rule will provide essential details of the new program that are lacking from this early announcement."

Independent practice will become unrealistic for those who experience the greatest financial penalty.

DR. MATHERS

James A.L. Mathers Jr., MD, FCCP, pointed out that "under the MIPS system, based on comparison with peer practices, roughly a quarter of the providers choosing to remain in fee for service will see a significant financial penalty at the end of each year. The escalating financial penalties will make independent practice unrealistic for the 25% of practices that experience the greatest financial penalty," Dr. Mathers said. While recent CMS announcements "are encouraging, no details have been released and any relief in reporting requirements will be short term."

Nitin Damle, MD, president of the American College of Physicians, said in a statement that the ACP is pleased that "CMS plans … to give physicians more options to participate in the quality payment programs in 2017 without being at risk of negative adjustments. These changes are consistent with recommendations made by ACP and other physician stakeholders to exempt small practices from negative adjustments and to provide more flexible options for practices of all sizes to be successful."

Early details of the plan were announced in September in a blog post by CMS Acting Administrator Andy Slavitt.

The agency is currently reviewing comments on its proposed regulations to implement MACRA (Medicare Access and CHIP Reauthorization Act of 2015), with a final rule expected in November.

The QPP required CMS to divide physician compensation into two main tracks, the MIPS, which applies to those wishing to continue billing fee for service, and Advanced Alternative Payment Models (APMs).

Those who choose the MIPS track now have three options for when they must start reporting data next year. Data reported in 2017 will serve as the benchmark for bonus payments paid in 2019.

Option 1

Report "some data" in 2017. Doctors who report some data to the QPP will not face a Medicare pay cut. CMS considers even this low level of reporting a test for whether physicians will be ready for more intense MACRA involvement in 2018 and 2019. Exactly how much "some data" is currently is not defined.

Option 2

Participate for part of 2017. Those who choose to report data to QPP for some of the year also will be testing their systems for future MACRA compliance and may end up with a small Medicare pay increase. Again, the duration of reporting was not defined by the CMS at press time.

Option 3

Participate for the full year. Doctors who begin to report data from all parts of QPP on Jan. 1 will be eligible for a "modest" Medicare pay increase in 2019. Data on quality measures, use of technology, and practice improvement must be reported.

"While the recent comments by Acting Administrator Slavitt are encouraging, no details have been released and any relief in reporting requirements will be short term," according to Dr. Mathers.

For those who are eligible for participation in APMs, that track will begin Jan. 1, 2017.

The American Medical Association commended federal officials "for listening to physicians' concerns about the timeline that was originally proposed for MACRA," AMA President Andrew Gurman, MD, said in a statement. "The AMA believes the actions that the administration announced today will help give physicians a fair shot in the first year of MACRA

Continued on following page

Twice as much time spent on EHRs as on patients

BY GREGORY TWACHTMAN
Frontline Medical News

Physicians are spending twice as much time on electronic health records as they are face to face with patients, according to a new study by the American Medical Association.

Researchers observed 57 physicians in four specialties (family medicine, internal medicine, cardiology, and orthopedics) and found that for every hour of direct clinical face time with patients, nearly 2 additional hours is spent on EHR and desk work within the clinic day. Additionally, based on

EHR regulations need to focus on reducing the time-cost of providing care on their platforms and provide flexibility.

DR. SINSKY

diaries kept by 21 of the participating physicians, another 1-2 hours of personal time were spent each night doing additional computer and clerical work, according to the study published Sept. 5 in Annals of Internal Medicine (2016. doi: 10.7326/M16-0961).

"Over the years, doctors have recognized that more and more of their time was spent on nonpatient care, activities but probably haven't recognized the magnitude of that change," Christine Sinsky, MD, vice president of professional satisfaction at the AMA and lead author on the study, said in an interview. "Our study was able to help to quantify that and paint that picture."

Overall, physicians spent 27% of their day dealing directly with patients, while 49% of the time was spent on EHR and desk work. In the examination room with patients, physicians spent 53% of time on direct clinical face time and 37% on EHR and desk work.

The situation "is the cumulative effect of many, many well-intended efforts that individually might have made sense, but taken collectively have paradoxically made it harder for physicians to deliver quality of care and harder for patients to get the quality of care they deserve," she said.

EHR development should be focused on reducing the time-cost of providing care on their platforms, Dr. Sinsky recommended. She noted that for her practice, it takes 32 clicks to order and record a flu shot. "I think vendors have a responsibility to minimize time, to minimize clicks involved in a task."

She added that "regulators have a responsibility to not just add more and more regulations without first identifying the time-cost of complying with that regulation and without adding up the total cost of complying with regulation."

Future regulations on EHRs must add flexibility when it comes to who is entering information into the system, she said. "Many regulations are either written with the explicit statement – or it is implied or an institution might overinterpret the regulation – that the physician is the one who must do the keyboarding into the record," she said, noting that although not primarily studied in the research, preliminary data suggests that doctors who had documentation support were able to spend more time with their patients.

Finally, physicians themselves need to be stronger advocates for the changes they need to enable them to better serve their patients.

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In addition to Dr. Sinsky, three other study authors are employed by AMA, which funded the study.

No other financial conflicts were reported.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: This study finally quantified what many physician have known since EHRs were introduced ... patient time is being sacrificed to computer time. Perhaps equally or more important is the sacrifice of "family time" later in the evening. The discussion in the paper suggests that the loss of time related to EHRs may be contributing to the current level of physician dissatisfaction. The effect of age was also not a factor that was directly assessed in the study but the implication was that older physicians might be less efficient with technology compared with their younger counterparts. I suspect both of these suppositions may be accurate. I would, however, suggest an alternative method to deal with the issue of physician inefficiency with technology. Rather than attempting to fit square (pulmonologist), triangular (obstetrician), pentagonal (surgeon), etc, pegs into a round hole (EHR), regulators should craft rules that compel the multiple EHR vendors to provide platforms that limit clicking and scrolling to maximize patient/physician interaction. Thirty-two clicks for a flu shot is a bit ridiculous. Additionally, prior to mandating meaningful use, regulators should verify that it is truly meaningful to patient care and doesn't detract from physicians' time with patients.

Continued from previous page

implementation. This is the flexibility that physicians were seeking all along."

The new flexibility may not be a good thing, particularity for larger group practices that are ready to fully participate in MACRA as of Jan. 1, some said.

"This flexibility is especially important for small provider groups that may have legitimate logistical issues around MACRA's reporting requirements," Donald Fisher, PhD, president and CEO of AMGA, said in a statement. (AMGA was formerly known as the American Medical Group Association.)

"However, our membership is deeply concerned that the creation of these new reporting options will have the unintended result of penalizing the very provider groups that have made the largest investments to meet MACRA's goals of better quality, improved clinical practice activities, better use of electronic medical records, and lower resource use. These groups have already begun the transition from volume to value, and it is disappointing the rewards for their effort will be compromised rather than rewarded, as was MACRA's stated purpose by Congress and the administration," Dr. Fisher said.

By offering options for compliance, the CMS could potentially limit the amount of bonus payments in order to meet MACRA's budget-neutral requirements, according to Chet Speed, vice president of public policy at AMGA. There will be no potential penalties that would offset bonuses for organizations that are performing at a high rate, which could result in having to lower the maximum bonuses an organization would be eligible to receive.

"You've compressed rewards to a level where it just penalizes those who have made the investments" in upgrading their systems to prepare for the Jan. 1 start date, Mr. Speed said.

He emphasized that the CMS could still address this and make the full bonus payments available to those who are prepared to participate on Jan. 1, but that will not be known until the final rule is published.

He applauded the agency's efforts in continually reaching out to the physician community throughout the MACRA development process and said he is hopeful there will be resolution to these concerns in the final rule.

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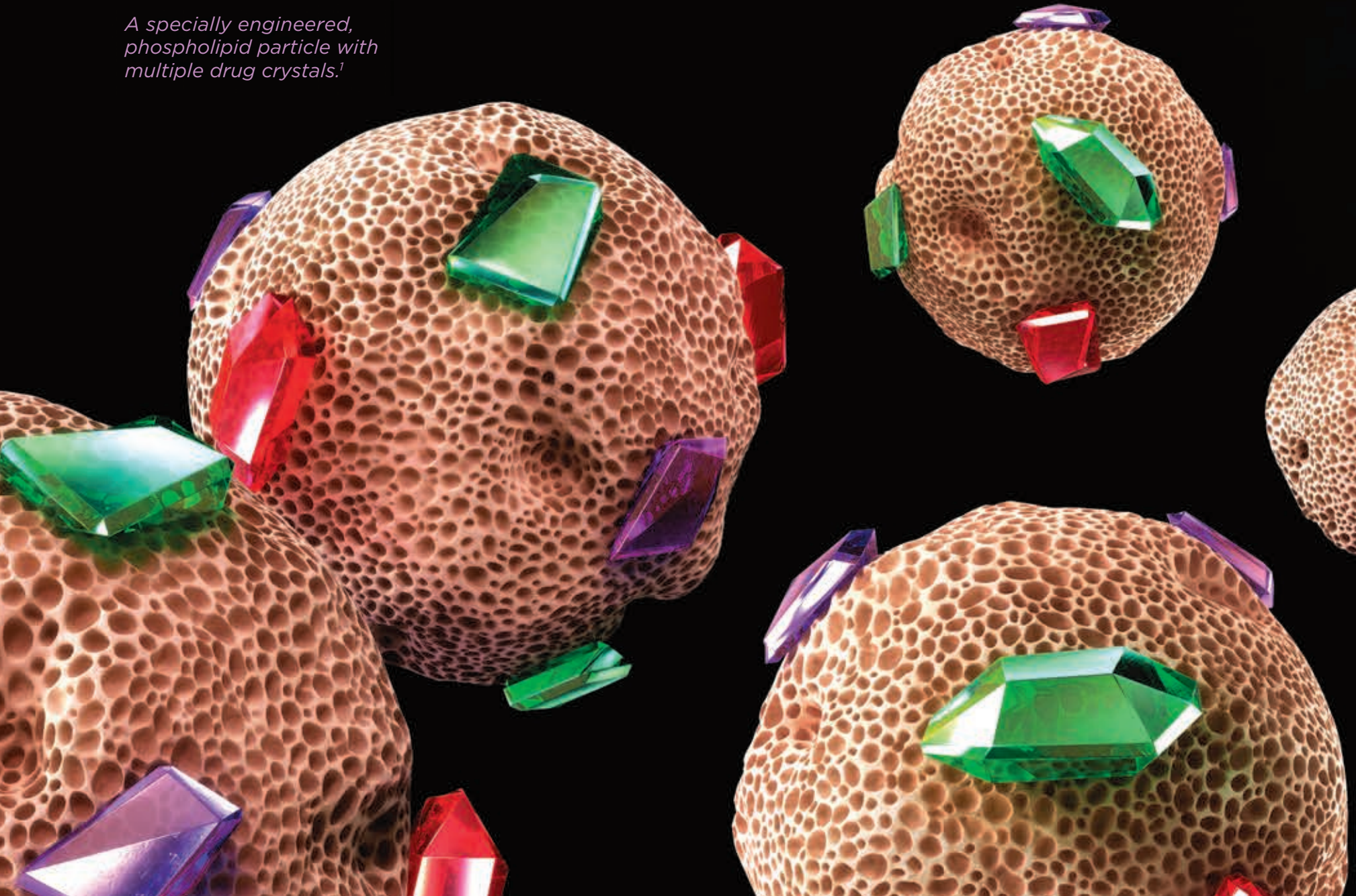

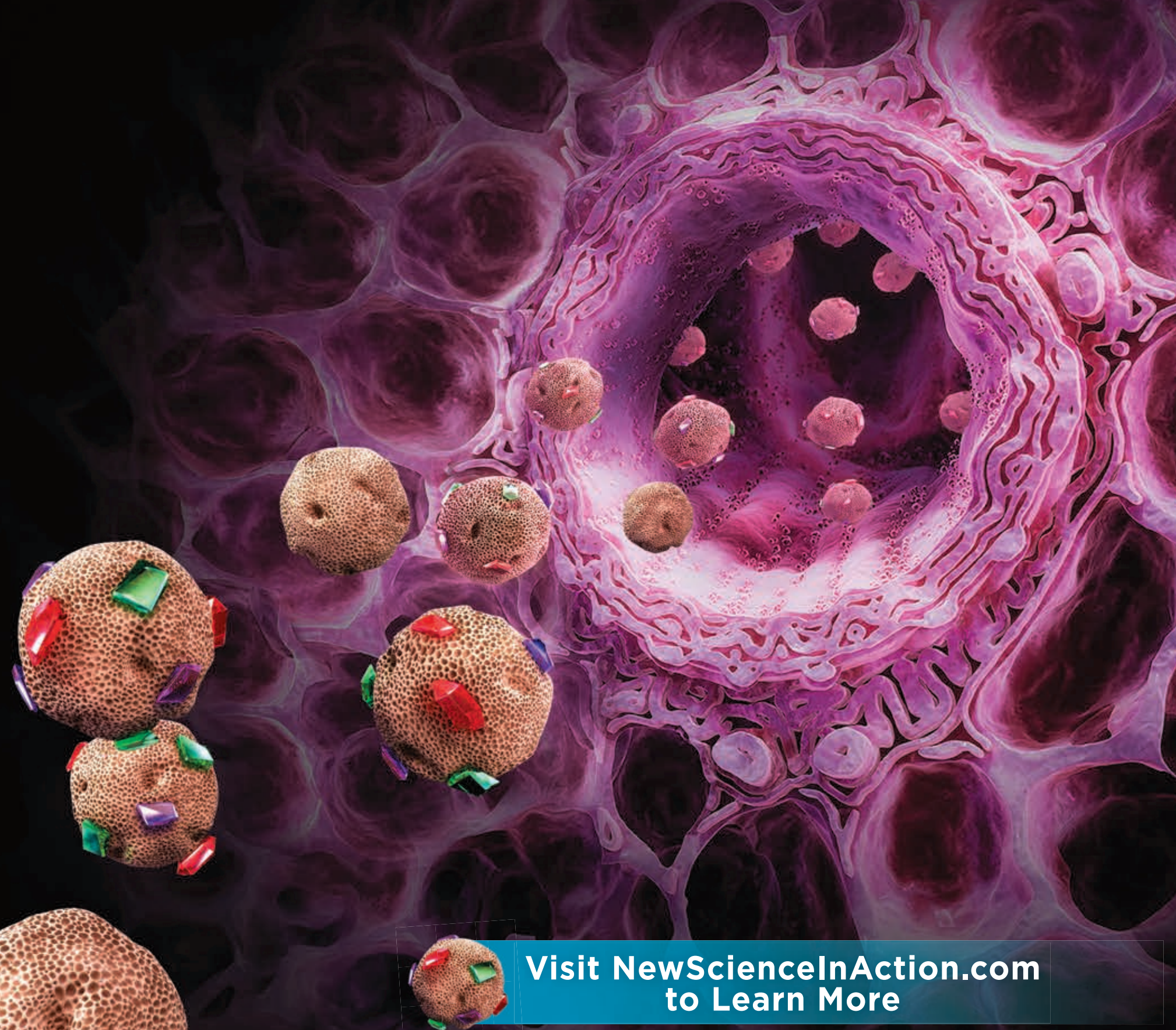

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Reference: 1. Vehring R et al. *Langmuir*. 2012;28(42):15015-15023.

AstraZeneca

New method proposed for phenotyping COPD patients

BY TED BOSWORTH
Frontline Medical News

LONDON – Based on readily available clinical data, patients with chronic obstructive pulmonary disease (COPD) can be placed into five phenotypes with different characteristics and risk profiles, according to data generated by a cluster analysis and presented at the European Respiratory Society International Congress 2016.

The algorithm that places patients into these phenotypes was developed from a cluster analysis, reported Pierre-Regis Burgel, MD, PhD, professor of respiratory medicine, Université Réné Descartes, Paris. Mortality rates at 3 years for these phenotypes ranged from 2.6% to 49.5%

"We think that this could be the basis for recognizing clinically distinct COPD phenotypes and designing better tailored management," Dr. Burgel explained. "We also think it has potential use in routine clinical assessment."

To create these phenotypes, data from 2,049 COPD patients enrolled in a French-Belgian collaborative cohort were evaluated with Classification And Regression Tree (CART) analyses. The five phenotypes were derived from symptom burden, respiratory function, relative age, and presence of comorbidities.

Based on these characteristics, "a set of clinical rules" to phenotype patients was developed, according to Dr. Burgel. This algorithm was then further validated with the 3,651 COPD patients enrolled in the prospective COPD Cohorts Collaborative International Assessment (3CIA) initiative.

"We think [this algorithm] could be the basis for recognizing clinically distinct COPD phenotypes and designing better tailored management. We also think it has potential use in routine clinical assessment," said Dr. Burgel.

The two initial branches in the algorithm are created by dividing patients into those with and without cardiovascular comorbidities or diabetes. In those without cardiovascular disease, the phenotypes are defined by relative symptom severity, using cut-off scores from the modified Medical Research Council (mMRC) dyspnea assessment tool and relative degrees of lung function impairment as measured with forced expiratory volume in 1 second (FEV_1).

In those with cardiovascular disease or diabetes, mMRC-defined symptoms and FEV_1-defined lung function impairment also create decision points in the algorithm, but age and body mass index (BMI) are additional variables that direct patients to a specific phenotype. Class 4 and 5 are reached in the absence of cardiovascular disease or diabetes only, while cardiovascular disease is a prerequisite to reach Classes 4 and 5. Class 2 is the only phenotype that can be reached through the algorithm irrespective of the presence or absence of cardiovascular disease.

Using this algorithm, each of the phenotypes was associated with similar relative hierarchy in mortality in the two cohorts, even though mortality rates for each phenotype were consistently lower in the 3CIA group.

For class 1, which was reached by patients with cardiovascular disease or diabetes, the greatest symptom burden, and the lowest lung function, the mortality rates at 3 years were 49.5% and 23.2% for the French-Belgian and 3CIA cohorts, respectively.

For class 4, which was also defined by the greatest symptom burden and the lowest lung function without cardiovascular disease or diabetes the mortality rates were 45.3% and 27.3%, respectively. The lowest mortality rates, which were 2.6% and 4.0%, respectively, were found in the class 5 phenotype, which contained patients with a low symptom burden (mMRC less than or equal to 1), relatively good lung function (FEV_1 greater than or equal to 60%), and no history of cardiovascular disease or diabetes.

In classes 2 and 3, the mortality rates fell in between those of the lowest- and highest-risk phenotypes. Specifically, these 3-year mortality rates were 22.9% and 24%, respectively, in the French-Belgian cohort, and 11.1% and 14.1%, respectively, in the 3CIA cohort.

The consistency of the hierarchy of outcomes in the two cohorts provides the basis for suggesting that these phenotypes are effective for categorizing relative risk, according to Dr. Burgel. He believes that the phenotypes are clinically important, and he emphasized that the algorithm relies on clinical information that is already routinely collected and readily accessible.

"There is growing awareness that COPD phenotypes are important and are likely to be valuable in managing patients," Dr. Burgel explained. "We feel that we have created simple rules for allocating patients that we think will be useful for research and for clinical application."

Dr. Burgel reported financial relationships with a number of drug companies.

Modified COPD assessment simplifies risk prediction

BY TED BOSWORTH
Frontline Medical News

LONDON – Four questions from the eight-question COPD Assessment Test (CAT) provide about the same prognostic accuracy in patients with chronic obstructive pulmonary disease (COPD) as does the full CAT, according to an analysis presented at the annual congress of the European Respiratory Society.

When the four- and eight-question versions were compared for exacerbation and other clinical outcomes over a 1-year period of follow-up, "both strategies demonstrated similar discrimination," reported Carlos H. Martinez, MD, division of pulmonary and critical care medicine, University of Michigan Health System, Ann Arbor.

The CAT is an eight-item tool for evaluating the health status of patients with COPD as well as for predicting risk of COPD-related events, particularly exacerbations. The test is designed for self-administration by patients. For each of the questions, which address symptoms and activity limitations, patients are asked to answer on a scale ranging from one (indicating no clinical burden) to five (indicating severe burden). Based on the maximum score of 40, a score below 10 signifies a low impact from COPD, a score of 10-20 signifies a medium impact, and a score above 20 signifies a high impact.

In this study, a simplified version of the CAT that employed just four of the questions was evaluated in 880 participants in the observational SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study), which was funded by the National Heart, Lung, and Blood Institute and has prospectively enrolled COPD patients at seven participating centers. Ever-smokers from SPIROMICS were eligible for this analysis if they had a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of greater than or equal to 0.70 and an FVC above the lower limit of normal.

The four questions that were retained were about cough, phlegm, chest tightness, and breathlessness. The four questions that were eliminated were about activity limitation, sleep, energy, and the effect of lung symptoms on willingness to leave the house.

With the traditional test, using a cut point of greater than or equal to 10, 51.8% were classified as having a significant COPD burden. In this group, 15.3% experienced one or more exacerbations during 1 year of follow-up. With the simplified version focused on respiratory-related symptoms alone and using a cut point of greater than or equal to 7, 45.8% were classified as having a significant COPD burden, and 15.6% had one or more exacerbations during the same period of follow-up.

"The two strategies largely identified the same individuals," according to Dr. Martinez, who reported the agreement as 88.5% (Kappa 0.77; *P* less than .001). There was no difference in the area under the curve (AUC) to predict exacerbations at 1 year. In further analysis, "subjects identified by either method also had more depression and anxiety symptoms, poorer sleep quality, and greater fatigue [than did the lower risk group]," Dr. Martinez added.

An AUC ROC (receiver operating characteristic) statistical analysis to compare the traditional and abbreviated CATs for cross-sectional associations showed close agreement. The values were nearly identical for such variables as dyspnea, impairment as measured with the 6-minute walking distance (6MWD) test, and quality of life as measured by the St. George's Respiratory Questionnaire.

Antibiotics overprescribed for asthma inpatients

BY DEEPAK CHITNIS
Frontline Medical News

Antibiotics are overprescribed in asthma-related hospitalizations, even though guidelines recommend against prescribing antibiotics during exacerbations of asthma in the absence of concurrent infection, reported Peter K. Lindenauer, MD, MSc, of Baystate Medical Center in Springfield, Mass., and his colleagues.

They examined the hospitalization records of 51,951 individuals admitted to 577 hospitals in the United States between 2013 and 2014 with a principal diagnosis of either asthma or acute respiratory failure combined with asthma as a secondary diagnosis. Each patient type and the timing of antibiotic therapy was noted.

These findings suggest a significant opportunity to improve patient safety and reduce the spread of resistance.
DR. LINDENAUER

A total of 30,226 of the 51,951 patients (58.2%) were prescribed antibiotics at some point during their hospitalization, while 21,248 (40.9%) were prescribed antibiotics on the first day of hospitalization, without "documentation of an indication for antibiotic therapy."

Macrolides were most commonly prescribed, given to 9,633 (18.5%) of patients, followed by quinolones (8,632, 16.1%), third-generation cephalosporins (4,420, 8.5%), and tetracyclines (1,858, 3.6%). After adjustment for risk variables, chronic obstructive asthma hospitalizations were found to be those most highly associated with receiving antibiotics (odds ratio 1.6, 95% confidence interval 1.5-1.7).

"Possible explanations for this high rate of potentially inappropriate treatment include the challenge of differentiating bacterial from nonbacterial infections, distinguishing asthma from chronic obstructive pulmonary disease in the acute care setting, and gaps in knowledge about the benefits of antibiotic therapy," the authors posited, adding that these findings "suggest a significant opportunity to improve patient safety, reduce the spread of resistance, and lower spending through greater adherence to guideline recommendations."

The National Heart, Lung, and Blood Institute and Veterans Affairs Health Services Research and Development funded the study. Dr. Lindenauer and his coauthors did not report any relevant financial disclosures.

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Benralizumab reduces severe asthma events

BY SARA FREEMAN
Frontline Medical News

LONDON – The investigational treatment benralizumab significantly reduced the number of exacerbations that patients with severe, uncontrolled asthma experienced during the course of a year in two phase III studies.

In the SIROCCO and CALIMA trials, which altogether involved more than 2,000 adult patients, the annual exacerbation rate (AER) was cut by 28%-51%, compared with placebo when benralizumab was added to standard combination therapy of an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA).

Benralizumab treatment was also associated with significant improvements in lung function (up to 159 mL increase in FEV_1), and reduced daily

asthma symptoms of wheeze, cough, and dyspnea versus placebo.

There were also improvements seen in patient-reported measures of asthma control and quality of life.

The results of these two multicenter, randomized, double-blind, placebo-controlled, parallel group studies were published in full online in The Lancet to coincide with their presentation at the annual congress of the European Respiratory Society.

Benralizumab has been shown to rapidly and almost completely deplete the number of eosinophils in the blood, airways, and bone marrow, said Dr. Bleecker.

Benralizumab is a humanized, monoclonal antibody that has been shown to rapidly and almost completely deplete the number of eosinophils in the blood, airways, and bone marrow, Eugene R Bleecker, MD, who presented the results of the SIROCCO study, explained at the meeting.

Dr. Bleecker, who is the director of the Center for Genomics and Personalized Medicine Research at Wake

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Forest University in Winston-Salem, N.C., observed that benralizumab "works a little bit differently" than other interleukin (IL)-5–targeting monoclonal antibodies, such as mepolizumab and reslizumab. Rather than target the IL-5 ligand itself, benralizumab binds to IL-5 receptors present on the surface of eosinophils. This action activates natural killer cells, which then destroy the eosinophils via antibody-dependent cell-mediated cytotoxicity.

Phase IIb data have already shown a benefit for benralizumab versus placebo in patients with uncontrolled asthma with high (300 cells/mcL or greater) eosinophil counts in the blood. The aim of the SIROCCO and CALIMA phase III trials was thus to examine the efficacy and safety of the novel agent further in this patient population.

In SIROCCO, 1,205 patients were randomized, and 1,306 were randomized in CALIMA. Key inclusion criteria were physician-diagnosed asthma requiring ICS/LABA therapy and at least two exacerbations in the past 12 months. Patients also needed to be symptomatic during a 4-week run-in period before being randomized to one of three study groups. The groups included one that received

benralizumab at a subcutaneous dose of 30 mg every 4 weeks; another that received benralizumab at a subcutaneous dose of 30 mg every 4 weeks for the first three doses then a 30 mg dose or placebo injection alternating every 4 weeks; and a third group that received placebo injections every 4 weeks.

The mean age of patients in both studies and across treatment arms was broadly similar, ranging from 47 to 50 years. Around two thirds of the study population was female, with similar baseline characteristics.

The primary endpoint was the AER in patients with a blood eosinophil count of 300 cells/mcL or higher. In SIROCCO this was measured at 48 weeks and in CALIMA at 56 weeks.

The respective AERs for placebo and for the 4- and 8-week dosing regimens of benralizumab were 1.33, 0.73, and 0.65 in SIROCCO and 0.93, 0.6, and 0.66 in CALIMA. This represented a 45% reduction in the AER for the 4-week and a 51% reduction for the 8-week regimens of benralizumab versus placebo in SIROCCO, and a 36% and 28% reduction, respectively, in CALIMA.

There was a large placebo effect and the overall population recruited

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into CALIMA may have had less severe asthma than the patients who participated in SIROCCO, the principal investigator for CALIMA, Mark FitzGerald, MD, pointed out during a press briefing organized by AstraZeneca. "But when you look at the composite of both studies together, you can see that the results are quite robust," said Dr. FitzGerald, the director of the Centre for Lung and Heart Health at Vancouver Coastal Health Research Institute.

There was also some evidence that patients who had three or more prior exacerbations fared better, he said, highlighting the importance of defining the patient population who may benefit the most from this treatment.

Something that needs to be investigated further is why patients given the 8-week benralizumab regimen seemed to do better, at least numerically, than those given the 4-week regimen. Dr. FitzGerald suggested that "because eosinophil cells are such a powerful driver of disease, perhaps you may not actually need to be treated as frequently as historically we might have done."

Other similar biologic agents need dosing every 2 to 4 weeks, but perhaps every 8 weeks is a possibility in the future for benralizumab. A lot can be learned from how biologics are used in rheumatology, he suggested, where treatments have started being given less frequently, because the biology of the various rheumatic diseases is now better understood.

Why 8 weeks of benralizumab seemed better for patients than 4 weeks of benralizumab needs to be investigated.
DR. FITZGERALD

Any adverse event was reported by a similar percentage of actively-treated (71%-75%) and placebo-treated (73%-78%) patients. The frequency and nature of other adverse events were similar to placebo.

The SIROCCO and CALIMA trial data will form part of AstraZeneca's U.S. and EU regulatory submissions later this year for benralizumab as a treatment for severe, uncontrolled, eosinophilic asthma.

"Potentially, when it becomes available, benralizumab will provide a new therapeutic option for this class of patient." Dr. FitzGerald said.

Benralizumab is also being investigated as a possible treatment for patients with less severe eosinophilic asthma in the BISE phase III study and as an option for those with severe chronic obstructive pulmonary disease who have high levels of eosinophils in the phase III VOYAGER program.

AstraZeneca and Kyowa Hakko Kirin funded the studies.

Dr. Bleecker is the principal investigator for the SIROCCO trial and disclosed receiving research funding or consulting for AstraZeneca-MedImmune, Boehringer Ingelheim, Genentech/Roche, GlaxoSmithKline, Johnson & Johnson (Janssen), Merck, Novartis, Sanofi, Cephalon/Teva, and Regeneron-Sanofi.

Dr. FitzGerald disclosed acting as an advisory board participant, receiving funding or fees, or both from AstraZeneca, ALK Abello, Boehringer Ingelheim, Hoffman-La Roche, Genentech, GlaxoSmithKline, MedImmune, Merck, Novartis, and Teva.

RPL-554 adds to short-acting drugs' benefits in COPD

BY SARA FREEMAN
Frontline Medical News

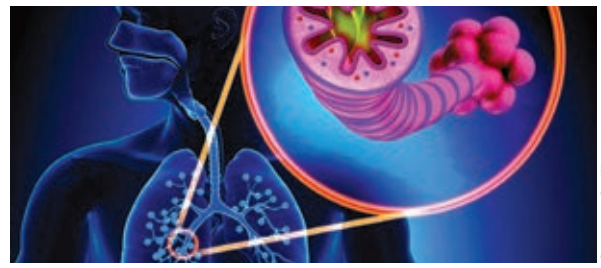
LONDON – Improved lung function was seen in patients with chronic obstructive pulmonary disease (COPD) when an inhaled dual phosphodiesterase (PDE) inhibitor, RPL-554, was used on top of standard short-acting treatment in a single-center, crossover study.

There was a 51% increase in the peak forced expiratory volume in 1 second (FEV_1) from baseline to the time of measurement up to 12 hours later in patients given RPL-554 in addition to the short-acting beta2-agonist (SABA) salbutamol versus the SABA alone. A benefit also resulted from adding RPL-554 to the short-acting muscarinic antagonist (SAMA) ipratropium. Taking this second combination of drugs resulted in a 66% higher FEV_1, when compared with taking the SAMA alone (*P* less than .001 comparing the combinations with the SABA or SAMA alone).

"We were primarily interested to know if giving this novel drug in addition to a beta-agonist or antimuscarinic could produce more bronchodilation, and that's what we saw," said David Singh, MD, of the University of Manchester (England), who presented the study findings at the annual congress of the European Respiratory Society.

In addition to inducing "significant and clinically relevant" additional bronchodilation, a single dose of RPL-554 was found to increase lung volumes when administered on top of standard-of-care bronchodilators. The peak forced vital capacity (FVC) increased by 79.5% when RPL-554 was added to salbutamol and by 43.2% when it was added to ipratropium. There were also improvements in the baseline residual lung volume and in airway conductance.

RPL-554 is a novel inhaled dual PDE-3/4 inhibitor under investigation in the treatment of both COPD and asthmatic patients. "This is a reformulation of RPL-554, delivered by nebulization," Dr. Singh observed. It has been shown to have both anti-inflammatory and bronchodilatory properties



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in clinical studies, he added, with the latter action thought to be additive to beta-agonists and synergistic with antimuscarinic agents according to preclinical data.

The aim of the study was to look at the potential additive or synergistic bronchodilatory effects of RPL-554 in a clinical study for patients who had moderate to severe COPD. A total of 36 patients (19 men and 17 women) were recruited; 30 completed the study. The mean age of the recruited patients was 61 years; mean body mass index was 27.7 kg/m^2, mean baseline FEV_1 was 50.4% or 1.44 L, and the patients exhibited a mean increase in FEV_1 of 17.7%, 30 minutes after being given salbutamol or ipratropium at screening. The latter "gives you an idea of the reversibility of the population," Dr. Singh said.

Six treatment options were compared: salbutamol 200 mcg, salbutamol 200 mcg plus RPL-554 6 mg, ipratropium 40 mcg, ipratropium 40 mcg plus RPL-554 6 mg, RPL-554 6 mg, and placebo. At each treatment visit patients were dosed, in a double-blind fashion, with salbutamol, ipratropium, or placebo via a metered-dose inhaler (MDI), and then randomized to receive either inhaled RPL-554 or a placebo via a nasal nebulizer. Spirometry was performed before and up to 12 hours after treatment, and plethysmography was performed before and at 1 and 4 hours after dosing.

The addition of RPL-554 to standard bronchodilator therapy was associated with a faster onset of bronchodilation when compared to either the SABA or SAMA as monotherapies – at 3.6 minutes when added to salbutamol versus 5.2 minutes for the SABA alone, and 4.2 minutes when added to ipratropium versus 18.4 minutes for the SAMA alone. Used alone, however, RPL-554 had an onset of effect of 14.3 minutes.

Overall, the single-doses of RPL-554 used were well tolerated when given alone or in combination with the other treatments. "Obviously with a PDE-3 inhibitor we want to be careful about cardiovascular changes and monitor that, but we did not see anything," Dr. Singh reported.

Verona Pharma Plc sponsored the study. Dr. Singh reported receiving sponsorship, honoraria, or research funding from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GlaxoSmithKline, Glenmark, Johnson and Johnson, Merck, NAPP, Novartis, Pfizer, Skyepharma, Takeda, Teva, Theravance, and Verona Pharma Plc.

Artificial intelligence bests physicians' diagnoses

BY TED BOSWORTH
Frontline Medical News

LONDON – In a proof-of-principle study, artificial intelligence (AI) led more frequently to the correct diagnosis of underlying lung disease than did physicians' use of standard algorithms, such as those recommended by the American Thoracic Society and the European Respiratory Society, according to late-breaker data presented at the annual congress of the European Respiratory Society.

"The beauty of this approach is that artificial intelligence can simulate the complex reasoning that clinicians use to reach their diagnosis but in a more standardized and objective fashion, so it removes any bias," reported Wim Janssens, MD, PhD, of the division of medicine and respiratory rehabilitation at University of Leuven (Belgium).

The AI employed in this study was based on a subfield of computer science that relies on patterns within statistics to build decision trees. Often called machine learning, this type of AI grows smarter as it learns from the patterns it finds in the data provided.

In this case, the AI was designed to provide diagnoses for lung diseases based on patterns drawn from clinical and lung function data. The computer-based choices were compared to diagnoses reached by clinicians. The final diagnoses were validated by a consensus of expert clinicians.

"The computer-based choices were in almost all cases better than the choices made by standard diagnostic algorithms," reported Marko Topalovic, PhD, a researcher in AI who is affiliated with the University of Leuven. Dr. Topalovic presented the data at the ERS.

The study involved 968 patients presenting with lung symptoms to a pulmonary clinic for the first time. Standard clinical data, such as smoking history, body mass index, and age, were collected. Lung function studies conducted in all patients included spirometry, body plethysmography, and airway diffusion, although participating clinicians were permitted to order additional tests at their own discretion. Clinical diagnoses were separated into 10 predefined disease groups.

The average accuracy of clinicians' diagnoses was 38%. The clinicians were best at identifying chronic obstructive pulmonary disease (COPD), having accurately diagnosed 74% of the cases of this disease. For other disease groups, the clinician's accuracy rarely exceeded 50%. The diagnoses made by AI, on the other hand, on average, were 68% accurate. For diagnosing COPD, the AI achieved a positive predictive value of 83% and a sensitivity of 78%. The positive predictive value and sensitivity of AI for asthma (66% and 82%, respectively) and interstitial lung disease (52% and 59%) were both significantly greater than those achieved by the clinicians.

The AI eliminates the potential for a physician's bias to cause one clinical variable to be given more weight relative to another, Dr. Janssens said. Dr. Topalovic and Dr. Janssens reported no relevant financial relationships.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Although most pulmonary physicians are successful at diagnosing common conditions like COPD and asthma, other diseases of the lungs are more difficult to identify. The news that the use of artificial intelligence systems may improve diagnostic accuracy is thought provoking. No one expects computer-based systems to replace physicians, but the employment of these systems may benefit patients by leading to more rapid and accurate diagnoses. Testing might therefore be performed in a more parsimonious fashion.

Trials confirm benefits of triple COPD therapy

BY SARA FREEMAN
Frontline Medical News

LONDON – Phase III evidence confirms the multiple benefits of using a triple, fixed-dose combination (FDC) therapy over standard options in patients with severe chronic obstructive pulmonary disease (COPD), according to a presentation on two trials at the annual congress of the European Respiratory Society.

In the TRINITY trial, the combination of the inhaled corticosteroid (ICS) beclometasone diproprionate (BDP), the long-acting beta-agonist (LABA) formoterol fumarate (FF), and the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide (GB) delivered via a single pressurized metered-dose inhaler (pMDI), was more effective at reducing exacerbations than was tiotropium bromide (Spiriva, Boehringer Ingelheim) monotherapy.

Results of the TRILOGY trial, which were simultaneously published in The Lancet (doi: 10.1016/S0140-6736(16)31354-X) at the time of their presentation at the ERS meeting, showed that the novel single-inhaler, triple fixed-dose combination could induce greater improvements in lung function when compared to a double fixed-dose combination of BDP and FF (Foster, Chiesi Farmaceutici SpA).

"LAMA monotherapy or ICS/LABA are standard options for treating patients with advanced COPD," Jørgen Vestbo, MD, president of ERS and professor of respiratory medicine at the University of Manchester (England), said in an interview.

Dr. Vestbo, who was an investigator in both the TRINITY and TRILOGY trials, added that the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines also mention that these drugs can be combined in patients who continue to experience COPD exacerbations. "But the evidence behind that is fairly weak," he observed.

SARA FREEMAN/FRONTLINE MEDICAL NEWS

Dr. Jørgen Vestbo

Although many patients are already being treated with triple therapy, this is via two inhalers, and "there have not been that many really good, long-term outcome studies" that have proven this approach to be the best way to manage those at risk for continued exacerbations of COPD, he said.

Drug companies are now starting to combine these three drugs into one inhaler, however, and this means that registration studies need to be done to get the products licensed, and so "there is an interest in coming up with the evidence," Dr. Vestbo said.

"What is good about these two studies is that they are both 1-year studies and they are of sufficient size to give quite good estimates … These are studies that we should have done 5 years ago," he said. Although the ideal is to have patients on as little therapy as possible, the results of TRINITY and TRILOGY now provide much needed evidence that it will work better than either LAMA or ICS/LABA.

The piece of evidence that is still missing is what the benefit, if any, is over a LAMA/LABA combination, a fact noted during discussion following the presentations of these data at the ERS meeting and in an editorial by Peter Calverley, MD, of the University of Liverpool (England) that accompanied the published TRILOGY findings (Lancet. 2016;388:937-8). There also is a question over whether twice daily is really better than once daily dosing, or vice versa.

"Until these next studies become available, we can be comforted by the knowledge that three therapies can be combined in a single inhaler which offers more effective therapy than at least one of the recommended treatment regimens for patients with severe COPD," Dr. Calverley observed in reference to TRILOGY only. He added, "I am not sure that the guidelines [for treating severe COPD] will change much, but at least they can say with better certainty that you can use the triple."

TRINITY – can triple be better than LAMA monotherapy?

The TRINITY study looked at whether patients with GOLD 3-4 COPD would be better off treated with LAMA monotherapy (tiotropium 18 mcg, one puff per day), the triple fixed-dose combination of BDP (100 mcg), FF (6 mcg), and GB (12.5 mcg) given via the novel pressurized metered-dose inhaler (two puffs twice daily), or a "free" triple combination of BDP (100 mcg) and FF (6 mcg) given via one pressurized metered-dose inhaler (two puffs daily) plus the same dose of the once-daily LAMA.

In all, 2,690 patients were randomized to these three treatments arms. The mean age of patients was 63 years and the majority (74%-77%) were men, with an average FEV_1 predicted of 36% and one COPD exacerbation in the past year. Just under half of the study population were current smokers. Most (75%) had received prior treatment with an ICS/LABA combination, with about 11% receiving LAMA, and the rest either ICS/LAMA (3%), or LABA/LAMA (12%)

The annualized exacerbation rate (the primary endpoint) was 0.457 in the 1,077 patients who were treated with the triple fixed-dose combination versus 0.571 in the 1,074 patients who received tiotropium alone. The rate ratio was 0.8 indicating a 20% reduction in exacerbations was achieved ($P = .003$).

The annualized exacerbation rate in the 532 patients given the "free" triple combination (BDP/FF plus tiotropium) was 0.452, with a rate ratio of 0.790 ($P = .010$) versus those who received the LAMA as monotherapy.

There was no significant difference between the two triple combination strategies.

Presenting these data, Dr. Vestbo noted that the benefit was seen in preventing both severe and moderate COPD exacerbations. Significantly improved lung function, as measured by the change in FEV_1 from baseline to week 52, was also observed to a greater degree with the triple therapy approaches than with the LAMA monotherapy.

"All three treatments were well tolerated and there were no particular safety concerns in this study," he said.

TRILOGY – are three drugs better than two?

In contrast to the TRINITY study, the TRILOGY study looked at whether patients with severe COPD would be better off taking an ICS/LABA or the new triple fixed-dose combination pressurized metered-dose inhaler.

Just over 1,200 patients were recruited into the study, which had two co–primary endpoints: change from baseline to week 26 in predose morning FEV_1 and 2-hour postdose FEV_1, and the change in transition dyspnea index focal score at week 26.

Results showed that the triple fixed-dose combination improved predose FEV_1 by 0.081 L and 2-hour postdose FEV_1 by 0.117 L compared with the ICS/LABA combination (P less than .001 for both comparisons). Mean transition dyspnea index scores were 1.71 and 1.50, with a nonsignificant difference of 0.21.

"To be honest, I don't think we had expected that [the triple combination] would mean much for patients, but we were hoping there would be a significant increase in lung function and a reduction of symptoms," Dr. Vestbo said about the TRILOGY study. "What we saw was there was [symptomatic improvement] but it was not quite as impressive as we thought, but we reduced exacerbations."

There was a significant, 23% reduction in the annualized exacerbation rate via the triple combination versus the ICS/LABA combination (0.41 vs 0.53, adjusted rate ratio 0.77, $P = .005$).

The triple approach was well tolerated, with no increase in adverse events versus the dual combination.

Chiesi Farmaceutici SpA funded the studies. Dr. Vestbo was an investigator for both TRINITY and TRILOGY and has received honoraria for advising and presenting from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Novartis. Dr. Calverley has consulted for Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: The evidence provided from these two trials affirms the treatment strategy employed by many practitioners who treat patients with severe COPD (i.e. using triple therapy). As mentioned in the article, it is not known if this strategy is superior to a LAMA/LABA combination, and if there is any real importance of dosing interval/product selection. In the end, these studies support a prevailing clinical approach and importantly showed a reduction in exacerbation rates.

The power of flexibility is yours with **REVATIO Oral Suspension**

With REVATIO you have 3 dosage forms to treat pulmonary arterial hypertension (PAH): oral suspension, tablet, and injection.

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Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α–blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

REVATIO is available in the following dosage forms:

- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)

The Revatio® Family

Available in OS, tablet, and injection forms.

Please see brief summary of Full Prescribing Information on following pages.

Revatio® sildenafil

Revatio® sildenafil 20 mg tablets

Brief Summary of Prescribing Information. Consult Full Prescribing Information at REVATIOHCP.com

INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension *[see Warnings and Precautions]*, Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations]*.

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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.

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). 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.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications]*.

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over 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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only Rev. June 2015

Low doses may revive therapy for chronic cough

BY TED BOSWORTH
Frontline Medical News

LONDON – AF-219, a promising targeted therapy for chronic cough derailed by taste disturbances, has been revived by new studies suggesting that there is a therapeutic window that preserves benefits but reduces the risk of the adverse effect, according to new data presented at the annual congress of the European Respiratory Society.

The median duration of chronic cough of the patients on which the new data is based was 13 years. For patients with this type of durable cough history, there is a major unmet need for effective agents, reported Dr. Jacky Smith, MB, ChB, PhD, and professor of respiratory medicine at the University of Manchester (England).

Much lower doses appear to provide near maximum antitussive effects.

The P2X3 antagonist AF-219 "is showing real promise as an antitussive agent when used at low doses," Dr. Smith said.

P2X3 receptors are expressed by afferent neurons on the vagus nerves and appear to be a strong trigger of cough when stimulated, according to previous work by Dr. Smith and others. AF-219 is an oral antagonist of P2X3 and produced a 75% reduction in cough frequency when administered in a dose of 600 mg twice daily in a previously reported double-blind, placebo-controlled pilot study (Abdulqawi R et al. Lancet. 2015;385:1198-205). "However, there was a small wrinkle. All of the patients had taste disturbances. At this dose, it was primarily loss of taste," Dr. Smith explained. As P2X3 is also found on neurons mediating taste, the adverse event was consistent with the mechanism of AF-219.

A series of studies have since been conducted to show that much lower doses than the twice-daily 600 mg dose employed in the original trial provide an antitussive effect but impose a much reduced risk of affecting taste.

In the latest dose-ranging study, 30 patients, who on average were aged 60 years, were randomized in a crossover design to receive placebo or active therapy in sequential doses over 4 days each of 7.5 mg, 15 mg, 30 mg, or 50 mg twice daily. At the end of the initial 16-day study period and a washout of 14 to 21 days, the patients who were initially randomized to placebo were evaluated on the sequential doses of active therapy, and those previously treated with active therapy took placebo.

On placebo, there was no change in cough frequency. On active therapy, there were incremental reductions in cough at 7.5 and 15 mg, but the differences relative to placebo did not reach statistical significance. Significant reductions in cough frequency relative to placebo were reached on both the 30 mg ($P = 0.001$) and the 50 mg dose ($P = 0.002$). The reductions on these two doses, however, were not significantly different from each other, suggesting that 30 mg may be an adequate dose to achieve clinically relevant antitussive benefits.

Taste disturbances, which were reported in 6.7% of patients taking both the 7.5 mg and 15 mg dose, increased to 46.7% in those taking the 30 mg dose and then to 53.3% of those taking the 50 mg dose. Lack of taste was only reported by 6.7% of those taking the 50 mg dose and none of those taking lower doses. Other adverse events, such as nasal dryness and rhinitis, were infrequent (less than 10%) and not dose related.

"Significantly lower doses than we originally tested appear to provide near maximum antitussive effects but with a much reduced risk of changes in taste," Dr. Smith reported.

She added that in this dose-ranging study, there was a correlation between increasing dose and increasing cough-specific measures of quality of life.

"These data support a separation of the dose response relationships for antitussive effects and taste disturbance," Dr. Smith reported. "Studies of longer duration are needed to test sustained efficacy and tolerability."

Simtuzumab did not help IPF patients

BY TED BOSWORTH
Frontline Medical News

LONDON – Despite very promising activity in animal models of idiopathic pulmonary fibrosis (IPF), a monoclonal antibody targeted at an enzyme considered to be important to collagen cross-linking did not produce any improvement in progression-free survival (PFS), according to results of a multicenter study presented at the annual congress of the European Respiratory Society.

"This was such a negative study, there is no point in doing another," reported Ganesh Raghu, MD, FCCP, director of the Pulmonary Fibrosis Program at the University of Washington Medical Center, Seattle.

The focus of this study was simtuzumab, a monoclonal antibody targeted at lysyl oxidase like 2 (LOXL2), an enzyme which catalyzes a step in the formation of collagen crosslinks, which are thought to be important in fibrosis formation. Simtuzumab has been entered into clinical trials for treatment of several forms of fibrosis, including fibrosis in the liver.

"In animal models, simtuzumab has demonstrated efficacy in reducing fibrosis when administered prior to fibrosis formation or after the process has already begun," Dr. Raghu explained. He said a large trial was initiated in IPF because the agent seemed so promising and because a large study was thought to be the best strategy to arrive at a definitive answer regarding safety and efficacy.


DR. RAGHU

The drug was found safe but not effective. The independent data monitoring and safety committee terminated the trial early for futility.

In the study, 544 IPF patients were randomized to 125 mg simtuzumab or placebo administered subcutaneously once weekly. The primary endpoint was PFS, but there were a large number of secondary endpoints including hospitalization for progressive disease, change in 6-minute walk distance (6MWD), and overall survival.

For the endpoint of PFS, "there was absolutely no difference" between the groups receiving simtuzumab or placebo. When the patients were stratified for demonstrating above or below median expression of LOXL2, which was a prespecified analysis for the trial, there was still no difference between groups. Even when those in the top quarter percentile of LOXL2 expression were compared with those with less [expression of the enzyme], there was still "absolutely no difference."

There was also no significant evidence of benefit for simtuzumab observed on key secondary endpoints, such as overall survival. When patients were stratified by baseline lung function as expressed by percentage of predicted forced expiratory volume in 1 second (FEV_1), there was no signal of benefit for those with severe, moderate, or mild impairment.

One criticism of this study raised after the presentation was that patients with 26% or greater of predicted FEV_1 were permitted into the study. It was suggested that such patients would be expected to already have a high degree of fibrosis and therefore would be less likely to benefit from an antifibrosis therapy. Dr. Raghu acknowledged this criticism, but he said it was important to include patients with advanced disease in order to generate an adequate event rate. Even with inclusion of patients with severe lung impairment, the mortality rate was less than 10%.

He concluded that there was no signal of benefit even among those with the greatest expression of the target.

"We absolutely need better markers for IPF," Dr. Raghu maintained. While other members of the LOXL family of enzymes may still prove to be valuable markers of IPF risk and targets of therapy, these data appear to rule out a therapeutic role for blocking LOXL2.

Dr. Raghu is a consultant for Boehringer Ingelheim, Biogen, FibroGen, Gilead, Janssen, MedImmune, Promedior, Sanofi-Aventis, and Veracyte.

IPF Patient Registry will expand

BY KATIE WAGNER LENNON
Frontline Medical News

The number of patients enrolled in the Idiopathic Pulmonary Fibrosis–Prospective Outcomes (IPF-PRO) Registry will be increased to 1,500, Boehringer Ingelheim Pharmaceuticals and the Duke Clinical Research Institute have announced.

The organizations plan to accomplish this goal by increasing the number of sites they use to gather IPF patient data, according to a statement; the patients enrolled in the registry will now come from 45 sites instead of 18 sites.

IPF-PRO, which was launched in June 2014, is the first multicenter longitudinal disease state registry in the United States focused specifically on IPF. It was designed for the purpose of studying the progression of IPF and the effectiveness of various treatment approaches for the disease. The registry includes a biorepository that stores blood samples that provide patient genetic material.

"In collecting data from a larger, more diverse group of patients ... this registry will allow us to better assess the impact of the disease over time on clinical and patient-centered outcomes," said Scott M. Palmer, MD, director of pulmonary research at the Duke Clinical Research Institute, Durham, N.C., in the statement.

More information on the registry is available at clinicaltrials.gov/ct2/show/NCT01915511.

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USPSTF: Screen for tuberculosis in those at greatest risk

BY HEIDI SPLETE
Frontline Medical News

Screening for latent tuberculosis infection (LTBI) can help prevent progression to active disease, and the availability of effective tests supports screening asymptomatic adults aged 18 years and older at increased risk for infection, according to new recommendations from the U.S. Preventive Services Task Force.

The recommendations were published online Sept. 6 in JAMA.

"The USPSTF concludes with moderate certainty that the net benefit of screening for LTBI in persons at increased risk for tuberculosis is moderate," wrote lead author Kirsten Bibbins-Domingo, MD, PhD, of the University of California, San Francisco, and her colleagues (JAMA 2016 Sep 6;316[9]:962-9).

TB infection spreads through the coughing or sneezing of someone with active disease. Individuals at high risk for TB include those who are immunocompromised, residents of long-term care facilities or correctional facilities, or homeless individuals. Those born in countries known to have a high incidence of TB, including China, India, Mexico, and Vietnam, have an elevated risk of getting the infection, compared with people born in countries with low numbers of TB cases.

Other populations at increased risk for TB are contacts of patients with active TB, health care workers, and workers in high-risk settings, the researchers noted.

TB remains a preventable disease in the United States, with a prevalence of approximately 5%, the researchers said.

The two most effective screening tests, tuberculin skin test (TST) and interferon-gamma release assays (IGRA), demonstrated sensitivity and specificity of 79% and 97%, and at least 80% and 95%, respectively.

The recommendations are supported by an evidence review, also published in JAMA (2016 Sep 6;316[9]:970-83). This review included 72 studies and 51,711 adults.

The studies in the evidence review did not assess the benefits vs. harms of TB screening, compared with no screening, noted Leila C. Kahwati, MD, of RTI International in Research Triangle Park, N.C., and her colleagues.

"The applicability of the evidence on accuracy and reliability of screening tests to primary care practice settings and populations is uncertain for several reasons," the investigators said.

However, the findings suggest that "treatment reduced the risk of active TB among the populations included in this review."

The researchers reported having no financial conflicts.

Gene mutations predispose to pulmonary fibrosis

BY MARY ANN MOON
Frontline Medical News

Rare frameshift mutations in the NAF1 gene were discovered to cause a telomere-shortening syndrome which, among other adverse effects, predisposes carriers to develop pulmonary fibrosis (PF) and emphysema, according to a report published in Science Translational Medicine.

"Our findings here ... highlight how telomere shortening is a relevant mechanism for PF-emphysema susceptibility in a subset of patients beyond those with mutations in the telomerase core components. It is thus possible that efforts to reverse the telomere defect, or other regenerative approaches, will influence the natural history of these progressive pathologies in patients with telo-

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Pertussis often goes undiagnosed

BY ABIGAIL CRUZ
Frontline Medical News

A majority of pertussis cases in the United States may go undetected in people under the age of 50, particularly in adults, results of a retrospective database cohort study suggest.

"The incidence of pertussis in adolescents and adults is very difficult to quantify," wrote Chi-Chang Chen, MD, of IMS Health, Plymouth Meeting, Pa., and associates, in a study published in Human Vaccines & Immunotherapeutics (2016 May. doi: 10.1080/21645515.2016.1186313). Symptoms may be misdiagnosed as other respiratory illnesses, infected individuals may not seek treatment, and pertussis may not be considered as a possible diagnosis in adults, they noted.

To project the possible range of pertussis incidence in this population, the investigator used three different models to analyze information from private insurance and laboratory databases as well as data from the Centers for Disease Control and Prevention for a 6-year period. The first method, which used medical claims for ICD-9 diagnosed pertussis, found an annual incidence rate of 9/100,000 population. The second used a proxy pertussis model that was based on symptoms that could indicate undiagnosed pertussis, showing an incidence rate of 21/100,000. The third method used pathogen data to estimate the fraction of cough illness statistically attributable to pertussis, resulting in an incidence rate of 649/100,000 population, which is 58-93 times higher than the ICD-9 estimated incidence.

These estimates "highlight the need for improved preventive measures – such as increased vaccination – against pertussis," the investigators said.

The study was funded by GlaxoSmithKline Vaccines.

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mere-mediated lung disease," said Susan E. Stanley, an MD-PhD candidate in the department of oncology, Johns Hopkins University, Baltimore, and her associates.

Pulmonary fibrosis and emphysema cluster in some families, but the genetic basis of such cases is poorly understood.

Both PF and emphysema have been linked to premature aging of lung tissue and to abnormalities in the maintenance of telomere length. In addition, at least half of patients with familial and sporadic PF, and many with emphysema, have the clinical features of a short-telomere syndrome, including bone marrow failure/myelodysplastic syndrome, liver disease, and infertility. The diagnosis of a short-telomere syndrome, as opposed to isolated PF-emphysema, is essential for appropriate treatment because if the defect is systemic, patients will "show exquisite sensitivity to otherwise tolerated medications and procedures, especially in the setting of lung transplantation," the investigators said (Sci Transl Med. 2016;8:351ra107).

To explore the genetic basis of familial PF-emphysema, the researchers performed a series of studies,

beginning with whole-genome sequencing on peripheral blood samples from five unrelated probands in familial PF-emphysema pedigrees. These participants had abnormally short telomeres and extrapulmonary features of short-telomere syndrome. Three of them who had low levels of the telomerase RNA component TR were selected for a candidate gene search, which revealed the NAF1 mutations.

The mutations were found to be present in 2 of 30 (7%) affected members of a prevalence cohort but in none of 134 unaffected control subjects (0%), and in none of 9,006 samples from a public database of unaffected people (0%). Further genetic laboratory and mouse studies were performed to link the mutations with specific pathologies and to trace their functional effects. Their results led the researchers to conclude that these rare NAF1 variants interfere with RNA biogenesis, causing short telomeres resulting in lung disease and other abnormalities.

This work was supported by the National Institutes of Health, the Commonwealth Foundation, and the American Cancer Society.

Ms. Stanley and her associates reported no relevant financial disclosures.

Noninvasive ventilation prevents rehospitalization

BY SARA FREEMAN
Frontline Medical News

LONDON – Patients with chronic obstructive pulmonary disease (COPD) and persistent hypercapnia were half as likely to be readmitted to hospital 1 year after an acute hypercapnic exacerbation if they had received home mechanical ventilation (HMV) in addition to home oxygen therapy (HOT) than if they had not.

The median admission-free survival time in the HOT-HMV U.K. trial was 4.3 months when HMV was used in addition to HOT, versus 1.4 months for HOT alone (unadjusted hazard ratio = 0.54, $P = .007$).

"I think what's really important is that we now have a treatment that we know that if we direct toward [patients with persistent hypercapnia after acute hypercapnic exacerbation] that we effect a significant change in

their outcomes," said study investigator Patrick Murphy, MBBS, PhD, a consultant physician and honorary senior lecturer at the Lane Fox Respiratory Unit at Guy's and St Thomas' NHS Foundation Trust (London).

Speaking at the annual congress of the European Respiratory Society, he added: "We need to titrate the home ventilation to control nocturnal hypoventilation, and although I've not presented the data as time is short, there is no deleterious effect on quality of life."

Nicholas Hart, MBBS, PhD, co–study investigator and clinical and academic director of Lane Fox Re-

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VIEW ON THE NEWS

Lee E. Morrow, MD, FCCP, comments: This is a ridiculously common problem that all pulmonologists manage. In an era of pay-for-performance and the dreaded re-admission being foremost in our minds, this is a fascinating and widely applicable article.

[PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, 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 inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). 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.

Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT 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, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10) in full Prescribing Information]*. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. 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, post menopausal 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.

Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.1) and Use in Specific Populations (8.4) in full Prescribing Information]*.

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications 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.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids 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 study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol *[see Warnings and Precautions (5.1) in full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

- Candida albicans infection *[see Warnings and Precautions (5.4) in full Prescribing Information]*
- Pneumonia or lower respiratory tract infections in patients with COPD *[see Warnings and Precautions (5.5) in full Prescribing Information]*
- Immunosuppression *[see Warnings and Precautions (5.6) in full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in full Prescribing Information]*
- Growth effects in pediatric patients *[see Warnings and Precautions (5.14) in full Prescribing Information]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15) in full Prescribing Information]*

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.

Clinical Trials Experience in Asthma Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	80/4.5 mcg N = 277 %	160/4.5 mcg N = 124 %	80 mcg N = 121 %	160 mcg N = 109 %	4.5 mcg N = 237 %	N = 400 %
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3

Continued from previous page

spiratory Unit, said in a statement issued by Philips Respironics that the results "have the ability to change the way that COPD patients are treated worldwide."

"We're looking forward to continuing the trial over the next 5 years to monitor survival rates, which we hope will rise, and readmission rates, which will hopefully fall," he added.

The HOT-HMV UK Trial was conducted in 15 centers and involved patients with severe COPD who had persistent hypercapnia 2-4 weeks after experiencing an acute, life-threatening hypercapnic exacerbation requiring hospitalization. Persistent hypercapnia was defined as a pH of 7.3 or more and a PaCO2 of 7 kPa or higher. Patients had to have a 20-year or more pack year history of smoking, a forced expiratory volume in 1 second (FEV_1) of 50% or less, and FEV_1 to forced vital capacity (FVC) ratio of below 60%.

Dr. Murphy observed that the trial design assumed that the rate of hospital readmission at 1 year could be reduced from 55% to 25% with the use of noninvasive ventilation (NIV). The hypothesis was that HMV plus long-term HOT would increase admission-free survival compared with HOT alone.

More than 2,000 patients were initially screened for inclusion in the trial, with 116 randomized. Of the excluded patients, 1,609 did not meet inclusion criteria, 296 declined to participate, and 8 patients were not included for other reasons.

The average age of patients participating in the study was 67 years. The patients had a median body mass index of 21.6 kg/m^2 and most (61%) were female. Prior long-term oxygen therapy had been used by most (80%), and 61% had three or more COPD-related hospital admissions in the last year.

"[We] now have a treatment that we know that if we direct toward [patients with persistent hypercapnia after acute hypercapnic exacerbation] that we effect a significant change in their outcomes ... There is no deleterious effect on quality of life," Dr. Murphy said.

Putting the primary endpoint data into perspective, Dr. Murphy said that six patients with persistent hypercapnia after treatment for an acute exacerbation needed to be treated with HMV to prevent one readmission in the following 12-month period.

Improved nocturnal hypercapnia and sleep-disordered breathing led to improved daytime hypercapnia, he observed. The change in daytime hypercapnia after 6 weeks and 3 months showed a clear statistical benefit for the combined HMV/HOT approach over HOT alone, although this lost statistical significance after 6 and 12 months' follow-up. "That's in part explained by the fact that the patient numbers were reduced, but also by the fact that, as part of the trial protocol, once [HOT only] patients had reached the primary outcome we allowed them to move onto HMV."

Guy's and St. Thomas' Charity, Philips Respironics, ResMed, and the ResMed Foundation supported the study. Dr. Murphy has received hospitality for conferences, lecturing, or both from Philips Respironics, Fisher & Paykel Healthcare, and ResMed.

Cytokine shows promise as biomarker for sepsis

BY TED BOSWORTH
Frontline Medical News

LONDON – A cytokine known as tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) is showing potential as a biomarker for evaluating the severity of sepsis and septic shock, according to results of a prospective study presented at the annual congress of the European Respiratory Society.

In a prospective study undertaken in patients administered to an intensive care unit, "lower levels of plasma TRAIL correlated with both organ system dysfunction and mortality," reported Thomas Nicholson, MD, of Cornell University, New York.

A series of studies associating low levels of TRAIL with increased sepsis severity have attracted attention to this potential biomarker, according to Dr. Nicholson. In a mouse model of sepsis, for example, exogenous administration of TRAIL was associated with improved survival. In a clinical study conducted in CHINA that was cited by Dr. Nicholson, low levels of TRAIL correlated with lower rates of survival.

In the data presented at the ERS Congress, plasma TRAIL was collected from 108 patients on the first day of ICU admission. Of these patients 59 (54%) had sepsis and 23 (21%) had septic shock. Those with a noninfectious critical illness served as controls.

All patients with sepsis or septic shock were required to meet diagnostic criteria from the recently published Third International Consensus Definitions for Sepsis and Septic Shock (JAMA. 2016;315[8]:801-10). This is important because the newer criteria, relative to previous criteria, have "moved conceptually away from a condition defined by inflammatory biomarkers toward one that emphasizes signs of organ dysfunction," Dr. Nicholson reported.

Although a dysregulated host response to infection is still a fundamental concept to the newer definition of sepsis, the importance of biomarkers of inflammation has been deemphasized, a change that would not be expected to favor an inflammatory cytokine as a biomarker.

Despite this, plasma TRAIL levels, which were measured with commercially available ELISA kits, were significantly lower for those with sepsis (P = .038) and for those with septic shock (P less than .001) relative to those with a noninfectious critical illness. There was a trend (P = .077) for lower plasma levels of TRAIL in patients with septic shock relative to sepsis.

In addition, there was a positive and significant correlation (r = –0.1983; P = .0397) between plasma TRAIL and degree of organ dysfunction as measured with the Sequential Organ Failure Assessment (SOFA) score. Higher plasma TRAIL levels also predicted survival at 28 days (P = .016). Although the overall mortality for patients with sepsis or septic shock in this series was 23%, there were no deaths among sepsis or septic shock patients with a TRAIL above the mean, which was 26.8 pg/mL.

"For every 10 mg/mL increase in TRAIL the odds ratio for survival increased by 1.9-fold," Dr. Nicholson reported.

TRAIL is implicated in several processes that may explain these observations, according to Dr. Nicholson. For example, he reported that there is evidence that TRAIL induces apoptosis in neutrophils, a suspected mediator of sepsis-related injury.

"The observations in our study are consistent with a growing literature suggesting that TRAIL is an important mediator of inflammatory cells, such as neutrophils, tempering the degree of inflammation," Dr. Nicholson explained.

He added that the biomarker is being developed as a potential tool for evaluating sepsis severity.

Dr. Nicholson reported no relevant financial relationships.

VIEW ON THE NEWS

Jennifer D. Cox, MD, FCCP, comments: Biomarkers are an evolving field that seem to be everywhere. Having a biomarker to help delineate the sepsis/septic shock patient from a noninfectious critical illness patient could be helpful especially when talking to families about severity of illness and possible prognosis. However, ... it should not take the place of clinical judgment.

CRITICAL CARE COMMENTARY: Common Canister Policy

BY MARK A. MALESKER, PHARM D, FCCP

Metered-dose inhalers (MDIs) have been available for more than 50 years and are routinely used. Given the ever-escalating costs of health care, various measures have been targeted by hospitals or health systems to eke out savings. Given the ubiquity of MDIs in the ICU, collaborative efforts, intended to curb rising costs and waste associated with MDI use, have resulted in a variety of protocols generically referred to as common canister policies (CCPs). While the concept of CCPs came into existence in the mid-1990s, casual observation suggests they are gaining momentum at hospitals and long-term care facilities. Most data regarding CCPs come from abstracts or posters; few studies have been published in peer-reviewed journals. Data on the efficacy and safety of CCPs in the ICU are particularly limited. Although most reports on CCPs have originated in community-based hospitals, some academic medical centers have also explored this concept.

What is common canister policy?

CCPs allow a single MDI canister to be shared among patients in a designated care area (typically a ward or ICU), with each individual having his/her own one-way valve holding chamber or spacer (Larson T, et al. *Curr Med Res Opin*. 2015;31[4]:853). Each patient care unit or respiratory therapist has a set of inhalers to use until actuations run out, at which point new inhalers are delivered from the pharmacy. Because the holding chamber or spacer is not shared, the risk of patient-to-patient spread of disease is minimized. In addition, the provider involved in administration of the inhaler must follow a standardized cleaning protocol to ensure the common canister is sterilized after each use.

This policy is designed to be used with inhaled therapies delivered by MDI (albuterol, ipratropium, albuterol/ipratropium, fluticasone, budesonide/formoterol, fluticasone/salmeterol). CCP does not apply to other types of inhalers, such as dry powder or mist inhalers, because the use of a separate holding chamber or spacer is not feasible with these devices. CCP savings are realized through a reduction in the number of MDIs purchased and the ability of patients to be charged per inhalation of medication delivered. An alternative CCP practice is to issue an MDI to a single patient and, upon his/her discharge, to clean and reissue the patient's partially used MDIs to subsequent patients until the medication is exhausted (Liou J, et al. *Hosp Pharm*. 2014;49:437).

What are the risks and benefits of CCP?

CCP was implemented to minimize costs associated with drug wasting, since patients would not need individual inhalers. Some analysts believe dispensing individual inhalers creates an inherent financial burden as the average length of stay for an acute respiratory hospitalization is 4-5 days (Larson T, et al). Two studies of MDI and dry powder inhaler use in real-world practice found that 11%-13% of the total amount of drug was utilized, leaving 87%-89% of each device wasted at a cost of approximately $87,000 annually (Larson T, et al; Sakaan S, et al. *Hosp Pharm*. 2015;50[5]:386).

The decision to enact CCP requires careful analysis, planning, and communication by all key decision makers.

State laws must be reviewed for formal statements or regulations regarding CCP.

In addition to cost reductions, one study showed CCP reduced delays in delivery of MDI therapy to patients because the lag time between order entry and delivery of the MDI to the floor was eliminated (Filippelli A, et al. Abstract, ASHP Midyear Clinical Meeting, Dec 1997). In this study, CCP allowed respiratory care practitioners immediate access to the common MDI for their entire shift, creating more efficient delivery of MDI treatments. On a par with findings in prior studies, these investigators observed a 55% reduction in hospital purchase costs for MDIs. Patient-level costs were similarly reduced, as each patient was billed only for the number of doses administered from an MDI, rather than for an entire canister.

While CCPs appearsto reduce inhaler-related costs, it is still unclear whether CCP increases the risk of iatrogenic infection. There is a particular paucity of information on the use of CCP in high-risk patients – those with cystic fibrosis, those in isolation, patients receiving mechanical ventilation, and those who are post transplant or otherwise immunocompromised (Larson T, et al). These patients have an inherently increased risk of developing nosocomial infections including ventilator-acquired pneumonia. A recent prospective study compared MDI CCP with single-patient MDI use in 353 patients supported by mechanical ventilation. Although CCP was associated with cost savings and similar rates of ventilator-acquired pneumonia, hospital mortality, and length of stay, there was a greater frequency of ventilator-associated events among patients in the CCP arm of the study (Gowan M, et al. *Respir Care*. 2016 May 3. pii: respcare.04550. [Epub ahead of print]).

The safety of CCP hinges on proper cleaning of the MDI between users. Typical cleaning protocols include: 1. spraying the MDI mouthpiece with compressed air; 2. cleaning the entire MDI with 70% isopropyl alcohol spray, immersion in isopropyl alcohol for 2 minutes, or cleaning with a bleach swab; and 3. allowing the MDI to air dry before returning it to the shared stock for reissue (Larson T, et al). Although cleaning protocols minimize potential patient harm, they may not always be followed properly. Human errors that put patients at risk for nosocomial infection while utilizing CCP have been reported. In two such instances, patients isolated for methicillin-resistant *Staphylococcus aureus* infection had their individual MDIs put back into the common canister stock and utilized by other patients for approximately 24 hours (Larson T, et al). Once this was noticed, the patients who received inhalations from the "at-risk" MDI were monitored in isolation.

No cross-infection occurred, but the mistake paradoxically increased hospital costs. In another reported instance, a bone marrow transplant patient received MDI therapy from the common canister stock (Larson T, et al). Although no harm occurred, this broke protocol as these patients were excluded from the program because of their increased risk of infection from cross-contamination. Other reports describe protocol breaches such as clinicians not returning MDIs to stock in a timely manner or keeping MDIs in their coat pockets. These events highlight the need for health care professionals associated with CCP to adhere to protocols.

Cross-contamination has been studied at institutions utilizing CCPs. While the majority of reports show no growth in postuse MDI cultures, one study reported growth of group D streptococci when alcohol disinfection did not occur and *Staphylococcus epidermidis* in 5% of the cultures taken after disinfection per protocol (Grissinger M. *P T*. 2013;38[8]:434). Although the bacteria that grew in these studies could be considered environmental contaminants, these findings reinforce the need for concern regarding iatrogenic infection.

The legal landscape

The decision to enact CCP requires careful analysis, planning, and communication by all key decision makers. State laws must be reviewed for formal statements or regulations regarding CCP. Protocol standards should also be evaluated against Joint Commission and Centers for Medicare & Medicaid Services standards for medication administration and storage. Before initiating CCP, communication should occur among risk managers, the pharmacy and therapeutics committee, pulmonologists, respiratory therapists, the medical executive committee, infection control personnel, and the professional liability insurance provider. A contingency plan should be put in place should cross-contamination occur. Note that while the goal of CCP is cost savings, no economic analysis to date has considered the incremental costs of cross-contamination and iatrogenic infection.

What alternative strategies to CCP exist?

CCP aims to turn a single-user multidose inhaler into one that is a unit-dose inhaler shared by multiple patients. One alternative strategy of unit-dose inhalations is nebulization as each treatment consists of a single-use ampule of medication. Another strategy is the use of institutional dose packages that allow hospitals to purchase single-user inhalers limited to five or seven doses of therapy. The prices for nebulized treatments and institutional dose packages may offer cost savings similar to CCP while obviating the increased risk of nosocomial infection.

Dr. Malesker is professor of pharmacy practice and medicine, department of pharmacy practice, School of Pharmacy and Health Professions, Creighton University, Omaha.

Clinical decision tree pinpointed risk

BY AMY KARON
Frontline Medical News

A new classification tool helped guide the treatment of bacteremic patients while clinicians awaited antibiotic resistance results, investigators reported.

The clinical decision tree had a positive predictive value of 91% and a negative predictive value of 92% for determining whether certain gram-negative infections produced extended-spectrum beta-lactamase (ESBL), Catherine Goodman, PhD, of the Johns Hopkins Bloomberg School of Public Health, Baltimore, and her associates wrote online in Clinical Infectious Diseases. "These predictions may assist empiric treatment decisions in order to optimize clinical outcomes while reducing administration of overly broad antibiotic agents that can select for further resistance emergence," they added.

Bacteria that produce ESBL can hydrolyze all broad-spectrum beta-lactam antibiotics except carbapenems. Rapid tests for beta-lactamase genes can shorten the lag time between gram-stain identification and antimicrobial resistance results, but are cost prohibitive for most clinical laboratories and often do not assess ESBL gene groups, the researchers said. To find a way to predict which infections are characterized by ESBL production, they studied adults hospitalized at Johns Hopkins from October 2008 to March 2015 with bloodstream isolates of *Klebsiella pneumoniae* (40% of patients), *Klebsiella oxytoca* (4% of patients), and *Escherichia coli* (56% of patients). Most bacteremias began as urinary tract infections (34% of cases), followed by intra-abdominal infections (24%), catheter-related infections (16%), and biliary infections (14%) (Clin Infect Dis. 2016 Jul 26. doi:10.1093/cid/ciw425).

Rapid tests for beta-lactamase genes can shorten the lag time between gram-stain identification and antimicrobial resistance results but are cost prohibitive for most clinical laboratories.

A total of 194 patients (15%) had bacteremias that produced ESBL, according to the investigators. Using a technique called binary recursive partitioning, they compared these patients with ESBL-negative patients to create a clinical decision tree based on five yes-or-no questions. The tree first asked if the patient had been colonized or infected with ESBL-producing bacteria within 6 months, and if so, whether the patient currently had an indwelling catheter. Patients meeting both criteria had a 92% chance of being ESBL positive. Patients with a recent history of ESBL but no catheter had an 81% chance of being ESBL positive if they were at least 43 years old, but a 75% chance of being ESBL negative if they were under age 43 years.

Among patients with no recent history of ESBL, the decision tree asked about hospitalization in a country with a high ESBL burden and antibiotic therapy during the past 6 months. Patients responding "yes" to both questions had a 100% chance of being ESBL positive. Patients with only the geographic risk factor had a 63% chance of being ESBL negative, and patients with neither risk factor had a 93% chance of being ESBL negative.

VIEW ON THE NEWS

Lee E. Morrow, MD, FCCP, comments: [This study] is remarkably timely as the American Thoracic Society/Infectious Diseases Society of America pneumonia guidelines were just revised a couple of months ago and they do a pretty big 180 from the prior recommendation of empiric broad-spectrum antibiotics to the current narrow-spectrum therapy regimen with targeted broad-spectrum therapy in high-risk patients. This moves us a step towards knowing who the high-risk patients are.

of ESBL cases because there was a subgroup with no recent ESBL history or geographic exposure, the investigators noted. "The poor predictive nature of health care–associated variables within this patient subset may suggest a high proportion of community-acquired ESBL infections.

The National Institutes of Health funded the study and the researchers reported no conflicts.

Smoking thickens LV wall, worsens function

BY MARY ANN MOON
Frontline Medical News

Current smoking, as well as higher levels of cumulative cigarette exposure from past smoking, were both associated with higher left ventricular mass, a higher LV mass-to-volume ratio, and worse diastolic function in an elderly community-based population with no overt indications of coronary artery disease or heart failure, according to a report published online Sept. 13 in Circulation: Cardiovascular Imaging.

"These findings suggest that smoking is associated with subtle alterations in LV structure and function, which might help explain the higher risk of heart failure [HF] reported for smokers, independent of coronary artery disease [CAD]," said Wilson Nadruz Jr., MD, of the cardiovascular division, Brigham and Women's Hospital, Boston, and his associates.

They analyzed links between smoking and echocardiographic features using data from the Atherosclerosis Risk in Communities (ARIC) study, an ongoing prospective observational study involving community-dwelling adults who were aged 45-64 years at baseline in 1987-1989. For their study, Dr. Nadruz and his colleagues assessed echocardiographic images taken for 4,580 ARIC participants at follow-up roughly 25 years later. None of these adults had any indication of CAD or HF; 287 (6.3%) were current smokers, 2,316 (50.5%) were former smokers, and 1,977 (43.2%) never smoked.

Compared with never smokers, current smokers showed a greater LV mass index (80.4 vs. 76.7), a greater LV mass-to-volume ratio (1.93 vs. 1.83), and a higher prevalence of LV hypertrophy (15% vs. 9%), as well as a higher prevalence of concentric LV hypertrophy and worse LV diastolic function. The same association was found between never smokers and former smokers who had higher levels of cumulative cigarette exposure, the investigators said (Circ Cardiovasc Imag. 2016 Sep 13. doi: 10.1161/circimaging.116.004950). This association between smoking and altered LV structure and function remained robust after the data were adjusted to account for numerous cardiac risk factors such as older age, higher BMI, diabetes, hypertension, greater alcohol consumption, and higher heart rate. It also didn't vary by patient sex, race, or income level. In contrast, there was no association between smoking and right ventricular structure or function.

"These data suggest that smoking can independently lead to thickening of the heart and worsening of heart function, which may lead to a higher risk for heart failure, even in people who don't have heart attacks," Dr. Nadruz said in a statement.

"The good news is that former smokers had similar heart structure and function, compared with never smokers," said senior author Scott D. Solomon, MD, professor of medicine at Harvard University, Boston.

Elevated HDL levels predict reduced lung function

BY TED BOSWORTH
Frontline Medical News

LONDON – Having an elevated level of high-density lipoprotein cholesterol (HDL-C) is associated with an increased rate of lung function decline over time, according to results from a cohort analysis of more than 30,000 adults presented at the annual congress of the European Respiratory Society.

For forced expiratory volume in 1 second (FEV_1), "there was a highly statistically significant inverse association for HDL-C for both cross-sectional and longitudinal measures of lung function," reported Elizabeth C. Oelsner, MD, Columbia University Medical Center, New York. Those in the top quartile for HDL-C, on average, had a 9-mL greater decline in FEV^1, compared with patients in the

Continued on following page

Continued from previous page

lowest quartile (*P* less than .001). To put this in perspective, Dr. Oelsner said this decline is comparable "to a 10-year increment in pack-years of smoking."

The study, which pooled six population-based cohorts in the United States, included 31,843 adults for whom there were baseline HDL-C levels and at least two longitudinally collected spirometry readings. According to Dr. Oelsner, quality control criteria were rigorously applied. For example, spirometry measures were obtained according to contemporary standards issued by the American Thoracic Society (ATS).

These data suggest that having an excessively high HDL-C may incur risk just as an excessively low HDL may incur risk.
DR. OELSNER

The average age of the study patients was 57 years, and 45% were classified as never smokers. The mean FEV_1 decline over a median follow-up of 5 years was 37 mL per year (range of 22-49 mL/year across the six cohorts). Approximately 15% of individuals had airflow limitation at baseline. There were more than 300,000 total person-years of observation in the pooled data.

In a fully adjusted cross-sectional analysis, each 1 mmol/L increase (38.67 mg/dL) in HDL-C was associated with a 9-mL lower FEV_1, according to Dr. Oelsner. He said the list of adjusted variables included age, gender, pack-years of smoking, weight, and height.

Results were consistent across age groups, presence or absence of smoking history, body mass index, and the presence or absence of airflow limitations at baseline, according to Dr. Oelsner.

HDL-C's inverse correlation with lung function has been shown in other studies, such as the MESA Lung Study, another population-based analysis, according to Dr. Oelsner. In that study, a 0.4% increase in emphysema on CT lung scans was observed for every 10 mg/dL increase in HDL-C (Am J Respir Crit Care Med. 2010;181:A2878).

In this study, "being in the highest quartile for HDL at baseline was associated with an odds ratio of 1.2 for incident airflow limitation relative to being in the lowest [quartile]," Dr. Oelsner said.

The risk of a decline in airway function from an elevated HDL-C, if confirmed, should be considered in the context of the well-known protective effect exerted by HDL against cardiovascular events, according to Dr. Oelsner.

However, she added, these data suggest that "having an excessively high HDL-C may incur risk just as an excessively low HDL may incur risk." She noted, "there may be a limitation to the good of the good cholesterol."

When asked after these data were presented whether she would prefer to have a low or high HDL-C, Dr. Oelsner responded, "Everything in moderation."

She also advised that studies of treatments designed to raise HDL-C to reduce cardiovascular risk should take lung function into consideration.

The adverse effects of HDL-C on lung function are a potential "off-target risk" from such therapies, Dr. Oelsner warned.

Rule allows select women to stop anticoagulation

BY BRUCE JANCIN
Frontline Medical News

ROME – Half of all women who experience a first unprovoked venous thromboembolism (VTE) can safely be spared lifelong anticoagulation through application of the newly validated HERDOO2 decision rule, Marc A. Rodger, MD, reported at the annual congress of the European Society of Cardiology.

"We've validated that a simple, memorable decision rule on anticoagulation applied at the clinically relevant time point works. And it is the only clinical decision rule that has now been prospectively validated," said Dr. Rodger, professor of medicine, chief and chair of the division of hematology, and head of the thrombosis program at the University of Ottawa.

50% of women with unprovoked vein blood clots can be spared the burdens, costs, and risks of lifelong blood thinners.
DR. RODGER

He presented the results of the validation study, known as the REVERSE II study, which included 2,779 patients with a first unprovoked VTE at 44 centers in seven countries. The full name of the decision rule is "Men Continue and HERDOO2," a name that says it all: the rule posits that all men as well as those women with a HERDOO2 (Hyperpigmentation, Edema, Redness, D-dimer, Obesity, Older age, 2 or more points) score of at least 2 out of a possible 4 points need to stay on anticoagulation indefinitely because their risk of a recurrent VTE off-therapy clearly exceeds that of a bleeding event on-therapy. In contrast, women with a HERDOO2 score of 0 or 1 can safely stop anticoagulation after the standard 3-6 months of acute short-term therapy.

"Sorry, gentlemen, but we could find no low-risk group of men. They were all high risk," he said. "But 50% of women with unprovoked vein blood clots can be spared the burdens, costs, and risks of lifelong blood thinners."

Dr. Rodger and colleagues began developing a multivariate clinical decision rule in 2001. They examined 69 risk predictors, which they winnowed down to four potent risk predictors identified by the acronym HERDOO2.

The derivation study was published 8 years ago (CMAJ. 2008;Aug 26;179[5]:417-26). It showed that women with a HERDOO2 score of 2 or more as well as all men had roughly a 14% rate of recurrent VTE in the first year after stopping anticoagulation, while women with a score of 0 or 1 had about a 1.6% risk. The International Society on Thrombosis and Haemostasis suggests that it's safe to discontinue anticoagulants if the risk of recurrent thrombosis at 1 year off-therapy is less than 5%, given the significant risk of serious bleeding on-therapy and the fact that a serious bleed event is two to three times more likely than a VTE to be fatal.

The researchers recognized that a clinical decision rule needs to be externally validated before it's ready for prime-time use in clinical practice. Thus, they conducted the REVERSE II study, in which the decision rule was applied after the 2,799 participants had been on anticoagulation for 5-12 months. All had a first proximal deep vein thrombosis and/or a segmental or greater pulmonary embolism. Patients were still on anticoagulation at the time the rule was applied, which is why the cut point for a positive D-dimer test in HERDOO2 is 250 mcg/L, half of the threshold value for a positive test in patients not on anticoagulation.

They identified 631 women as low risk, with a HERDOO2 score of 0 or 1. They and their physicians were instructed to stop anticoagulation at that time. The 2,148 high-risk subjects – that is, all of the men and the high-risk women – were advised to remain on anticoagulation. The primary study endpoint was the rate of recurrent VTE in the 12 months following testing and patient guidance. The lost-to-follow-up rate was 2.2%.

The recurrent VTE rate was 3% in the 591 low-risk women who discontinued anticoagulants and zero in 31 others who elected to stay on medication. In the high-risk group identified by the HERDOO2 rule, the recurrent VTE rate at 12 months was 8.1% in the 323 who opted to discontinue anticoagulants and just 1.6% in 1,802 who continued on therapy as advised, a finding that underscores the effectiveness of selectively applied long-term anticoagulation therapy,.

Scoring using the HERDOO2 rule

	Risk predictor	Value
H	Hyperpigmentation,	1 point
E	Edema, or	1 point
R	Redness in either leg	1 point
D	D-dimer test positive at 250 mcg/L or more	1 point
O	Obesity, with a BMI of 30 kg/m^2 or more	1 point
O	Older age (65 years or greater)	1 point
2	2 or more points place a woman at high risk of recurrent VTE if she is off anticoagulant therapy	

Note: The REVERSE II validation study involved 2,779 patients with a first unprovoked venous thromboembolism.

Source: Dr. Rodger

The recurrent VTE rate among the 291 women with a HERDOO2 score of 0 or 1 who were on exogenous estrogen was 1.4%, while in high-risk women taking estrogen the rate was more than doubled at 3.1%. But in women aged 50-64 identified by the HERDOO2 rule as being low risk, the actual recurrent VTE rate was 5.7%, a finding that raised a red flag for the investigators.

"There may be an evolution of the HERDOO2 decision rule to a lower age cut point. But that's something that requires further study in postmenopausal women," he said.

An unprovoked index venous thromboembolism was defined as occurring in the absence of the following conditions: a leg fracture or lower-extremity plaster cast, immobilization for greater than 3 days, surgery using a general anesthetic in the 3 months before the index event, and a diagnosis of a malignant disease in the past 5 years.

Venous thromboembolism is the second most common cardiovascular disorder and the third most common cause of cardiovascular death. Unprovoked VTEs account for half of all VTEs. Their management has been a controversial subject. Both the American College of Chest Physicians and the European Society of Cardiology recommend continuing anticoagulation indefinitely in patients who aren't at high bleeding risk.

"But this is a relatively weak 2B recommendation because of the tightly balanced competing risks of recurrent thrombosis off anticoagulation and major bleeding on anticoagulation," Dr. Rodger said.

He added that he considers REVERSE II to be practice changing, and predicted that once the results are published the guidelines will be revised.

Discussant Giancarlo Agnelli, MD, was a tough critic who gave fair warning.

"I am friends with many of the authors of this paper, and in this country we are usually gentle with enemies and nasty with friends," declared Dr. Agnelli, professor of internal medicine and director of internal and cardiovascular medicine and the stroke unit at the University of Perugia, Italy.

He didn't find the REVERSE II study or the HERDOO2 rule persuasive. On the plus side, he said, the HERDOO2 rule has now been validated, unlike the proposed DASH and Vienna rules. And it was tested in a diverse multinational patient population. But the fact that the HERDOO2 rule is only applicable in women is a major limitation. And REVERSE II was not a randomized trial, Dr. Agnelli noted.

Moreover, 1 year of follow-up seems insufficient, he continued. He cited a French multicenter trial in which patients with a first unprovoked VTE received 6 months of anticoagulants and were then randomized to another 18 months of anticoagulation or placebo.

During that 18 months, the group on anticoagulants had a significantly lower rate of the composite endpoint comprised of recurrent VTE or major bleeding, but once that period was over they experienced catchup. By the time the study ended at 42 months, the two study arms didn't differ significantly in the composite endpoint (JAMA. 2015 Jul 7;314[1]:31-40).

More broadly, Dr. Agnelli, the lead investigator in the AMPLIFY study, also questioned the need for an anticoagulation discontinuation rule in the contemporary era of new oral anticoagulants (NOACs). "Why should we think about withholding anticoagulation ... when we now have such a safe approach?" he asked. AMPLIFY was a randomized trial of fixed-dose apixaban (Eliquis) versus conventional therapy with subcutaneous enoxaparin (Lovenox) bridging to warfarin in 5,395 patients with acute VTE. The NOAC was associated with a 69% reduction in the relative risk of bleeding (N Engl J Med. 2013 Aug 29;369[9]:799-808).

Dr. Rodger reported receiving research grants from the French government and Biomerieux, which funded the REVERSE II study. Dr. Agnelli reported having no financial conflicts.

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Interventional Chest/ Diagnostic Procedures

Evolving approaches to manage central airway obstruction

Central airway obstruction (CAO) is a major cause of morbidity and mortality in patients with malignant and nonmalignant pulmonary disorders (Ernst et al. *Am J Respir Crit Care Med*. 2004;169[12]:1278). It is associated with postobstructive pneumonia, respiratory compromise, and even respiratory failure. It often precludes the patients with malignancy from getting definitive treatment, such as surgical resection or chemotherapy. Therapeutic bronchoscopy using a rigid bronchoscope plays a central role in managing these patients.

DR. MAHMOOD

Different modalities used during therapeutic bronchoscopy include debridement, airway dilation, and different heat therapies, such as laser, electrocautery, and argon plasma coagulation (Bolliger et al. *Eur Respir J.* 2006;27[6]:1258). Airway stents are often placed to achieve durable airway patency. Endobronchial therapies with delayed effect include brachytherapy, photodynamic therapy, and cryotherapy (Vergnon et al. *Eur Respir J.* 2006;28[1]:200). There is improvement in symptom control, quality of life, and spirometry with successful bronchoscopic intervention (Mahmood et al. *Respiration*. 2015;89[5]:404). Patients with respiratory failure secondary to CAO can be weaned from mechanical ventilation (Murgu et al. *Respiration*. 2012;84[1]:55).

It is often difficult to predict which patients will have a successful bronchoscopic intervention. Endobronchial disease and stent placement have been associated with successful outcome (Ost et al. *Chest*. 2015;147[5]:1282). Patients with unsuccessful bronchoscopic intervention often have a poor prognosis, despite concurrent chemotherapy and radiation (Mahmood et al. *Respiration*. 2015;89[5]:404).

As more fellowship programs are offering training in rigid bronchoscopy, there is a need to standardize the training and use validated tools to assess competency. RIGID-TASC (Rigid bronchoscopy Tool for Assessment of Skills and Competence) is one such tool, which can be utilized for this purpose to provide objective feedback to the trainee (Mahmood et al. *Ann Am Thor Soc.* 2016. doi: 10.1513/ Epub ahead of print).

Kamran Mahmood, MD, MPH, FCCP
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Pediatric Chest Medicine

CHEST Foundation campaign to fight difficult-to-control asthma

The CHEST Foundation and the Asthma and Allergy Network have joined forces to combat difficult-to-control asthma with the campaign "Asthma: Take Action. Take Control." Affecting approximately 235 million people worldwide, asthma morbidity continues to have a significant impact on quality of life for both children and adults with asthma. In the United States alone, it accounts for health-care costs of approximately 60 billion dollars.

The campaign educates patients, caregivers, families, and health-care providers about current


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treatment options for asthma, highlights the importance of specialist referrals, and encourages patients to participate with their health-care provider to achieve asthma control. Because asthma may fall into this difficult-to-control category for many reasons, including poor adherence, unresponsiveness to conventional therapies, failure to recognize and manage triggers, and co-morbidities, this campaign developed materials to improve health literacy so that patients can take an active and informed role in asthma self-management. Written in an easy to understand format and language, the "Take Control" campaign highlights four key steps:

- Tell your doctor when it's hard to breathe.
- Ask your doctor for an asthma action plan.
- Practice your asthma action plan.
- Know that asthma shouldn't hold you back.

Newly developed materials include tips and resources for children and adults to learn about asthma and raise awareness about difficult-to-control asthma. These materials can be found at asthma.chestnet.org.

Mary Cataletto MD, FCCP
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Current clinical usefulness of the P_{ETCO_2} during exercise testing

Dynamic measurement of the P_{ETCO_2} in cardiopulmonary exercise testing may demonstrate unique changes throughout exercise in specific diseases and is often underutilized during interpretation.


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Though it can be affected by hyperventilation and the VD/VT relationship, normally it rises from rest to lactate threshold (LT), then declines from peak exercise through recovery (Ramos RP, et al. *Pulm Med*. 2013;2013:359021. doi: 10.1155/2013/359021.) In severe pulmonary hypertension and shunts, the reverse occurs, declining in early exercise and then rising during recovery (Sun XG, et al. *Circulation*. 2002;105[1]:54). Blunting or reversal of this exercise decline in P_{ETCO_2} has been correlated with clinical improvement in therapeutic trials (Oudiz RJ, et al. *Eur J Heart Fail*. 2007;9[9]:917). Studies in severe CHF have correlated prognosis with lower values at rest and greater decline from rest to peak exercise, the latter being affected by adequacy of effort and assessed by RQ. They, however, do not take into account the normal rise and fall before and after LT (Arena R, et al. *Am Heart J*. 2008;156[5]:982) (Hoshimoto-Iwamoto M, et al. *J Physiol Sci*. 2009;59[1]:49). In pulmonary hypertension, as the disease progresses, the unique reversal of the normal slopes of the P_{ETCO_2} that occurs, negative in early exercise and positive during recovery in association with an excessive alveolar ventilator response, needs further clinical investigation and correlation (Yasunobu Y, et al. *Chest*. 2005;127[5]:1637). The dynamic changes that occur in the P_{ETCO_2} throughout exercise may be an additional tool to use in selective conditions to more accurately assess prognosis and monitor response to therapy.

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Pulmonary Vascular Disease

Estrogen in PAH: Is it good or bad?

The role of sex hormones in the development and perpetuation of pulmonary arterial hypertension (PAH) continues to be an open field of active research. Epidemiology reveals that PAH is more prevalent in women in both idiopathic and heritable cases.[1] On the other hand, data demonstrate that prognosis of PAH in men is worse than in women and, in animal research, estrogens provide a protective effect. This constitutes the "estrogen paradox." Estrogen plays a protective role in the vasculature, modulating proliferative and vasoactive signaling by direct and receptor-mediated mechanisms.[2,3] In animal models of PAH, estrogen increases nitric oxide and prostacyclin production and decreases endothelin-1, resulting in beneficial vascular effects.[4] However, the Women's Health Initiative revealed that hormone replacement therapy increases the risk for adverse cardiovascular events.[5] In familial PAH, estrogen is a potent mitogen of pulmonary vascular smooth muscle cells.[6] A recently published study, first in humans, by Ventetuolo et al.[7] showed higher levels of estrogen (E2) and lower level of dehydroepiandrosterone-sulfate (DHEAS) in men with PAH, compared with normal men without cardiovascular disease (MESA study), supporting the role of the estrogen pathway in the development of PAH. Experimental data implicate estrogens as promoters of vascular proliferation and cell damage but also as inhibitors of pulmonary vasoreactivity. In vitro, estrogen is mitogenic and promotes proliferation of pulmonary vascular smooth muscle cells.[6] Despite advances, the role of sex and estrogen in PAH is not fully understood. More preclinical and clinical data are necessary to establish a potential role for estrogen-based therapies in this disease.


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Thoracic Oncology

The "new" lung cancer staging system

Definition of lung cancer stage is an essential part of defining prognosis, developing treatment plans, and conducting and reporting on clinical research studies. The stage classification system is determined by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC). The 7th edition of the lung cancer staging system, published in 2009, was a landmark effort based on a large multicenter international database created by the Staging and Prognostic Factors (SPFC) of the International Association for the Study of Lung Cancer (IASLC) and backed by careful validation and statistical analysis.


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The IASLC Lung Cancer Staging Committee has been working on the 8th edition of the TNM classification for lung cancer. The database used for analysis consists of 94,708 patients diagnosed between 1999 and 2010, and included cases from 35 sources and 16 countries. Multiple analyses were performed to assess the ability of T, N, and M descriptors to predict prognosis and to identify new cutpoints for inclusion in the eighth edition.[1-3] The proposed changes include new cutpoints for the T component based on 1-cm increments, new categories for the N component, a new M category to specifically identify patients with oligometastatic disease, and multiple updates to the overall TNM stage groupings.[4] In addition, the proposal includes recommendations for coding T stage for subsolid nodules and assessment of tumor size in part-solid nodules.[5] These proposed changes will be submitted to the UICC and AJCC for inclusion in the eighth edition and will be enacted in January 2017.

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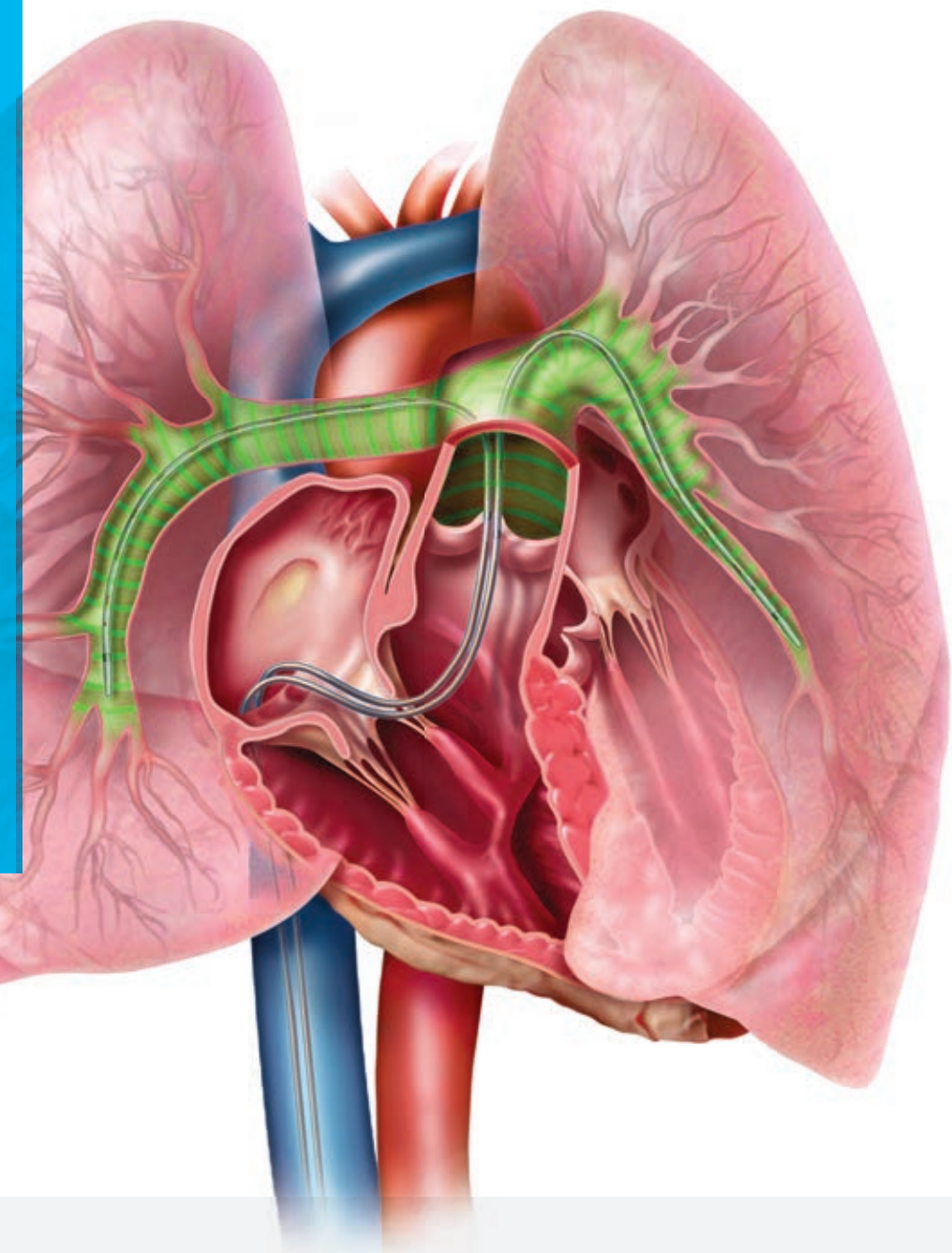

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2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

3 *Kucher, N., et al., Circulation, Vol. 129, No. 4, 2014, 479–486.*

4 *Piazza, G., et al., American College of Cardiology 63rd Annual Scientific Session, Wash D.C., March 30, 2014.*

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