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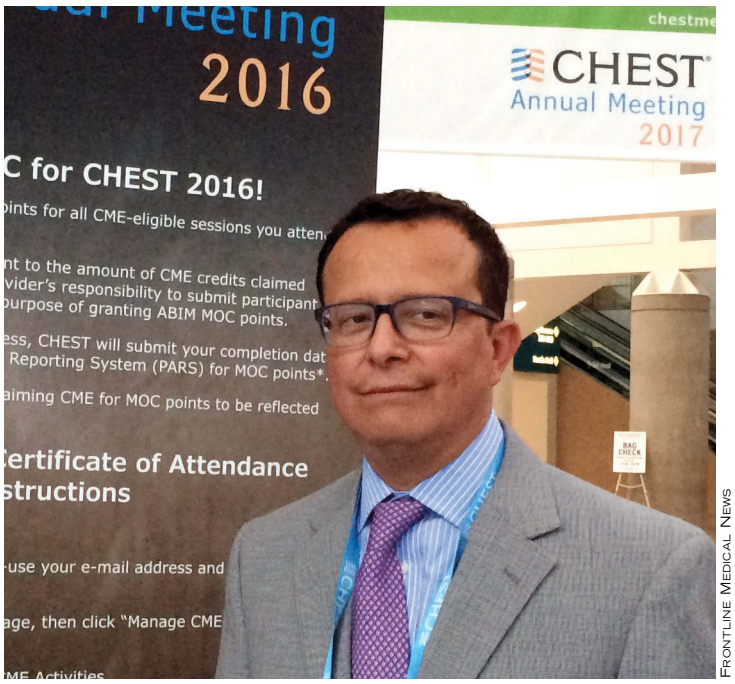

FRONTLINE MEDICAL NEWS

We have proved that simple physical tests could be part of future prognostic models, said Dr. Carlos H. Martinez.

Grip strength a sign of respiratory risk

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Hand grip strength was independently predictive of risk for respiratory events in smokers who have or are at risk for chronic obstructive pulmonary disease, results from a single-center study presented at the annual meeting of the American College of Chest Physicians showed.

In a second multicenter study also presented at the meeting, a high resting heart rate appeared to predict the risk of future exacerbations in patients with recent exacerbations of COPD.

The findings of the two studies indicate that straightforward clinical measures performed in an office setting can provide valuable information for predicting the prognosis of at-risk patients.

"Measures of lung function, including spirometry, are used as the main descriptors of COPD severity and prognosis," Carlos H. Martinez, MD, MPH, the lead author of the study on hand grip strength, said in an interview

See **Hand grip strength** • *page 4*

Oxygen therapy not advantageous for stable COPD

Subgroups had similar hospitalizations

BY MARY JO DALES
Frontline Medical News

Longterm supplemental oxygen had no benefit on multiple outcome measures in patients with stable chronic obstructive pulmonary disease (COPD) and resting or exercise-induced moderate desaturation, Robert Wise, MD, FCCP, and his colleagues in The Long-Term Oxygen Treatment Trial (LOTT) Research Group reported.

Recommendations that supplemental oxygen be administered to patients with severe desaturation – an oxyhemoglobin saturation of less than 89% on pulse oximetry (SpO_2) – date to two trials performed in the 1970s. Since that time, subsequent studies have been performed in patients with COPD and mild-to-moderate daytime hypoxemia, but the studies were underpowered to assess mortality and the impact of oxygen therapy on hospitalization, exercise performance, and quality of life were unclear.

In 2011, Medicare reimbursements for oxygen-related costs in patients with COPD surpassed $2 billion, according to the study.

Dr. Wise, professor of medicine and director of research, in the division of pulmonary and critical care medicine, Johns Hopkins

See **Oxygen therapy** • *page 8*

INSIDE

Reslizumab best with high eosinophils

BY MICHELE G. SULLIVAN
Frontline Medical News

FROM CHEST

Reslizumab was most effective in patients with high baseline eosinophil counts, two randomized, placebo-controlled studies have determined. The companion studies were simultaneously published in the October issue of Chest.

The drug reslizumab, an anti–interleukin-5 monoclonal antibody, is made by Teva Branded Pharmaceutical Products R&D, who sponsored both studies.

The larger study, comprising 492 patients, found no significant benefit of reslizumab over placebo, Jonathan Corren, MD, and his colleagues wrote (Chest. 2016;150:799-810). But this study didn't stratify patients by baseline eosinophil levels; a post-hoc subanalysis found a significant benefit in forced expiratory volume in 69 of the patients who had at least 400 eosinophils/microliter (mcL) when treatment began.

See **Reslizumab** • *page 7*

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- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[2,3]**
- **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006[2,4]**
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  - —eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Esbriet®
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Exacerbations tied to heart rate

Hand grip strength *from page 1*

in advance of the meeting. "These measurements, as important as they are, need to be improved, in order to develop better risk and prognostic models of the disease, to identify subgroups at higher risk of poor outcomes ... With our work, we have proved that simple physical tests could be part of future prognostic models."

"Resting heart [rate] is often a readily available clinical data," Ahmad Ismail, MD, FCCP, lead author of the study on resting heart rate, said in a separate interview. "Its significance is often overlooked in daily clinical practice until tachycardia or bradycardia happens. In COPD patients, it has been shown that the resting heart rate can predict mortality. However, there is a lack of data showing its association with the rates of exacerbations, the major player in determining overall outcome in patients with COPD."

Dr. Martinez noted that interest has grown in developing multidimensional models to predict respiratory prognosis. Such models include

BODE (body mass index, airflow obstruction, dyspnea and exercise capacity), ADO (age, dyspnea and airflow obstruction), and DOSE (dyspnea, airflow obstruction, smoking status, and exacerbation frequency).

Hand grip strength

In patients with or at risk for COPD, Dr. Martinez, of the University of Michigan Health System, Ann Arbor, and his colleagues tested the associations of hand grip strength with measures of body composition such as pectoralis muscle area and extent of subcutaneous fat, imaging phenotypes, and lung function.

Dr. Martinez and his colleagues obtained demographic, clinical, lung function, hand grip strength, and imaging data from 441 smokers with and without COPD participating in the Genetic Epidemiology of COPD Study (COPDGene) at the National Jewish Health in Denver. Imaging methods used in the study were developed by George R. Washko, MD, and his associates at Brigham and Women's Hospital, Boston, to evaluate patients' body composition, including chest CTs to obtain measures of airway thickness, emphysema percentage, pectoralis muscle area, and subcutaneous adipose tissue area.

Correlations between measures of lung function, imaging phenotypes, body composition, and hand grip strength were analyzed in univariate analysis and in multivariate linear models. The association between hand grip strength and exacerbations was analyzed at enrollment and during an average follow-up of 2.6 years.

Hand grip strength was similar

FRONTLINE MEDICAL NEWS

Dr. Ahmad Ismail

across groups categorized by spirometry severity and was not associated with emphysema severity.

After adjustment for demographics, smoking history, smoking intensity, comorbidities and lung imaging phenotypes, however, grip strength was associated with pectoralis muscle area (increase of 3.9 kg per one standard deviation of pectoral muscle area) and subcutaneous adipose tissue (a decrement of 5.1 kg per one standard deviation of subcutaneous adipose tissue). These associations were independent of body mass index and the presence of emphysema.

During follow-up, hand grip strength was associated with exacerbations (risk ratio 0.94 per one kg increment on grip strength) and incident exacerbations (incident risk ratio 0.92 per one kg increment on grip strength) in models adjusted for other factors known to be associated with exacerbations.

Research in body composition has mostly relied on dual absorptiometry and bioelectrical impedance, tools not routinely used in clinical practice, Dr. Martinez said. "We were surprised by the ability to show similar results using imaging data that are available from regular chest CTs."

"We have confirmed prior hypotheses that it is not just weight or

Continued on following page

Continued from previous page

BMI that matters (to risk of exacerbations), but how much muscle and how much fat are contributing to our patient's high or low BMI," Dr. Martinez said.

Hand grip testing can be challenging in this patient population, he said. Still, "asking relevant questions about [patients'] physical fitness will help us to understand better our patients' needs. We can also give more attention to the extrapulmonary structures included in the numerous chest CT scans that we order for our patients. These imaging studies, besides the information that they provide about parenchymal and mediastinal structures, include important and easy to discover clues to identify patients at higher risk of exacerbations – those with low muscle and low hand grip could benefit from close follow-up."

Dr. Martinez acknowledged certain limitations of the study, including the selection of the measures of body composition.

"We used analysis of chest CTs, instead of the gold standard of dual absorptiometry (DXA) or other methods such as bioelectrical impedance," he said. "A final limitation is that we tested a selected group of participants in a cohort study, not a representative sample of the population, [with a] low burden of emphysema and fewer African American participants."

Resting heart rate

In an effort to identify the association between resting heart rate and risk of exacerbation, Dr. Ismail of Universiti Teknologi MARA, Malaysia, and his associates at nine other centers evaluated 147 COPD patients who were recruited during hospitalization for acute exacerbations between April 2012 and September 2015.

The researchers recorded each patient's sociodemographic data, anthropometric indices, and medication history. Next, they followed up with the patients in clinic at 3 months after the hospitalization, and collected resting heart rate, spirometry, and COPD Assessment Test (CAT) scores. Subsequently, patients were followed up in clinic at 6 and 12 months, and followed up between clinic visits via telephone interviews.

Chest CT scans of extrapulmonary structures include important and easy to discover clues to identify patients at higher risk of exacerbations - those with low muscle and hand grip strength.

The mean age of the study population was 67 years, and 77% of them had resting heart rates that exceeded 80 beats per minute (BPM). The mean resting heart rate in the group with higher resting heart rates was 92 BPM; it was 70 BPM in the lower resting heart rate group.

At 3 months after hospitalization, patients with higher resting heart rates had a significantly higher proportion of exacerbations, compared with those who had a lower resting heart rates (54% vs. 27%; $P = .013$). There also was a statistically significant moderate strength linear correlation between resting heart rate and exacerbation frequency at 3, 6, and 9 months ($r = 0.400$; P less than .001: $r = 0.440$; P less than .001: and $r = 0.416$; $P = .004$, respectively). The mean exacerbation frequency was significantly higher in the higher resting heart rate group at month 3 and month 6 (2.00 vs. 0.48; P less than .001: and 3.42 vs. 1.14; $P = .004$).

Further study is required to determine whether lowering resting heart rate would affect the risk of exacerbation, Dr. Ismail said. He acknowledged that the limitations of the study are that it excluded patients who were on beta-blockers or any rate-modifying drugs, and those with history of cardiac failure and ischemic heart disease. Further, baseline echocardiograms were not performed, so little is known about whether patients had ischemic heart disease and other possible causes of the higher resting heart rates.

"We also had slightly higher than expected dropouts giving a nonsignificant result at 12 months follow-up, though the trend follows the overall results of the study," he said.

The study was funded by a grant from the Malaysian Thoracic Society. Dr. Ismail reported having no financial disclosures.

Dr. Martinez disclosed that his work is supported by the National Institutes of Health and that COPDGene also receives NIH funding. He acknowledged the support and effort of all COPDGene investigators and participants.

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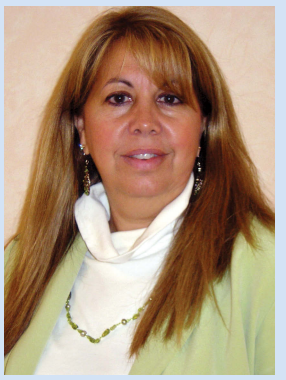

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FEV_1 better with drug

Reslizumab *from page 1*

The second study, which specifically targeted patients with a baseline eosinophil level of at least 400 cells/mcL, bolsters the conclusion that the drug works best in that population, said Leif Bjermer, MD, of Skane University, Lund, Sweden (Chest. 2016;150:789-98).

In these patients, the drug significantly improved not only lung function, but asthma symptoms and asthma-related quality of life scores.

"These efficacy findings are consistent with results from other reslizumab trials and combined with the favorable safety profile observed, support the use of reslizumab in patients with asthma and elevated blood eosinophils, uncontrolled by an inhaled corticosteroid-based regimen," Dr. Bjermer and his coauthors wrote.

The unstratified trial was conducted at 66 sites in the U.S. All of the patients had poorly controlled asthma despite using at least a medium-dosed inhaled corticosteroid. They were randomized to weekly infusions of reslizumab 3.0 mg/kg or placebo for 16 weeks.

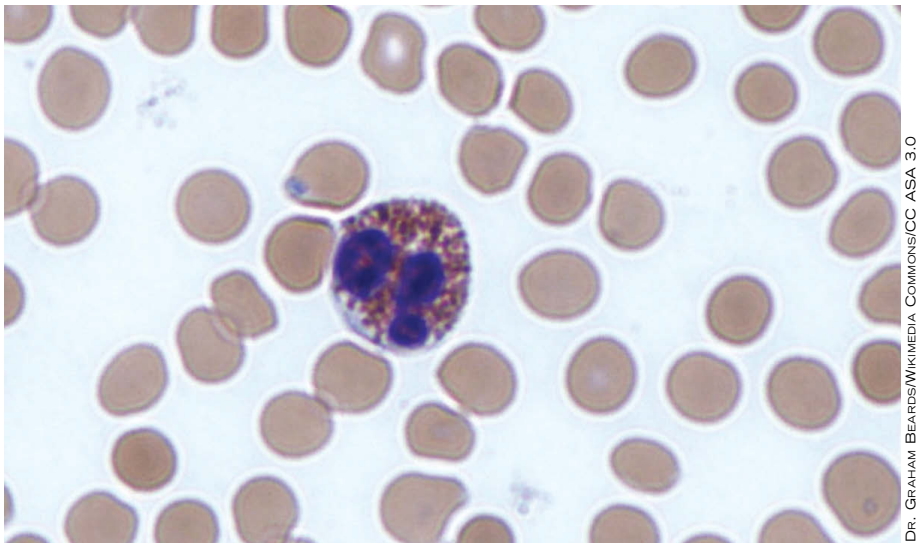
The primary endpoint was the change in forced expiratory volume in one second (FEV_1); secondary endpoints included quality of life scores; the need for rescue medication; forced vital capacity; and eosinophil count.

Patients in the placebo and reslizumab groups were an average age of 45.1 years and 44.9 years, respectively. The mean disease duration of patients in both groups was 26 years.

At week 16, the mean change in FEV_1 from baseline was 255 ml in the active group and 187 ml in the placebo group – not a significant difference.

The team performed a post-hoc subgroup analysis that dichotomized the cohort based on baseline eosinophil levels. For the 343 with counts of less than 400 cells/mcL, there was no difference in FEV_1 at 16 weeks, between the patients who received treatment and the patients who received a placebo. The FEV_1s of these two groups were separated by just 33 mL.

The story was different for the 82 patients with at least 400 cells/mcL, with 69 of such patients receiving the drug and 13 of such patients receiving the placebo. At 16 weeks, the difference in FEV_1 change was 270 mL, in favor of the active group. The strength of these findings may be weakened by the large difference in size between the treatment and placebo groups and the "near complete lack of response in the small number of placebo-treated patients."



Dr. Graham Beards/Wikimedia Commons/CC ASA 3.0

The first study didn't stratify patients by baseline eosinophil levels; a post-hoc subanalysis found a significant benefit in forced expiratory volume in 69 patients who had at least 400 eosinophils/microliter (mcL) when treatment began. A second study specifically targeted patients with a baseline eosinophil level of at least 400 cells/mcL and the findings suggest the drug works best in that population.

"Interpretation of the results in the [400 or more cells/mcL] subgroup is limited as the study was not designed or statistically powered to specifically test this group of patients," the team wrote. Nevertheless, they concluded that reslizumab is a reasonable treatment option for this group. "These findings support an acceptable benefit-risk profile for reslizumab in asthma patients with a blood eosinophil threshold" of at least 400 cells/mcL.

The stratified study examined more endpoints: pre-bronchodilator spirometry (forced expiratory volume in one second FEV_1, forced vital capacity, and forced expiratory flow), asthma symptoms, quality of life, rescue inhaler use, and blood eosinophil levels.

The 315 patients in this study all had a baseline eosinophil count of at least 400 cells/mcL. They were randomized to placebo or to 0.3 or 3.0 mg/kg reslizumab dose once every 4 weeks for 16 weeks. The mean ages for the patients taking the placebo, reslizumab 0.3 mg/kg, and reslizumab 3.0 mg/kg were 44.2, 44.5, and 43.0, respectively. The range of average disease durations for patients in the placebo group and two reslizumab groups was 20 to 20.7 years.

The final FEV_1 was significantly improved over placebo in both active groups, although the change was much more pronounced in those taking 3.0 mg/kg, compared with those taking 0.3 mg/kg (160 mL and 115 mL, respectively, relative to placebo). Forced vital capacity also improved significantly in the 3.0 mg/kg dose group (130 mL relative to placebo).

Reslizumab was generally well tolerated in both studies. The most frequent adverse events in the stratified study were asthma worsening, headache, nasopharyngitis, upper respiratory infections, and sinusitis.

In the unstratified study, there were two anaphylactic reactions, but only one was related to the study drug. No deaths occurred in either treatment group of this study.

Both trials were sponsored by Teva.

Dr. Bjermer has served on advisory boards or provided lectures for Aerocrine, Airsonett, ALK, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GlaxoSmithKline, Meda, Mundipharma, Nigaard, Novartis, Regeneron, Sanofi-Aventis, Takeda, and Teva.

Dr. Corren has been involved in speaker bureau activities for Genentech and Merck; he has served on advisory boards for Genentech, Merck, Novartis, and Vectura.

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VIEW ON THE NEWS

Reslizumab: Making the cut-point work

Persistent eosinophilic inflammation is present in about half of patients with severe asthma, and the studies by Corren and Bjermer represent important advances in learning how to target this inflammatory pathway, Richard Russell, MBBS, MRCP, and Christopher Brightling, PhD, FCCP, wrote in an accompanying editorial (Chest. 2016;150:766-8).

"The most advanced therapeutic target is IL-5, which is an attractive target because it is an obligate cytokine for eosinophil maturation and survival. Its inhibition is thus predicted to reduce bone marrow production of eosinophils and promote apoptosis," wrote Dr. Russell, a clinical research fellow, and Dr. Brightling, a professor, both at the University of Leicester (England).

"These findings support the view that an elevated blood eosinophil count is associated with a good clinical response [to the antibody reslizumab] but [the studies] did not find a clear correlation between the intensity of the baseline eosinophil count and response," the colleagues wrote. "Thus, the best cut-off for the blood eosinophil count to apply clinically remains uncertain."

Clinicians and patients may find a different answer to this riddle than do payers.

"From a patient perspective there is an argument to select a low or no cut-off as there is some benefit even with low baseline eosinophil counts, whereas from a payer's perspective the health economic benefit is better with a higher cut-off."

As is often the case, more study will help clarify these new concerns.

"We are moving into a new era of Type-2 immunity-mediated therapies that will bring new opportunities for clinicians and our patients, but with this opportunity comes new challenges. Biomarkers will increase in importance to help drive precision medicine, but we need to understand how to use them, and, in particular, what cut-points to apply. For anti-IL-5 approaches, we probably need to look towards elevated blood eosinophil counts, as aiming for a high cut-off is most likely the best way we shall achieve success."

Dr. Russell had no financial disclosures. Mr. Brightling reported financial relationships with several pharmaceutical companies, but not with Teva.

No benefit in stable COPD

Oxygen therapy *from page 1*

University, Baltimore, and his fellow LOTT researchers examined whether longterm treatment with supplemental oxygen would extend life and avoid hospitalization among patients who had stable COPD with moderate resting desaturation – defined as an SpO_2 of 89% to 93% – and patients who had stable COPD with moderate exercise-induced desaturation during the 6-minute walk test – defined as an SpO_2 of at least 80% for at least 5 minutes and less than 90% for 10 seconds or more.

The 738 study participants, about 75% of whom were men, were randomly assigned at one of 42 centers either to receive (368) or not to receive (370) longterm supplemental oxygen. In the supplemental oxygen group, patients with resting desaturation were prescribed 24-hour oxygen, and those with desaturation only during exercise were prescribed oxygen during exercise and sleep (N Engl J Med. 2016;375:1617-27. DOI: 10.1056/NEJMoa1604344).

The groups were balanced for oxygen-desaturation type: 60 (16%) and 73 (20%) had oxygen desaturation only at rest, 171 (46%) and 148 (40%) had oxygen desaturation only upon exercise, and 139 (38%) and 147 (40%) had oxygen desaturation at rest and upon exercise. Patients were followed for 1 to 6 years.

Supplemental oxygen, regardless of prescription type or adherence, failed to benefit patients overall or any subgroup of patients with stable COPD and moderate desaturation. The results were similar for all groups based on measures of time to death or first hospitalization (hazard ratio, 0.94; 95% confidence interval [CI], 0.79 to 1.12; $P = .52$), hospitalization for a COPD-related hospitalization (rate ratio, 0.99; 95% CI, 0.83 to 1.17), non–COPD-related hospitalizations (rate ratio, 1.03; 95% CI, 0.90 to 1.18), the rate of all hospitalizations (rate ratio, 1.01; 95% CI, 0.91 to 1.13), and the rate of all COPD exacerbations (rate ratio, 1.08; 95% CI, 0.98 to 1.19). Additionally, patients who did and did not receive oxygen treatment did not differ based on changes on measures of quality of life, depression, anxiety, or functional status.

Oxygen treatment also was not without risk. Among the 51 adverse events attributed to the use of supplemental oxygen were 23 reports of tripping over equipment, including two cases that necessitated hospitalization. There were five patients who reported six cases of fires or burns, including one who had to be hospitalized.

The researchers acknowledged that some patients may not have enrolled in the trial because they were too ill or felt that oxygen was beneficial.

"Highly symptomatic patients who declined enrollment might have had a different response to oxygen than what we observed in the enrolled patients," they noted.

Additionally, uniform devices weren't used for oxygen delivery, so the amount of oxygen delivered may have varied, and the study did not evaluate the immediate effects of oxygen on symptoms or exercise performance.

Nocturnal oxygen saturation was not measured, and "some patients with COPD and severe nocturnal desaturation might benefit from nocturnal oxygen supplementation," they pointed out. Moreover, "patients' self-reported adherence may have been an overestimate of their actual oxygen use," they added, noting, however, that there was good agreement with use "as measured by means of serial meter readings on the concentrator."

Based on the results, the authors concluded, "the consistency of the null findings strengthens the overall conclusion that long-term supplemental oxygen in patients with stable COPD and resting or exercise-induced moderate desaturation has no benefit with regard to the multiple outcomes measured."

LOTT was funded by the National Heart, Lung, and Blood Institute and the Centers for Medicare and Medicaid Services.

LOTT researchers reported relationships with a wide variety of drug companies.

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VIEW ON THE NEWS

Select patients might still benefit

This landmark study is the largest to date to provide quality evidence about clinically relevant outcomes of longterm oxygen therapy for COPD patients with moderate hypoxemia, a prescribing decision that is relatively costly and potentially places a burden on patients. For patients with moderate hypoxemia, longterm oxygen therapy consistently did not affect outcomes, and the results were not modified by the type of oxygen prescription, desaturation profile, oxygen use, sex, smoking status, or lung function.

Given the available current data, longterm oxygen therapy should be prescribed to prolong survival among patients with COPD who have more than 3 weeks of severe resting hypoxemia (PaO_2 of no more than 55 mm Hg or SaO_2 of less than 88%) while they are breathing ambient air. Oxygen therapy might still be appropriate in selected patients with moderate exertional hypoxemia and intractable breathlessness despite appropriate evidence-based treatment.

Ambient air or oxygen can be used to evaluate the potential benefit. Oxygen therapy can be discontinued if the patient perceives no benefit within a day or two. Selected patients who benefit should be prescribed oxygen, and I think that this treatment that should be covered by insurance payers. However, longterm oxygen therapy should not be routinely prescribed in patients with mild or moderate hypoxemia at rest or during exercise.

Magnus Ekström, MD, PhD, is with the Division of Respiratory Medicine and Allergology, Lund (Sweden) University, and the department of medicine, Blekinge Hospital, Karlskrona, Sweden. He had no relevant financial disclosures and made these remarks in an editorial that accompanied the published study (N Engl J. Med. 2016;375:1683-4*).*

Lung cancer screening effective in community hospitals

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Lung cancer screening with low-dose CT scans in a community hospital setting replicates results from international and multicenter trials when it comes to diagnosing early-stage lung cancer, findings from a single-center study showed.

"It's too early in our experience to say that we're saving lives, but the fact that we're detecting early lung cancers in the predicted percentages is good for community hospitals that are wondering, 'Is it worth it to screen for lung cancer? Can we do it?'" Richard P. Salzano Jr., MD, said in an interview in advance of the annual meeting of the American College of Chest Physicians.

Results from the International Early Lung Cancer Action Program (I-ELCAP), showed that with lung cancer screening, 80% of lung cancers diagnosed within a program would be stage I disease, while the National Lung Screening Trial (NLST), sponsored by the National Cancer Institute, documented a 20% reduction in death from lung cancer with low-dose CT screening, compared with routine chest radiography. "However, there is a history of studies that are done in large centers, or multicenter studies, not translating well to a community hospital setting," said Dr. Salzano, chairman of the Griffin Hospital department of surgery, Derby, Conn.

In July 2013, the 130-bed Griffin Hospital launched a lung cancer screening program codirected by a pulmonologist and a cardiothoracic surgeon. All low-dose CT scans were read by two designated radiologists. Dr. Salzano reported results from 514 patients enrolled in the program between July 2013 and December 2015. A total of nine lung cancers were detected. Seven (78%) were stage I or II lung cancers, and the remaining two (22%) were stage II or IV, results that are in line with data from the I-ELCAP and NLST trials.

The researchers randomly selected 101 patients from the lung cancer screening program to answer questions intended to quantify their anxiety about lung cancer before and after participating in the program. On a scale of 0-10, with 10 being "very anxious," the mean anxiety level about lung cancer fell from a level of 4.69 before screening to 3.87 afterward, a difference that reached statistical significance. Five of the 53 respondents who were current smokers upon enrolling in the screening quit after intake.

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ANORO is for the once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).
ANORO is NOT for the relief of acute bronchospasm or for asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol.**
- **The safety and efficacy of ANORO in patients with asthma have not been established. ANORO is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- The use of ANORO is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- ANORO 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 ANORO should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

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

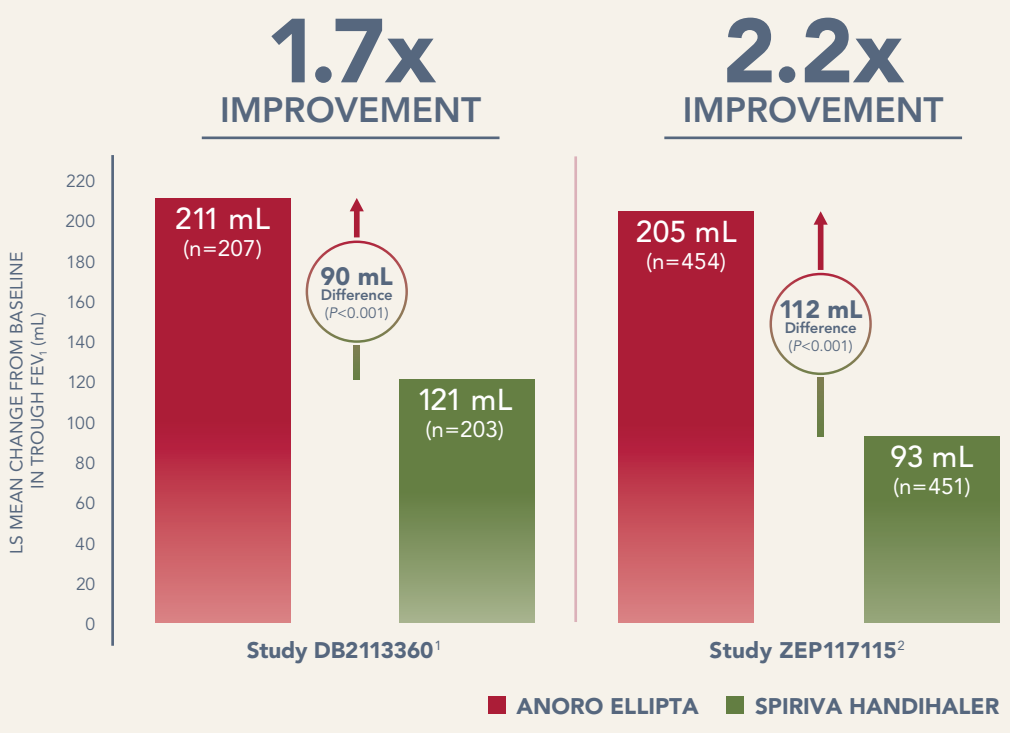
gsk | Theravance

ANORO® ELLIPTA®
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

START STRONG WITH ANORO INSTEAD OF SPIRIVA FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION

SIGNIFICANT IMPROVEMENT IN TROUGH FEV_1 AT DAY 169[1,2]

Studied in patients with moderate or worse COPD (GOLD 2-4)



ANORO ELLIPTA is a combination anticholinergic/LABA for the maintenance treatment of airflow obstruction in patients with COPD.

SPIRIVA HANDIHALER is an anticholinergic for the maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.[3]

FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; LS=least squares.

In a separate study (DB2113374), ANORO ELLIPTA (n=217) compared with SPIRIVA HANDIHALER (n=215) showed a 60-mL difference† (208 mL and 149 mL, respectively), but due to testing hierarchy, statistical significance cannot be inferred.[1]

†Reflects rounding.

DESCRIPTION OF STUDIES[1,2,4]

The efficacy and safety of a once-daily dose of ANORO ELLIPTA and SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) were evaluated in 24-week, multicenter, randomized, blinded, active-controlled, double-dummy, parallel-group studies in patients (mean age range: 62 to 65 years) with COPD. At screening, patients had a mean postbronchodilator FEV_1 range of 46.4% to 47.7% predicted. The studies were not powered to compare the safety profiles of the products.

PRIMARY ENDPOINT: Trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Caution should be exercised when considering the coadministration of ANORO with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO. Discontinue ANORO 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, or symptoms. If such effects occur, ANORO may need to be discontinued. ANORO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

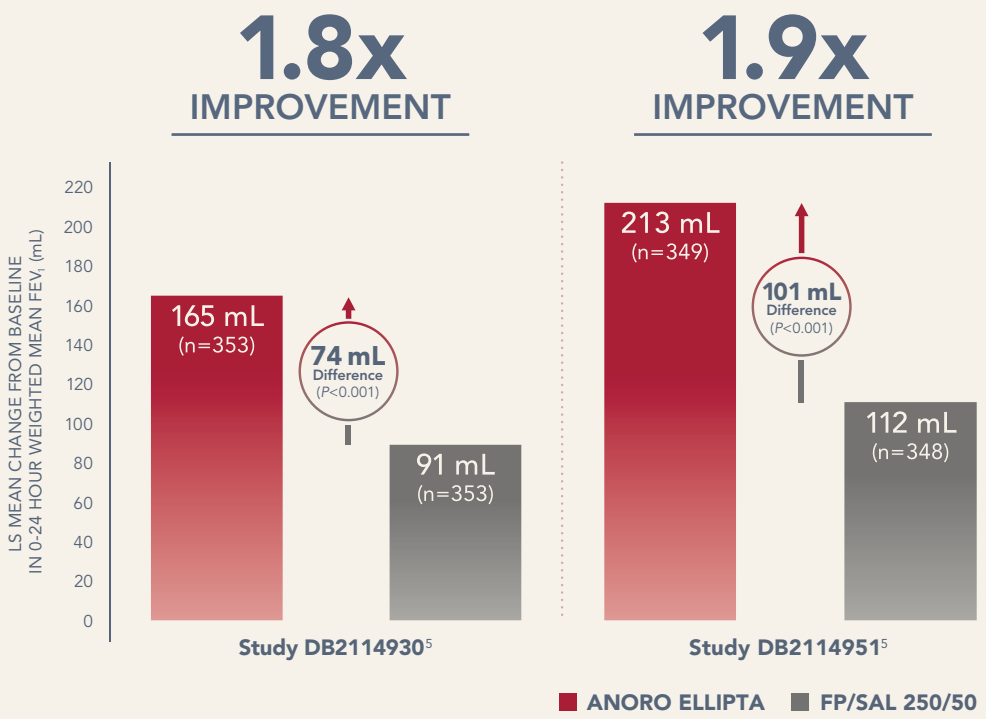
ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

START STRONG WITH ANORO INSTEAD OF FP/SAL 250/50 FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION

SIGNIFICANT IMPROVEMENT IN WEIGHTED MEAN FEV_1 (0-24 HOURS) ON DAY 84[5]

Studied in patients with moderate to severe COPD (GOLD 2 or 3)



ANORO ELLIPTA is a combination anticholinergic/LABA for the maintenance treatment of airflow obstruction in patients with COPD.

FP/SAL 250/50 mcg is indicated to reduce COPD exacerbations, whereas ANORO ELLIPTA is not.

FP=fluticasone propionate; SAL=salmeterol.

DESCRIPTION OF STUDIES[4,5]

The efficacy and safety of a once-daily dose of ANORO ELLIPTA and a twice-daily dose of FP/SAL 250/50 mcg (administered by the DISKUS® inhaler) were evaluated in 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group studies in patients (mean age range: 63 to 64 years) with COPD with no exacerbations (COPD symptoms requiring oral corticosteroids, antibiotics, and/or hospitalization) in the previous year. At screening, patients had a mean postbronchodilator FEV_1 range of 49.4% to 49.5% predicted. The studies were not powered to compare the safety profiles of the products.

PRIMARY ENDPOINT: Weighted mean FEV_1 (0-24 hours postdose) on Day 84.

Important Safety Information for ANORO ELLIPTA (cont'd)

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO 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 produce severe bronchospasm in patients with COPD.
- 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.
- Avoid coadministration of ANORO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Please see additional Important Safety Information for ANORO ELLIPTA on the preceding pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA on the following pages.

References: 1. Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med*. 2014;2(6):472-486. **2.** Maleki-Yazdi MR, Kaelin T, Richard N, et al. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med*. 2014;108(12):1752-1760. **3.** SPIRIVA HANDIHALER [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2016. **4.** Data on file, GSK. **5.** Donohue JF, Worsley S, Zhu C, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med*. 2015;109(7):870-881.

There's more to know about ANORO at StartWithANORO.com

ANORO ELLIPTA was developed in collaboration with Theravance

ANORO® ELLIPTA®
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

ANORO® ELLIPTA®
(umeclidinium and vilanterol inhalation powder), for oral inhalation
The following is a brief summary only; 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 ANORO ELLIPTA, 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 *[see Warnings and Precautions (5.1)]*.

The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full Prescribing Information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
A 28-week, placebo-controlled, US trial comparing 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 ANORO ELLIPTA.
No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.
5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA 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 ANORO ELLIPTA, 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 ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO ELLIPTA 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 ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO ELLIPTA. Discontinue ANORO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 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, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA 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.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, 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.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.11 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 medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%).
Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions with ANORO ELLIPTA with ≥1% Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %	Placebo (n = 555) %
Infections and infestations				
Pharyngitis	2	1	2	<1
Sinusitis	1	<1	1	<1
Lower respiratory tract infection	1	<1	<1	<1
Gastrointestinal disorders				
Constipation	1	<1	<1	<1
Diarrhea	2	<1	2	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	2	<1	2	1
Muscle spasms	1	<1	<1	<1
Neck pain	1	<1	<1	<1
General disorders and administration site conditions				
Chest pain	1	<1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.
6.2 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of ANORO ELLIPTA. 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 ANORO ELLIPTA or a combination of these factors.
Cardiac Disorders
Palpitations.
Immune System Disorders
Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.
Nervous System Disorders
Dysgeusia, tremor.
Psychiatric Disorders
Anxiety.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with 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 (5.4), 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 ANORO ELLIPTA, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD 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, such as vilanterol, a component of ANORO ELLIPTA, 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 ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA 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 ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 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 450 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.

Nonteratogenic Effects: *Umeclidinium:* There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments 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).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA

It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium

It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol

It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 years and older and 478 subjects aged 75 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

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed. *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium 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 case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA 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 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

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., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for the individual components, umeclidinium and vilanterol, as described below.

Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

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 that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD 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 medicine 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 ANORO ELLIPTA 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 medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA and contact their healthcare provider right away.

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.

Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

ANORO ELLIPTA was developed in collaboration with Theravance.

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Acoustic pharyngometry not best OSA diagnostic tool

BY BIANCA NOGRADY
Frontline Medical News

Assessment of upper airway cross-sectional area using acoustic pharyngometry is no better than the use of clinical variables to diagnose obstructive sleep apnea (OSA), according to a study in the Annals of the American Thoracic Society.

Tetyana Kendzerska, PhD, of the Institute for Clinical Evaluative Sciences, Toronto, and her colleagues found that the median upper airway cross-sectional area at functional residual capacity when sitting was significantly reduced in individuals with OSA, compared with those without the condition (3.3 cm^2 vs. 3.7 cm^2).

For every 1-cm^2 decrease in mean upper airway cross-sectional area when sitting, the researchers saw a 62% increase in the odds of OSA, even after controlling for age, sex, body-mass index, and comorbidities. This was significantly higher in women (90%) than in men (54%). However, the addition of upper airway cross-sectional area to the clinical variables of age; sex; body-mass index; and heart, kidney, and lung disease only led to a very small and nonsignificant increase in predictive ability for OSA, although it did improve the model fit.

The researchers found that, at a cut-off value of 3.75 cm^2, which struck the best balance of sensitivity and specificity, upper airway cross-sectional area had a sensitivity of 73% and specificity of 46%. Varying the apnea-hypopnea index to define OSA or varying the analysis of upper airway cross-sectional area did not improve its predictive or discriminative ability, nor was there any benefit to measuring upper airway cross-sectional area when an individual was supine, compared with sitting.

Dr. Kendzerska and her colleagues had hypothesized that acoustic pharyngometry could play a role in screening for OSA, based on previous studies suggesting significant differences in upper airway cross-sectional area measures in individuals with and without the condition.

Their cross-sectional study included 576 subjects with suspected OSA who underwent acoustic pharyngometry within 35 days of standard diagnostic polysomnography (Ann Am Thorac Soc. 2016 Aug 16. doi: 10.1513/AnnalsATS.201601-056OC).

"Although the mean [upper airway cross-sectional area] at [functional residual capacity] when sitting was a significant predictor of OSA controlling for important confounders, it had only fair discriminant validity for identifying those with OSA in a clinic population and had no significantly greater discriminant value than the use of clinical variables," the researchers reported. "Therefore, it is probably of no clinical utility in this setting."

The investigators said that they had no conflicts of interest.

Pediatric OSA improved with oral montelukast

BY KATIE WAGNER LENNON
Frontline Medical News

The majority of children with obstructive sleep apnea (OSA) who took oral montelukast showed reductions in their apnea-hypopnea index (AHI) scores, in a randomized, double-blind placebo-controlled study.

Typically, OSA in children is treated by adenotonsillectomy, according to Leila Kheirandish-Gozal, MD, director of clinical sleep research at the University of Chicago, and her colleagues. Prior to this study, only one randomized controlled trial had showed that children with mild OSA "responded favorably" to the leukotriene modifier montelukast (Pediatrics. 2012 Aug 31. doi: 10.1542/peds.2012-0310). Dr. Kheirandish-Gozal's study was conducted over a 16-week period in 57 children with OSA, who were 2-10 years (Ann Am Thorac Soc. 2016 Oct;13[10]:1736-41). Participants received either montelukast, which was given in 4-mg/day doses to children less than 6 years and in 5-mg/day doses to children at least 6 years of age, or a placebo. At the end of the trial, all remaining subjects, including those 15 who failed to use their assigned medication more than once a week (of which 7 received oral montelukast and 8 got the placebo), participated in an overnight polysomnographic study.

Twenty (71%) of the children who received montelukast had fewer AHI events per hour of total sleep time at the end of the study. The average number of such events for these patients was 4.2 plus or minus 2.8 after taking the drug, compared with 9.2 plus or minus 4.1 at the beginning of the study (*P* less than .0001). Only two (6.9%) of the patients who took the placebo had lower AHI scores at the end of the study, with the average AHI score for the placebo group having been 8.7 plus or minus 4.9 events per hour of total sleep time. At baseline, the average score for patients in the placebo group was 8.2 plus or minus 5.0 AHI events per hour of total sleep time at baseline. Another improvement seen by patients who received the drug was a decrease in the number of 3% reductions in arterial oxygen saturation per hour of sleep. At the beginning of the study, these patients had 7.2 plus or minus 3.1 of these events; by the end of the study, the number of these events was down to 2.8 plus or minus 1.8 (*P* less than .001). No significant decrease in the number of these events was seen among patients in the placebo group. Adverse events included headache and nausea.

Merck provided tablets used in this study. Dr. Kheirandish-Gozal reported grants from Merck and the National Institutes of Health.

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MRI measurements reveal effects of sleep deprivation

BY HEIDI SPLETE
Frontline Medical News

Lack of sleep had a significant impact on brain responses to an attention task, and circadian rhythms played a role, according to functional magnetic resonance imaging data from 33 healthy adults. The findings were published online Aug. 11 in Science.

Despite the data showing that acute sleep loss impacts cognition, "human performance remains remarkably well preserved until wakefulness is extended into the biological night," wrote Vincenzo Muto of the University of Liège, Belgium, and his colleagues (Science 2016;353:687-90. doi: 10.1126/science.aad2993).

Study participants stayed awake for 42 hours, beginning in the morning and covering 2 biological days, 1 biological night, and part of a second night. They periodically performed the psychomotor vigilance task (PVT), a visual reaction time task designed to measure attention; and an auditory *n*-back task, and the researchers collected functional and structural MRI data across 13 sessions. The average age of the participants (17 men and 16 women) was 21 years.

Overall, PVT performance was stable during the first day, but decreased significantly after sleep deprivation, then recovered during the second day, and returned to baseline after a period of recovery sleep, the researchers said.

Brain responses to the *n*-back task were "significantly modulated by a circadian oscillation, synchronous to the melatonin rhythm," they noted. "This finding rules out a global task-independent circadian influence and suggest the influence of a local, region-specific task-dependent circadian signal," they added.

Despite the data showing that acute sleep loss impacts cognition, human performance remains remarkably well preserved until wakefulness is extended into the biological night.

Although more research is needed on how different cognitive tasks are affected by sleep deprivation, the findings may help in "understanding of the brain mechanisms underlying the maintenance of daytime cognitive performance and its deterioration, as observed in shift work, jet lag, sleep disorders, aging, and neurodegenerative diseases," the researchers wrote.

They had no financial conflicts to disclose.

Adolescent sleep apnea linked to NAFLD, NASH

BY DEEPAK CHITNIS
Frontline Medical News

A new study has found that a strong association exists in adolescents who have obstructive sleep apnea, and their risks of developing more highly progressed forms of nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH).

"Substantial evidence suggests oxidative stress is a central mediator in NAFLD pathogenesis and progression, although the specific trigger for reactive oxygen species (ROS) generation has not been clearly delineated," wrote the authors, led by Shikha S. Sundaram, MD of the University of Colorado at Denver, Aurora, adding that "Emerging evidence demonstrates that obesity-related obstructive sleep apnea (OSA) and intermittent nocturnal hypoxia are associated with NAFLD progression."

Dr. Sundaram and her coinvestigators looked at patients admitted to the Children's Hospital Colorado Pediatric Liver Center from June 2009 through January 2014. Subjects included were children ages 8-18 years, male and female, who were classified as Tanner stage 2-4 with liver biopsy evidence of NAFLD.

"In our center, a clinical liver biopsy for suspected NAFLD is performed in overweight or obese children with chronically elevated aminotransferases in whom a diagnosis is unclear based on serologic testing," Dr. Sundaram and her coauthors clarified regarding the screening process.

Additionally, age-matched "lean" children, that is, those with a body mass index lower than 85%, were also enrolled as controls; these subjects were included if they had no evidence of hepatomegaly or liver disease – translated to AST and ALT levels of 640 IU/L – and were also Tanner stage 2-4. The authors explained that this Tanner stage range was chosen in order to "minimize variations in insulin sensitivity that may confound the interpretation of potential associations between OSA/hypoxia and NAFLD."

Ultimately, 36 NAFLD adolescent subjects and 14 controls completed the study. A total of 25 of the 36 NAFLD subjects (69.4%) had OSA and/or nocturnal hypoxia; of these, 15 were classified as having isolated OSA, 9 had both OSA and hypoxia, and 1 had isolated hypoxia. Polysomnograms found that all NAFLD subjects spent more than 12% of their total time asleep in REM sleep, which was deemed adequate enough to consider the findings valid.

Based on liver histology scoring, laboratory testing, urine F2-isoprostanes, and 4-hydroxynonenal liver immunohistochemistry tests that were conducted on all subjects, Dr. Sundaram and her coinvestigators found that subjects with OSA or hypoxia had more severe fibrosis than did those without. While the latter cohort were 100% stage 0-2, only 64% of those with OSA/hypoxia were stage 0-2, while the remaining 36% were stage 3 ($P = .03$). Additionally, higher F2-isoprostanes – used to measure lipid peroxidation – correlated

Continued on following page

Continued from previous page

with apnea/hypoxia index (r = 0.39; $P = .03$), and the most severe OSA/hypoxia occurred in subjects that had the greatest 4-hydroxynonenal staining ($P = .03$). Furthermore, an increase in both F2-isoprostanes and 4-hydroxynonenal hepatic staining was shown to lead to a higher risk of worse steatosis: r = 0.32 and r = 0.47, respectively ($P = .04$ and $P = .007$).

"These data support sleep disordered breathing as an important trigger of oxidative stress that promotes progression of pediatric NAFLD to NASH," the authors concluded, adding that "this study confirms that OSA/hypoxia is common in pediatric NAFLD and that more severe OSA/hypoxia is associated with elevated aminotransferases, hepatic steatosis, inflammation, NAS [NAFLD activity score], and fibrosis."

Dr. Sundaram and her coauthors call for further research to examine if "prevention or reversal of NASH following effective therapy of OSA and nocturnal hypoxia in obese patients" is viable. This study was supported by funding from the National Institutes of Health. Dr. Sundaram and her coinvestigators did not report any relevant financial disclosures.

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Adding salmeterol didn't boost asthma events in kids

BY MARY ANN MOON
Frontline Medical News

Adding the long-acting beta-agonist salmeterol to fluticasone in a fixed-dose combination didn't increase serious asthma-related events among children aged 4-11 years, according to a report published online Sept. 1 in the New England Journal of Medicine.

After long-acting beta-agonists were introduced as add-on therapy for uncontrolled asthma, two large studies involving adults linked the treatment to an increase in asthma-related death. Other studies found no such association.

The FDA mandated that all four manufacturers of those agents in the United States perform large postmarketing safety trials to establish the noninferiority of the approach. In response, GlaxoSmithKline, the only maker of a long-acting beta-agonist with a pediatric indication (salmeterol), performed this international randomized, double-blind, controlled trial at 567 medical centers in 32 countries, said David A. Stempel, MD, of Respiratory Clinical Development, GSK, Research Triangle Park, N.C., and his associates.

The trial involved 6,208 children aged 4-11 years who had controlled or uncontrolled asthma with a history of exacerbations during the preceding year. The participants were randomly assigned to receive 26 weeks of a lower fixed-dose combination of salmeterol plus fluticasone, a higher fixed-dose combination, a lower dose of fluticasone alone, or a higher dose of fluticasone alone, delivered twice daily via a disk device.

The primary safety endpoint was a composite of death, endotracheal intubation, and hospitalization. No deaths or intubations occurred.

A total of 27 patients taking combined therapy and 21 taking fluticasone alone required hospitalization for asthma (hazard ratio, 1.28). The number of severe asthma exacerbations was 14% lower when salmeterol was added to fluticasone, a nonsignificant difference.

The results demonstrate the noninferiority of the combined therapy, Dr. Stempel and his associates said (N Engl J Med. 2016 Sep 1;375[9]:840-9).

The percentage of children who withdrew from the study because of asthma exacerbations was identical in the two groups (1.1% of each), and the percentage who had a serious adverse event was nearly identical (1.8% vs 1.7%, respectively). The mean percentage of rescue therapy–free days also was similar (83.0% vs 81.9%), as was the mean percentage of days in which asthma was controlled (74.8% vs. 73.4%).

At the conclusion of the study, 88.1% of the fluticasone-plus-salmeterol group had controlled asthma, as did 88.5% of the fluticasone-only group. Meaningful differences between the two treatments could not be identified among various subgroups of patients – defined by age, sex, and race – because the overall number of adverse events was so low, the investigators added.

They cautioned that the trial excluded children who had a history of multiple asthma-related hospitalizations and intubations. Therefore, the findings may not be applicable to patients with very severe asthma, the researchers cautioned.

GlaxoSmithKline sponsored the trial in response to a Food and Drug Administration mandate for large postmarketing safety studies from the marketers of long-acting beta agonist–containing products sold in the United States. Dr. Stempel is an employee of GSK; his associates reported ties to numerous industry sources.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This is a large and very important pediatric study of over 6,000 children who have asthma. It looked at the safety of long-acting bronchodilator (LABA) therapy in combination with fluticasone.

The SMART study said long-acting bronchodilators (LABAs) were unsafe. This new study shows that we can use these drugs, as there were no deaths related to LABAs and there was no difference between how patients reacted to the therapies. However, that there was a low percentage of status asthmaticus admissions raises questions about the severity of asthma in the patients studied. That may have affected the efficacy results.

We use LABAs every day for poorly controlled asthma patients who have moderate and severe persistent asthma based on the asthma guidelines. I do feel that [these drugs] are helpful. There is also basic science information that states they work synergisticaly with inhaled steroids in airway inflammation and bronchoconstriction.

AAP report flags risks of prescribing codeine for children

BY TARA HAELLE
Frontline Medical News

The risks of using codeine to treat pain or cough in children may often outweigh the benefits, sometimes even leading to death, and call into question whether its widespread use should continue in pediatric patients, according to an American Academy of Pediatrics technical report.

"It is clear that one of the keys to improving analgesia and reducing opioid-related adverse effects is both provider and parental education regarding the effective use of nonopioid analgesics," wrote Joseph D. Tobias, MD, and his colleagues from the AAP Committee on Drugs' Section on Anesthesiology and Pain Medicine (Pediatrics 2016 Sept 19. doi: 10.1542/peds.2016-2396). "The answer may not lie in using more medication or different medications but merely using more effectively other options that are currently available."

Individual patients respond differently to codeine because the conversion rates of the liver enzyme that metabolizes codeine into morphine, CYP2D6, vary greatly according to genetic differences. Some children experience no therapeutic effect at all while others have stopped breathing or died, particularly those who metabolize the drug extremely rapidly. Those with at least two copies of the CYP2D6 gene have a particularly elevated level of enzyme activity. Also at high risk for respiratory depression or death are children with obstructive sleep apnea.

Poor metabolizers, who therefore experience less effect from codeine, include disproportionately more individuals of Northern European descent. Ultrarapid metabolizers, on the other hand, comprise approximately 29% of patients of African/Ethiopian heritage and 21% from Middle Eastern countries. An estimated 3.4%-6.5% of African Americans and whites are ultrafast metabolizers. Genetic tests can identify those at higher risk, but even children with normal metabolism can experience severe adverse effects.

The World Health Organization

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: I see many pediatricians still prescribe codeine preparations for coughing, even though the American Academy of Pediatrics has advised against it. This is terrible as it only suppresses the cough and does not help the underlying problem.

sential medications, the U.S. Food and Drug Administration added a black box warning to labels of codeine formulations used for tonsillectomy and/or adenoidectomy in children, and the European Medicines Agency recommended against using codeine in children under age 12 years and in those between 12 and 18 years who have breathing difficulties.

Yet research has shown that the use of codeine for pain relief in children remains very common; codeine is prescribed more than any other opioid in some studies. Otolaryngologists, dentists, pediatricians, and family practice physicians, respectively, prescribe it most often, likely because few safe, effective therapeutics exist for treating pain or cough in children. Oxycodone has been used as an alternative, but this drug also lacks adequate data on its use, and hydrocodone has similar concerns with rapid metabolizers.

Although most of the serious adverse events resulting in codeine use in children have followed adenotonsillectomy in children with disordered breathing, the authors warned that "physicians cannot assume such problems will occur only" after such procedures. "Given the increasing prevalence of obesity in the United States, it is likely that some patients presenting for nonotolaryngologic procedures may have undiagnosed sleep-disordered breathing and may also be at risk if they require extended postoperative analgesia," the authors wrote.

Checklist may prompt cuts in unneeded antibiotics

BY WILLIAM PERLMAN
Frontline Medical News

Primary care practitioners' use of a seven-item checklist may reduce the number of pediatric patients with respiratory tract infections who are prescribed unnecessary antibiotics, a prognostic cohort study suggests.

The study revealed short illness (a duration of illness of 3 days or less), temperature (a body temperature of 37.8°C or greater at presentation), age (being under 2 years), intercostal or subcostal recession, wheeze on auscultation, asthma, and vomiting (moderate or severe in the previous 24 hours) were each independently associated with hospital admission (*P* less than .01 for all associations). The checklist includes these seven characteristics or risk variables (mnemonic STARWAVe), which a primary care practitioner uses to evaluate patients. The physician assigns one point for the presence of each item in a patient then adds up the total number of points to determine a patient's risk level for future hospital admission for respiratory tract infection.

A score of 1 point or less, observed in 5,593 (67%) cases would be considered indicative of a very low rate of risk for hospitalization (0.3%, 0.2%-0.4%). A score of 2 or 3 points, found for 2,520 (30%) children, would be considered as a normal level of risk (1.5%, 1.0%-1.9%), and a score of 4 or more points, seen in 204 (3%) children, would signify a high risk level (11.8%, 7.3%-16.2%).

Of the 8,394 children assessed, 78 (0.9%; 95% confidence interval, 0.7%-1.2%) were admitted to a hospital. Most were admitted on days 2-7 (33, 42%) and on days 8-30 (30, 39%) following recruitment. Only 15 (19%) were admitted on the day of recruitment (day 1).

"Many clinicians report that they prescribe antibiotics just in case, to mitigate perceived risk of future hospital admission and complications, and that failing to provide a prescription for a child who subsequently becomes seriously unwell is professionally unacceptable. If primary care clinicians could identify children at low (or very low) risk of such future complications, the reduced clinical uncertainty could lead to a reduced use of antibiotics in these groups of patients," wrote first author Alastair Hay, MD, from the Centre for Academic Primary Care in the School of Social and Community Medicine at the University of Bristol (England), and his colleagues.

These researchers conducted the study based on a structured, blinded review of the medical records from children aged between 3 months and 16 years presenting with acute cough (less than or equal to 28 days) and respiratory tract infection treated by 519 general practitioners in 247 practices in England between July 2011 and June 2013. The primary study outcome was hospital admission for respiratory tract infection within 30 days.

Additionally, a multivariable model was employed to detect factors associated with increased risk of hospital admission. As measured by receiver operating characteristic curve analysis, the accuracy of the STARWAVe score checklist in predicting risk groups and associated risk of hospitalization was found to be high (0.81; 95% CI, 0.77-0.86). The suggested probability of hospital admission for children who did not have any of the seven characteristics included in the checklist was found to be exceptionally low (0.14%).

Significantly associated parent-reported variables included both moderate or severe vomiting and severe fever, each in the previous 24 hours. Significant clinician-reported variables included intercostal or subcostal recession and wheeze on auscultation.

"The main value of our results is to reduce clinical uncertainty and antibiotic use in children least likely to benefit from them, namely those at very low risk of future hospital admission," Dr. Hay and his associates noted in The Lancet Respiratory Medicine (Lancet Respir Med. 2016 Sep 1. doi: 10.1016/S2213-2600(16)30223-5).

Funding for this study was provided by the National Institute for Health Research and sponsored by the University of Bristol.

Only one of the study's authors, Dr. Peter Muir, reported ties to industry sources.

VIEW ON THE NEWS

STARWAVe will improve antimicrobial stewardship

There are few efficacious interventions for respiratory tract infection available to primary care clinicians beyond offering reassurance and self-management advice, so the modest benefit offered by antibiotics can persuade general practitioners to prescribe them.

To derive (and validate) a clinical prediction rule to improve targeted antibiotic prescribing in children with respiratory tract infections, Hay et al determined the seven characteristics independently associated (*P* less than .01 for all associations) with hospital admission for children presenting to primary care physicians with cough and respiratory tract infection (STARWAVe). Using this seven-item checklist to help structure point-of-care assessment for this patient population should predict the risk of hospital admission with remarkable accuracy (area under the received operating characteristic curve, 0.81; 95% CI, 0.76-0.85).

STARWAVe offers primary care clinicians an evidence-based practical tool to help guide antibiotic prescription decisions and, through shared decision-making, has the potential to reduce antibiotic prescription based on prognostic uncertainty or on nonmedical grounds.

If STARWAVe leads to an increase in antibiotic prescription (to 90%) in high-risk children and a parallel halving of prescription to those at low risk of hospital admission, it could achieve a 10% overall reduction in primary care antibiotic prescriptions for respiratory tract infections.

These comments are excerpted from a commentary by Dr. Christopher C. Winchester from Oxford PharmaGenesis and Durham University (England), Alison Chisholm, MSc, from the Respiratory Effectiveness Group in Cambridge (England), and Dr. David Price from the University of Aberdeen (Scotland) and the Observational and Pragmatic Research Institute in Singapore. Dr. Winchester and Dr. Price disclosed financial relationships with numerous industry sources; Ms. Chisholm indicated no financial relationships relevant to this article. Funded information was not provided. (Lancet Respir Med. 2016 Sep 1. doi: 10.1016/S2213-2600(16)30272-7).

RSV vaccines on the horizon

BY TARA HAELLE
Frontline Medical News

ATLANTA – New vaccines for respiratory syncytial virus may be on the horizon, according to Larry Anderson, MD, professor of infectious disease in the Emory University department of pediatrics.

During a conference sponsored by the Centers for Disease Control and Prevention, Dr. Anderson provided an overview on the progress of more than five dozen groups working on RSV vaccines. About 70% of the candidates are still in preclinical research. Six vaccines are in phase II or phase III testing, and MedImmune's Synagis is market approved. But not all candidate vaccines target the first and highest priority patient – the young infant.

Potentially "the lowest apple on the tree for immunization" of newborns would be their pregnant mothers, he said. "There, the primary purpose is to increase the kind of antibody that is transferred across the placenta to the fetus to protect from RSV." Data suggest antibody titers in infants can be increased for at least 4 months by maternal immunization.

For young children, five live attenuated RSV vaccines are in phase I testing, as are four others that use a virus vector to deliver the F protein – three using adenovirus and one with a modified vaccinia Ankara virus.

A handful of subunit vaccines have reached phase II, and Novavax is furthest along in phase III, but these vaccines target older children and adults, including pregnant women.

Dr. Anderson has consulted on RSV vaccines for MedImmune, Novartis, Crucell Holland, and AVC, and has served on a Moderna Therapeutics scientific advisory board. He coinvented several RSV-related vaccine and treatment patents held by the CDC.

Dr. Anderson's lab also has received grant funding from Trellis RSV Holdings.

MACRA final rule exempts many more doctors

BY GREGORY TWACHTMAN
Frontline Medical News

Physicians who do not have a large Medicare population or who do not bill much to Medicare Part B will get a bit more breathing room to avoid having to participate in MACRA's Quality Payment Program.

In a final rule posted Oct. 14 that sets out how the Medicare Access and CHIP Reauthorization Act (MACRA) will work, the Centers for Medicare & Medicaid Services increased the threshold for inclusion in the new value-based payment program from the initial proposal of physicians who bill Medicare more than $10,000 per year or treat more than 100 Medicare patients per year to those who bill more than $30,000 per year or provide care to more than 100 Medicare patients per year.

However, agency officials noted that it is committed to helping these small and solo practices become active participants in the Quality Payment Program.

CMS "heard from physicians in small and rural practices concerned about the impact of the new requirements," CMS Acting Administrator Andy Slavitt said in a blog post also published Oct. 14.

"We heard these concerns and are taking additional steps to aid small practices, including reducing the time and cost to participate, excluding more small practices, increasing the availability of Advanced APMs [Alternative Payment Models] to

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VIEW ON THE NEWS

Mike Nelson, MD, FCCP, comments: This is a bit of good news from our friends at CMS and builds on the options for participation released earlier this fall. Very small practices will likely meet the threshold for exemption and save themselves from the scheduled reimbursement reduction in 2019. It is still somewhat distressing that health-care providers are being saddled with additional administrative burdens that purportedly will improve patient care, while taking time away from the patient. Recently published data reveal that physicians now spend almost 2 hours documenting for every 1 hour they spend with their patients (Annals Int Med DOI: 10.7326/M16-0961). It is speculated that this activity may be accelerating the retirement of the "ol' timers" due to dissatisfaction with the trend away from the patient and toward satisfying administrative mandates from payers. One can only hope the speculation is inaccurate and that CMS continues to modify their requirements based upon physician input.

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small practices, allowing practices to begin participation at their own pace, changing one of the qualifications for participation in Advanced APMs to be practice-based as an alternative to total cost–based, and conducting significant technical support and outreach to small practices using $20 million a year over the next 5 years."

CMS officials estimate that the new threshold will exclude an estimated 380,000 physicians and health care providers, up from about 225,000 under the initially proposed threshold.

Mr. Slavitt added that with these changes, "we estimate that small physicians will have the same level of participation as that of other practice sizes."

The flexibility of participation was first announced Sept. 8, in a blog post outlining four options for participation in the Quality Payment Program:

- Option 1: Test the quality payment program in 2017 by submitting data without facing any negative payment adjustments. This will give physicians the year to make sure their processes are in place and ready for broader participation in 2018 and beyond.
- Option 2: Delay the start of the performance period and participate for just part of 2017. Depending on

how long a physician delays reporting quality information back to CMS, they could still qualify for a smaller bonus payment.

• Option 3: Participate for the entire calendar year as called for by the law and be eligible for the full participation bonuses.

• Option 4: For those who qualify, participate in an Advanced Alternative Payment Model beginning next year. That said, under the final rule, those who fail to do the bare minimum and report no data in 2017 will face a 4% pay cut in 2019.

"I am sure that is going to impact some providers," John Feore, director at Avalere Health, said in an interview. "But with the options, you can report on a very small number of measures, one for each of the categories, for a continuous 90-day period and you will be sort of held harmless [and able] to transition over time into the program."

Mr. Feore said that did not see any surprises in his initial quick scan of the final rule and that he views the increased flexibility as positive.

"CMS is understanding that MACRA is a pretty substantial change," he said. "They are calling [2017] a transition year. They are even referring to 2018 as a transition year with more details to come. They are responding

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to stakeholder concerns that it was a little too much too soon and there is varying degrees of readiness."

Physician organizations were supportive of the final rule, particularly regarding how it addresses the concerns of small/solo practices.

CMS officials "took a significant step last month to address AMA concerns about the original proposal," American Medical Association President Andrew W. Gurman, MD, said in a statement. "The final rule includes additional steps to help small and rural practices by raising the low-volume threshold exemption, and practices of all sizes will benefit from reduced MIPS reporting requirements. Our initial review indicates that CMS has been responsive to many concerns raised by the AMA."

American College of Cardiology President Richard A. Chazal, MD, said in a statement that the organization is "encouraged to see that CMS has made several changes in the final rule based on comments by the clinician community."

The American Osteopathic Association applauded the flexibility being offered, but found it "disappointing that many of those currently in patient-centered medical homes will still not qualify for

[APMs] and opportunities to enter other such value-based models remain limited."

To that end, CMS officials said that the agency is looking into creating an accountable care organization (ACO) "Track 1 Plus" model that would qualify for as an APM.

Currently, ACOs that are in Track 1 share savings but do not assume risk.

The agency said that the Track 1 Plus model would have organizations assuming some nominal level of risk that would be smaller, compared with those in the Medicare Shared Savings Program (MSSP) Track 2 and Track 3, as well as those that qualify as Next Generation ACOs. CMS plans to have the ACO Track 1 Plus Model ready for the 2018 reporting year.

The National Association of ACOs expressed disappointment that those ACOs that fall in the Track 1 of the MSSP do not qualify as an APM, but it is "incredibly pleased that CMS recognizes the need for a new model and is taking steps to develop a new MSSP Track 1 Plus," President and CEO Clif Gaus said in a statement.

More CMS-issued information and educational material about the MACRA final rule can be found at https://qpp.cms.gov/education.

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Four factors raise risk of post-TAVR endocarditis

BY MARY ANN MOON
Frontline Medical News

Four factors – younger patient age, male sex, diabetes, and moderate to severe residual aortic regurgitation – are associated with a significantly increased risk of infective endocarditis after transcatheter aortic valve replacement (TAVR), according to a report published online Sept. 13 in JAMA.

Until now, data pertaining to endocarditis following TAVR "have been limited to case reports and relatively small series with limited follow-up," said Ander Regueiro, MD, of Laval University, Quebec City, and his associates.

They performed a retrospective analysis of data in a large international registry of TAVR cases to better characterize post-TAVR endocarditis.

Dr. Regueiro and his colleagues focused on 20,006 TAVR procedures done at 47 medical centers in Europe, North America, and South America during a 10-year period. The median time to symptom onset was 5.3 months after the procedure.

Infective endocarditis was definitively diagnosed in 250 of these cases. This incidence is similar to that reported for endocarditis following surgical aortic valve replacement, indicating that TAVR is no less predisposing to endocarditis despite being a less invasive approach.

The mean age of patients who developed post-TAVR endocarditis was 78.9 years, compared with 81.8 years for those who did not (HR, 0.97). The reason for this association is unclear, but it is possible that younger patients chosen for TAVR because of their prohibitive surgical risk carry a higher burden of comorbidity than do older patients. Similarly, 62% of

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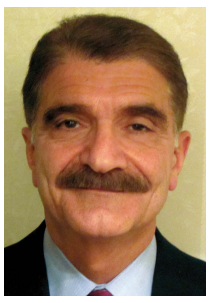
VIEW ON THE NEWS

Hossein Almassi, MD, FCCP, comments: Encouraging patients' outcome with TAVR has led to its application to younger and lower risk patients. The findings in this large retrospective review show that despite the less invasive nature of the TAVR, the incidence of endocarditis is similar to surgical aortic valve replacement (SAVR) as is the microbiology. The finding of moderate to severe residual aortic valve regurgitation having the highest HR of 2.05 for post-TAVR endocarditis is not surprising. With improvement in technology, one would expect that the issue of residual valvular regurgitation would be resolved. The study spans over 10 years, and it is not clear what percent of patients had trans-apical TAVR vs trans-femoral and if the rate of endocarditis was similar between the two groups.



CardioMEMS shows real-world heart failure benefit

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – Pulmonary artery pressure monitoring using an implanted device was even more effective for controlling pulmonary artery pressures in 2,000 real-world U.S. heart failure patients than it was in the pivotal trial that led to the device's regulatory approval.

The analysis focused on data from the first 2,000 U.S. heart failure patients to receive the CardioMEMS pulmonary artery (PA) pressure monitoring device since the device received Food and Drug Administration approval in 2014. Patients also had to have at least 6 months of follow-up data. Cumulative PA pressure reductions in these patients during the first 6 months of use averaged 434 mm Hg per patient when compared with baseline PA pressures. This was nearly threefold better than the average 150–mm Hg cumulative reduction in PA pressure per patient during 6 months of use seen in the CHAMPION trial, Dr. William T. Abraham reported at the annual scientific meeting of the Heart Failure Society of America.

With CardioMEMS pressure monitoring, clinicians are supposed to treat high PA pressure with dose adjustments even if the patient feels okay. The new data suggest that clinicians using the device know they need to do something with the data.

Although this analysis of data from the registry maintained for U.S. patients who receive the CardioMEMS device does not yet include information on how these patients fared clinically, and specifically how often they required rehospitalization for heart failure, the strikingly high level of PA pressure control seen in the first 2,000 U.S. patients bodes well for what the clinical findings will show once they are available.

"In our experience with PA pressure monitoring, there is almost a linear relationship between reduced PA pressures and reduced numbers of events" in the form of rehospitalizations for heart failure, said Dr. Abraham, professor of medicine and director of cardiovascular medicine at Ohio State University in Columbus. Once data on outcomes are analyzed for the registry patients, "I think they will be even better than they were in the trial," he said in an interview.

The PA pressure data in these initial patients "are very important because they tell us that in general use, clinicians – many of whom are at community hospitals – are very capable of using the CardioMEMS data to control patient pressures, and in CHAMPION we showed that there is a relationship between controlled pressures and improved outcomes," he said. The findings also help allay a key concern about the potential benefit from implanting a device to monitor PA pressure, which is that clinicians must respond to the information and tweak a patient's diuretic and vasodilator treatments in order for pressure monitoring to have an effect on heart failure outcomes.

"These data clearly refute that concern," Dr. Abraham said.

He expressed some surprise that PA pressure control with monitoring was so much more effective in real-world use than in the CHAMPION pivotal trial. "In the trial, it was a paradigm shift to manage heart failure patients based on their PA pressures and not according to their symptoms," he said. With CardioMEMS pressure monitoring, clinicians are supposed to treat high PA pressure with dose adjustments even if the patient feels okay. The new data suggest that clinicians now using the device "have gotten the message that if you don't do something with the data the patients won't improve."

The registry patients came from 47 states and 427 unique physicians who worked in a range of settings including large and small centers, and academic and nonacademic community centers.

The patients averaged 70 years, 40% were women, a third had a left ventricular ejection fraction at or above 40%, and their average PA pressure at the time they had their device implanted was 34.9 mm Hg. This pressure was notably higher than the average 31.6 mm Hg pressure among patients enrolled in CHAMPION, a fact that also helps explain why the registry patients received a larger pressure-reduction benefit: They started from a higher level than the trial patients, and during follow-up, their achieved pressures were always compared back to their high baseline pressures.

The registry patients were also substantially older than the trial patients, who had averaged 62 years, and the registry included substantially more women and more patients with higher ejection fractions. Dr. Abraham did not report data on their New York Heart Association class at entry, but labeling for CardioMEMS specifies that patients should have class III heart failure as well as a recent heart failure hospitalization.

Dr. Abraham's analysis also showed that the greatest degree of PA pressure control occurred in the patients who began device-based treatment with the highest PA pressures.

Nearly half the 2,000 registry patients had an entry PA pressure at or above 35 mm Hg, and over a period of 6 months, they averaged a cumulative 876–mm Hg reduction in their PA pressure relative to their baseline level.

The third of patients who began with a PA pressure of 25-34 mm Hg had an average 169–mm Hg cumulative pressure reduction over the 6 month period, and the 18% of patients who began with a PA pressure of less than 25 mm Hg actually had an average cumulative increase in the PA pressure of 163 mm Hg. Target PA pressures are usually in the normal range of 18-25 mm Hg.

The analyses also showed that the impact of PA pressure monitoring on pressure was roughly similar regardless of the left ventricular ejection fraction patients had at baseline, and regardless of their sex.

The registry data were collected by St. Jude, the company that markets the CardioMEMS device. Dr. Abraham is a consultant to St. Jude and was lead investigator for the CHAMPION pivotal trial.

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VIEW ON THE NEWS

Hossein Almassi, MD, FCCP comments: The CardioMEMS PA pressure monitor is an FDA approved device implanted in the pulmonary artery by catheter technology via a right femoral vein access. The results of this large registry data confirms those of the smaller CHAMPION trial (Lancet. 377;658-666, DOI:10.1016/S0140-6736(11)60101-3.) that the reduction in the PA pressure based on the continuous PA pressure monitoring by the CardioMEMS device reduces the hospital readmission rate in patients in NYHA class III. It would be interesting to see if these findings translate into improved patients outcomes.

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endocarditis cases arose in men (HR, 1.69), and sex differences in comorbid conditions may explain the higher risk among men.

More patients who developed endocarditis had diabetes (41.7%), compared with those who did not develop endocarditis (30%), for an HR of 1.52. And patients who had moderate to severe residual aortic regurgitation after TAVR also were at much higher risk for endocarditis than were those who did not (HR, 2.05), the investigators noted (JAMA. 2016 Sep 13;316[10]:1083-92).

The incidence of infective endocarditis was similar to that reported for endocarditis following surgical aortic valve replacement, indicating that TAVR is no less predisposing to endocarditis despite being a less invasive approach.

In contrast, factors that were not associated with endocarditis risk included chronic pulmonary disease, type of valve (self-expandable or balloon-expandable), and setting of the procedure (catheterization lab vs. operating room).

The bacteria that most commonly caused infective endocarditis were *Enterococci* species (24.6% of cases), *Staphylococcus aureus* (23.8%), and coagulase-negative staphylococci (16.8%). This should be taken into consideration when selecting antibiotics for prophylaxis before TAVR and when choosing empirical antibiotics for treatment while waiting for blood culture results, wrote Dr. Regueiro and his associates.

"This information may help clinicians identify patients at higher risk [for endocarditis] and aid in implementing appropriate preventive measures," they noted.

This study was supported by a grant from the Alfonso Martin Escudero Foundation.

Dr. Regueiro reported having no relevant financial disclosures; his associates reported ties to numerous industry sources.

Lung cryobiopsies unnecessary for most ILDs

BY SARA FREEMAN
Frontline Medical News

LONDON – The vast majority of surgical lung biopsies currently used to diagnose interstitial lung diseases (ILDs) could be avoided, suggests research presented at the annual congress of the European Respiratory Society.

During an oral presentation, Benjamin Bondue, MD, of Hopital Erasme, Brussels, presented the preliminary results of a Belgian prospective study evaluating the role of transbronchial lung cryobiopsies in 24 patients with undefined ILD treated at three participating centers.

Cryobiopsies were found to have a diagnostic yield of 79%, meaning that patients might be able to avoid undergoing a more invasive surgical removal of tissue in many cases. Compared with surgical biopsy, cryobiopsies offered the potential advantage of lower morbidity and shorter hospitalization time, Dr. Bondue said. He reported that patients needed to stay in hospital just 1.2 days after the procedure in the study.

"Our data also show that there is some benefit of surgical lung biopsy after cryobiopsy if we identify an NSIP [nonspecific interstitial pneumonia] pattern or idiopathic conditions, or if we cannot obtain a clear pathological diagnosis," he reported. Acknowledging the study was small and conducted in a single center, he said the use of cryobiopsies following surgical biopsy might be worth further study.

Transbronchial lung cryobiopsy is a relatively new technique that uses a cryoprobe inserted down through a bronchoscope about 1-2 cm from the thoracic wall. Once in place, the probe is cooled for between 3 and 6 seconds, lung tissue freezes to the probe, and the probe and bronchoscope are removed together. This method allows for larger samples of tissue to be taken than does traditional transbronchial biopsy, which involves using large forceps to obtain tissue samples (Respirology. 2014;19:645-54).

A fogarty balloon was used to control any bleeding and that four transbronchial lung cryobiopsies were obtained from two different segments of the same lobe of a patient's lungs. All biopsies were then analyzed by an expert pathologist in ILDs, and reviewed by two other expert pathologists when needed.

The patients included in the study had undergone chest X-ray and had inconclusive findings in the majority (84%) of cases. They then had the option to undergo cryobiopsy or surgical lung biopsy, with the latter performed following discussion among a multidisciplinary team's members.

Following cryobiopsy, 16 of the 24 patients – who were a mean age of 62 years, and over half of whom were past (56%) or current (12%) smokers – were diagnosed with a specific pattern of ILD not due to NSIP. Of the 16 cases, 6 were due to hypersensitive pneumonitis, 4 were due to interstitial pulmonary fibrosis, and 2 were due to sarcoidosis. The other four cases included patients with one of the following conditions: adenocarcinoma, desquamative interstitial pneumonia, eosinophilic pneumonia, and amyloidosis. Six of the 24 cases were defined as NSIP, with 2 reclassified as definite and 1 as probable hypersensitive pneumonitis, after discussion within the multidisciplinary team.

Five patients – three who had been diagnosed with NSIP and two who had been given no pathological diagnosis after cryobiopsy – underwent surgical lung biopsy. Of these, following the surgical biopsies, only one patient was considered to have NSIP and the other four were eventually diagnosed with interstitial pulmonary fibrosis.

Dr. Bondue has received research grants and fees for consulting from Boehringer Ingelheim and Roche.

Transplant recipients less susceptible to antibiotics

BY MARY ANN MOON
Frontline Medical News

Antibiotic susceptibility in bacteria cultured from transplant recipients at a single hospital differed markedly from that in hospital-wide antibiograms, according to a report published in Diagnostic Microbiology and Infectious Disease.

Understanding the differences in antibiotic susceptibility among these highly immunocompromised patients can help guide treatment when they develop infection, and reduce the delay before they begin receiving appropriate antibiotics, said Rossana Rosa, MD, of Jackson Memorial Hospital, Miami, and her associates.

The investigators examined the antibiotic susceptibility of 1,889 isolates from blood and urine specimens taken from patients who had received solid-organ transplants at a single tertiary-care teaching hospital and then developed bacterial infections during a 2-year period. These patients included both children and adults who had received kidney, pancreas, liver, heart, lung, or intestinal transplants and were treated in numerous, "geographically distributed" units throughout the hospital. Their culture results were compared with those from 10,439 other patients with bacterial infections, which comprised the hospital-wide antibiograms developed every 6 months during the study period.

The *Escherichia coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* isolates from the transplant recipients showed markedly less susceptibility to first-line antibiotics than would have been predicted by the hospital-antibiograms. In particular, in the transplant recipients *E. coli* infections were resistant to trimethoprim-sulfamethoxazole, levofloxacin, and ceftriaxone; *K. pneumoniae* infections were resistant to every antibiotic except amikacin; and *P. aeruginosa* infections were resistant to levofloxacin, cefepime, and amikacin (Diag Microbiol Infect Dis. 2016 Aug 25. doi: 10.1016/j.diagmicrobio.2016.08.018).

"We advocate for the development of antibiograms specific to solid-organ transplant recipients. This may allow intrahospital comparisons and intertransplant-center monitoring of trends in antimicrobial resistance over time," Dr. Rosa and her associates said.

Dr. Rosa and her associates had no relevant financial disclosures.

Giving beta-blockers to ICD patients reduces deaths

BY BRUCE JANCIN
Frontline Medical News

ROME – Beta-blocker therapy reduces the risks of all-cause mortality as well as cardiac death in patients with a left ventricular ejection fraction below 35% who get an implantable cardioverter-defibrillator for primary prevention, Laurent Fauchier, MD, PhD, reported at the annual congress of the European Society of Cardiology.

Some physicians have recently urged reconsideration of current guidelines recommending routine use of beta-blockers for prevention of cardiovascular events in certain groups of patients with coronary artery disease, including those with chronic heart failure who have received an ICD for primary prevention of sudden death. Indeed, the now–relatively old randomized trials of ICDs for primary prevention in patients with chronic heart failure don't provide any real evidence that beta-blockers reduce mortality in this setting. In fact, the guideline recommendation for beta-blockade has been based upon expert opinion. This was the impetus for Dr. Fauchier and coinvestigators conducting a large retrospective observational study in a contemporary cohort of heart failure patients who received an ICD for primary prevention during a recent 10-year period at the 12 largest centers in France.

Fifteen percent of the 3,975 French ICD recipients did not receive a beta-blocker. They differed from those who did in that they were on average 2 years older, had an absolute 5% lower ejection fraction, and were more likely to also receive cardiac resynchronization therapy. Propensity score matching based on these and 19 other baseline characteristics enabled investigators to assemble a cohort of 541 closely matched patient pairs, explained Dr. Fauchier, professor of cardiology at Francois Rabelais University in Tours, France.

During a mean follow-up of 3.2 years, the risk of all-cause mortality in ICD recipients not on a beta-blocker was 34% higher than in those who were. Moreover, their risk of cardiac death was 50% greater. In contrast, beta-blocker therapy had no effect on the risks of sudden death or of appropriate or inappropriate shocks.

This study was supported by French governmental research grants. Dr. Fauchier has served as a consultant to several companies.

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Procalcitonin flags intubation risk in pneumonia

BY MICHELE G. SULLIVAN
Frontline Medical News

FROM CHEST

Procalcitonin can help predict which patients with community-acquired pneumonia may require intubation for respiratory failure during a hospital admission.

Compared to those with undetectable levels, patients with a procalcitonin of 5 ng/mL were three times more likely to require invasive respiratory support, and those with a 10 ng/mL level were five times more likely, reported Wesley Self, MD, and his colleagues (Chest. 2016;150[4]:819-28. doi: 10.1016/j.chest.2016.04.010).

While predictive accuracy isn't good enough to merit use of procalcitonin as a stand-alone test, adding it to existing clinical management tools "is likely to improve identification of patients needing intensive care," wrote Dr. Self of Vanderbilt University, Nashville, and his colleagues. "An elevated procalcitonin level may help identify these patients without overt clinical signs of impending respiratory failure or shock but who would benefit from early [intensive care unit] admission."

The team examined serum procalcitonin as a biomarker in a subgroup of patients included in the Etiology of Pneumonia in the Community (EPIC) study of adults hospitalized with community-acquire pneumonia. The primary outcome was the need for invasive respiratory and/or vasopressor support (IRVS) within 72 hours.

Secondarily, they looked at whether adding procalcitonin boosted the performance of accepted pneumonia risk scores, including the American Thoracic Society minor criteria (ATS).

The cohort comprised 1,770 patients with a median age of 57 years. Of these, 115 (6.5%) needed IRVS within 72 hours of admission. Almost 16% were admitted directly into an intensive care unit; almost 7% experienced a delayed transfer from a medical unit into an ICU. The in-hospital mortality was about 2%.

Most (1,642) had an ATS score of less than 3; among these, about 5% needed IRVS. The remainder had a score of 3 or higher; about 30% required IRVS. All had procalcitonin levels pulled at admission. The levels were significantly higher among patients who required IRVS than those who didn't (1.43 ng/mL vs. 0.14 ng/mL).

A multivariate analysis found that procalcitonin was strongly associated with the risk of IRVS. In patients with undetectable levels, the risk was 4%. At 5-10 ng/mL, the overall risk of IRVS was about 14%. Every 1-ng/mL increase in this range boosted the risk of IRVS by 1%-2%.

Adding the measurement of procalcitonin to traditional pneumonia severity risk scores significantly improved the patients' performance. When stratified by ATS minor criteria, the risk of IRVS was 4.7% among low-risk patients. That decreased to 2.4% with the addition of undetectable procalcitonin, and increased to 12% with the addition of a 10 ng/mL level.

Conversely, without considering procalcitonin, ATS high-risk patients had almost a 30% risk of IRVS. Among these high-risk patients, IRVS risk dropped to 13% with undetectable procalcitonin and increased to 36% with high procalcitonin.

Adding the biomarker level to the ATS system improved its ability to correctly classify patients, the team said. "Using at least 3 ATS minor criteria alone to indicate high risk, 77 (4.4%) of the 1,770 total patients were misclassified as low-risk and experienced IRVS. Including procalcitonin of at least 0.83 ng/ml in addition … as a high-risk indicator reduced the number of patients with IRVS misclassified as low risk to 44 (2.5%). Adding procalcitonin of at least 0.83 ng/mL as a high-risk indicator resulted in 370 additional patients being classified as high risk, with 33 correctly classified as having IRVS."

Dr. Self reported financial relationships with multiple pharmaceutical companies.

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On Twitter @Alz_Gal

VIEW ON THE NEWS

Procalcitonin alone cannot diagnose pneumonia

While measuring procalcitonin adds valuable information to pneumonia risk stratification schemes, this process lacks the accuracy needed to enable the diagnosis of pneumonia as a stand-alone test, Daiana Stolz, MD, MPH, FCCP, wrote in an editorial.

"This study further supports the notion that procalcitonin has a limited prognostic accuracy as a stand-alone test. It also does not seem to outperform the risk estimation of a combination of clinical and laboratorial parameters. However, it also emphasizes its potential to capture nuances elusive to the clinical assessment, which do not seem to be consistently reflected even in elaborated severity scores recommended for clinical routine use," she said (Chest. 2016;150[4]:769-71. doi: 10.1016/j.chest.2016.07.017).

[Procalcitonin] values vary according to the pneumonia severity and this association is stronger than the one between disease severity and other clinical and laboratory variables," she said.

Risk scores like the ATS system can be weak, "in particular with regard to positive predictive values," Dr. Stolz wrote. And this is an important issue. "It is clear that patients fulfilling major criteria (endotracheal intubation and mechanical ventilation; shock-requiring vasopressors) should be considered for ICU admission; however, there is still controversy about the value of the minor criteria. ICU care is costly and a limited resource worldwide."

She called for "a randomized study evaluating the outcome and cost-effectiveness of a procalcitonin-refined clinical score in severe [community acquired pneumonia]."

Dr. Stolz is a pulmonologist at the University Hospital Basel, Switzerland. She reported financial relationships with several pharmaceutical companies.

Conservative oxygen therapy in the ICU reduces mortality

BY SUSAN LONDON
Frontline Medical News

A strategy of conservatively controlling oxygen delivery to patients in the intensive care unit results in lower mortality than the conventional, more liberal approach whereby patients are often kept in a hyperoxemic state, finds a randomized controlled trial.

The trial, known as Oxygen-ICU, enrolled more than 400 adult ICU patients from an Italian center. Initially planned to last 2 years, it was terminated early because of slow enrollment after an earthquake reduced ICU capacity, with the decision supported by positive results of an interim analysis.

Patients had an absolute nearly 9% lower risk of dying in the ICU with use of the conservative oxygen strategy as compared with the conventional one, according to data reported at the annual congress of the European Society of Intensive Care Medicine and simultaneously published (JAMA. 2016 Oct 5. doi: 10.1001/jama.2016.11993).

"To our knowledge, this is the first randomized clinical trial to evaluate the effect of a conservative oxygen therapy on mortality compared with a standard, more liberal approach in a medical-surgical population of adult critically ill patients," write the investigators, who were led by Massimo Girardis, MD, of the Intensive Care Unit, Department of Anesthesiology and Intensive Care, University Hospital of Modena (Italy).

Among critically ill patients with an ICU length of stay of 72 hours or longer, a conservative protocol for oxygen therapy compared with conventional therapy resulted in a lower ICU mortality," they conclude. "However, these preliminary findings were based on unplanned early termination of the trial, and a larger multicenter trial is needed to evaluate the potential benefit of such conservative oxygen therapy in critically ill patients."

In the trial, consecutive patients were randomized evenly to receive conservative oxygen therapy (maintenance of PaO_2 between 70 and 100 mm Hg or arterial oxyhemoglobin saturation [SpO_2] between 94% and 98%) or conventional oxygen therapy (allowance of PaO_2 values up to 150 mm Hg or SpO_2 values between 97% and 100%) on an open-label basis.

Results of modified intent-to-treat analyses showed that daily time-weight-

Continued on page 34

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

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

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

Important Safety Information

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

ADVERSE REACTIONS

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

NUCALA IS PROVEN TO:

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

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

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

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

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

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

Important Safety Information (cont'd)

ADVERSE REACTIONS (cont'd)

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

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

USE IN SPECIFIC POPULATIONS

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

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

Reference: 1. Data on file, GSK.

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

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

NUCALA®
(mepolizumab) for injection, for subcutaneous use

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

INDICATIONS AND USAGE

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

Limitations of Use

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-Term Safety

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

Immunogenicity

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

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

DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

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

Clinical Considerations

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

Data

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

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

OVERDOSAGE

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity Reactions

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

Not for Acute Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

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

Pregnancy Exposure Registry

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

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Seven days of antibiotics sufficient for most hospital-acquired pneumonia

BY MARY ANN MOON
Frontline Medical News

A 1-week course of antibiotics is sufficient for most hospital-acquired and ventilator-associated pneumonia, regardless of the microbial etiology of the infection, according to an updated Clinical Practice Guidelines for managing adults with these disorders.

In addition, every hospital should develop its own antibiogram to align clinicians' choice of treatments with the local distribution of likely pathogens and their antimicrobial susceptibilities. Both of these recommendations, as well as others that are also new to the updated guidelines, are intended to minimize patient exposure to unnecessary antibiotics and reduce antibiotic resistance, said Andre C. Kalil, MD, and Mark L. Metersky, MD, FCCP, cochairs of the guidelines panel of 18 experts in infectious diseases, pulmonary medicine, critical care medicine, laboratory medicine, microbiology, pharmacology, and guideline methodology.

For the same reason, the updated guidelines also recommends that each hospital's antibiogram be used to steer clinicians away from unnecessary dual therapy with gram-negative plus empiric anti–Methicillin-resistant *Staphylococcus aureus* (MRSA) agents, said Dr. Kalil, of the division of infectious diseases at the University of Nebraska Medical Center, Omaha, and Dr. Metersky, of the division of pulmonary and critical care medicine at the University of Connecticut, Farmington.

The guidelines, an update of the last version issued in 2005 and developed jointly by representatives of the Infectious Disease Society of America (including Dr. Kalil) and the American Thoracic Society (including Dr. Metersky), are intended for use by all clinicians who care for patients at risk for hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP), including surgeons, anesthesiologists, and hospitalists as well as specialists in infectious diseases, pulmonary diseases, and critical care. The guidelines no longer use the concept of health care–associated pneumonia (HCAP), chiefly because new evidence shows that designation is too general: HCAP patients are not at high risk for multidrug-resistant organisms simply because of their contact with the health care system, the guidelines panel wrote (Clin Infect Dis. 2016 Sep 1;63[5]:e61-e111).

The guidelines address empiric treatments when MRSA is suspected and give detailed guidance for selecting antibiotics once the causative organism is identified.

The IDSA/ATS Guidelines strongly recommend short-course (1-week) antibiotic therapy instead of longer courses for both HAP and VAP and assert that antibiotic doses should be de-escalated rather than fixed. It advises that serum procalcitonin level plus clinical criteria, not just clinical criteria alone, should be used to guide antibiotic discontinuation, and suggests that the Clinical Pulmonary Infection Score not be used to guide discontinuation.

Regarding individual antibiograms for all hospitals, the guidelines recommend that medical centers regularly create and disseminate a local antibiogram, ideally one that is specific to its intensive-care population. Each facility should determine the frequency for doing so, based on its resources, the rate of change of pathogens at the hospital, and the amount of data available to inform the antibiogram.

The guidelines also address empiric treatments when MRSA is suspected and give detailed guidance for selecting antibiotics once the causative organism is identified, including *Pseudomonas aeruginosa*, extended-spectrum beta-lactamase–producing gram-negative bacilli, *Acinetobacter* species, and pathogens resistant to carbapenem.

The guidelines include numerous other recommendations concerning the diagnosis of HAP and VAP, the optimal initial treatments, the pharmacokinetic and pharmacodynamic optimization of antibiotic therapies, and the use of inhaled antibiotics. All the recommendations "are a compromise between the competing goals of providing early appropriate antibiotic coverage and avoiding superfluous treatment that may lead to adverse drug effects, *Clostridium difficile* infections, antibiotic resistance, and increased costs," the guidelines panel noted.

The full-text guidelines, including details about the panel's methodology in reviewing the current literature and the summaries of evidence that support each recommendation, is available free on the Clinical Infectious Diseases website.

The Infectious Diseases Society of America and the American Thoracic Society provided financial and administrative support to develop the guidelines. No industry funding was permitted. Dr. Kalil reported having no potential conflicts of interest; Dr. Metersky reported ties to Aradigm, Gilead, Pfizer, Bayer, and their associates reported ties to numerous industry sources.

VIEW ON THE NEWS

'Little downside' seen to careful oxygen titration

The reduction in mortality seen with conservative oxygen therapy in the Oxygen-ICU trial was "striking," according to editorialist Dr. Niall D. Ferguson. However, "it is likely that to some extent, this trial has overestimated the true treatment effect of conservative oxygen therapy," he cautions, given baseline imbalances between groups, early stopping based in part on an unplanned interim analysis, and the small number of deaths. The editorialist noted that the study was underpowered and criticized its use of a modified intent-to-treat analysis.

The trial's findings contrast with those of a pilot study conducted by the ANZICS clinical trials group that did not find better outcomes with use of lower oxygen targets, according to Dr. Ferguson. However, in that trial, both arms had lower target and actual PaO_2 levels. Thus, the optimal clinical approach remains uncertain.

"It is important to recognize that this study [Oxygen-ICU] is not a trial of permissive hypoxemia, which has been proposed but is as yet a completely unproven therapeutic strategy. This trial involved targeting relative normoxia, avoiding both significant desaturations and exposure to supraphysiological PaO_2," he points out.

"Until the results of further trials addressing this issue are available, there appears to be little downside in the careful titration and monitoring of supplemental oxygen in the ICU to achieve physiologically normal levels of PaO_2 while avoiding potentially dangerous hyperoxia," he concludes.

Dr. Ferguson disclosed that he has no relevant conflicts of interest.

Niall D. Ferguson, MD, MSc, is with the Interdepartmental Division of Critical Care Medicine and Departments of Medicine and Physiology, University of Toronto; the Institute of Health Policy, Management, & Evaluation, University of Toronto; the Division of Respirology, Department of Medicine, University Health Network and Mount Sinai Hospital; and the Toronto General Research Institute.

Continued from page 29

ed PaO_2 averages during patients' ICU stays were higher in the conventional group than in the conservative group (median PaO_2, 102 vs. 87 mm Hg; *P* less than .001).

The rate of ICU mortality, the trial's primary endpoint, was 11.6% with conservative therapy, about half of the 20.2% seen with conventional therapy (absolute mean difference, 0.086; *P* = .01). The conservative group also had lower rates of shock (3.7% vs. 10.6%, *P* = .006), liver failure (1.9% vs. 6.4%, *P* = .02), and bacteremia (5.1% vs. 10.1%, *P* = .049). And they spent a day less on the ventilator (median mechanical ventilation–free hours, 72 vs. 48; *P* = .02). Lengths of ICU stay and hospital stay did not differ between the two groups.

One of the study authors has served as a data monitoring chair and on advisory boards for drug companies. The study was supported by the National Fund for Scientific Research of the University of Modena and Reggio Emilia.

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

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Revatio® sildenafil

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

PP-REV-USA-0090-01

July 2016

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

Organ dysfunction risk not reduced by levosimendan

BY BIANCA NOGRADY
Frontline Medical News

Levosimendan does not reduce the likelihood of severe organ dysfunction in adults with sepsis, nor does it lower the mortality rate, according to research presented at the annual congress of the European Society of Intensive Care Medicine and published in the New England Journal of Medicine.

Levosimendan is a calcium-sensitizing drug with inotropic and vasodilatory properties, which is commonly used to treat decompensated heart failure. "Small studies that have investigated the use of levosimendan in patients with septic shock have shown improvements in hemodynamic variables, microcirculatory flow, and renal and hepatic function, as compared with dobutamine," wrote Anthony C. Gordon, MD, of Imperial College London and Imperial College Healthcare NHS Trust and his coauthors.

A meta-analysis also supported the use of levosimendan in patients with sepsis, but the authors noted that only 125 patients were included in that analysis (N Engl J Med. 2016 Oct 5. doi: 10.1056/NEJMoa1609409).

In the Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) trial, 516 patients were randomized to 24 hours of a blinded infusion either of levosimendan (.05-0.2 mcg per kilogram of body weight per minute) or placebo in addition to standard care.

Researchers saw no significant difference in the mean daily Sequential Organ Failure Assessment (SOFA) score between the two groups (mean difference, 0.61; 95% confidence interval, −0.07 to 1.29; $P = .053$). When the SOFA score was analyzed by system, the mean daily cardiovascular score was significantly higher in the levosimendan group, compared with the placebo group, indicating greater dysfunction in that system.

"The cardiovascular SOFA score was higher in the levosimendan group than in the placebo group, which reflects the higher doses of norepinephrine that were required to maintain the mean arterial pressure," researchers reported.

There was no significant difference in 28-day mortality between the levosimendan and placebo groups (34.5% vs. 30.9%; 95% CI, −4.5 to 11.7; $P = .43$), and both groups had a similar number of catecholamine-free days. However, among the patients who required ventilation at baseline, those treated with levosimendan were less likely than those given placebo to be successfully weaned from ventilation over the 28-day follow-up.

Patients treated with levosimendan also had a higher incidence of serious adverse events, and supraventricular tachyarrhythmia was significantly more common in the levosimendan group than in the placebo group (3.1% vs. 0.4%; 95% CI, 0.1- 5.3; $P = .04$).

The two groups showed similar cardiac index, stroke volume, central venous oxygen saturations or pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and serum creatinine and bilirubin levels.

The authors drew attention to several limitations of the study, including the fact that levosimendan was added to standard care rather than being compared with an alternative inotrope such as dobutamine.

"Less than 10% of the patients in the placebo group received dobutamine, although the rate of use in the placebo group was higher than in the levosimendan group and may explain in part why the cardiac index and stroke volume were not higher in the levosimendan group than in the placebo group," they wrote.

The study did not include echocardiographic analysis to discover any changes in myocardial function with levosimendan, and there were only a small number of patients with low cardiac index.

"Therefore, this trial cannot provide guidance as to which inotrope is best to use in the management of sepsis if a low cardiac index is present," the authors said. "The target mean arterial pressure of 65-70 mm Hg, which was recommended in the protocol and reiterated at investigator meetings, was frequently exceeded (as in other trials involving patients with shock), which suggests that the norepinephrine doses that were administered could have been reduced in the two trial groups."

The study was supported by the Medical Research Council and National Institute for Health Research, United Kingdom, and Tenax Therapeutics. Four authors declared grants, personal fees, advisory board positions, and other funding from the pharmaceutical industry, including one author receiving support from Tenax Therapeutics.

Age of transfused blood did not affect mortality

BY MARY JO DALES
Frontline Medical News

In-hospital mortality did not vary for patients who received transfusions of blood that had been stored for 2 weeks and for patients who got blood that had been stored for 4 weeks, based on results from 20,858 hospitalized patients in the randomized, controlled INFORM (Informing Fresh versus Old Red Cell Management) trial which was conducted at six hospitals in four countries.

There were 634 deaths (9.1% mortality) among patients in the short-term blood storage group and 1,213 deaths (8.7% mortality) in the long-term blood storage group.

While previous trials have concluded that the storage time of blood did not affect patient mortality, those studies largely included high-risk patients and were not statistically powered to detect small mortality differences, Nancy M. Heddle, professor of medicine and director of the McMaster (University) transfusion research program, Hamilton, Ont., and colleagues reported in an article published online in the New England Journal of Medicine (doi: 10.1056/NEJMoa1609014).

Standard practice is to transfuse with the oldest available blood, which can be stored up to 42 days.

Their study included general hospitalized patients who required a red cell transfusion.

From April 2012 through October 2015, patients were randomly assigned in a 1:2 ratio patients to receive blood that had been stored for the shortest duration (mean duration 13 days, 6,936 patients) or the longest duration (mean duration 23.6 days, 13,922 patients).

Only patients with type A or O blood were included in the study's primary analysis, because of the difficulty of achieving a difference of at least 10 days in the mean duration of blood storage with other blood types.

There were 634 deaths (9.1% mortality) among patients in the short-term blood storage group and 1,213 deaths (8.7% mortality) in the long-term blood storage group. The difference was not statistically significant. Similar results were seen when the analysis was expanded to include all 24,736 patients with any blood type; the mortality rates were 9.1% and 8.8%, respectively.

An additional analysis found similar results in three prespecified high-risk subgroups – patients undergoing cardiovascular surgery, those admitted to intensive care, and those with cancer.

INFORM, Current Controlled Trials number ISRCTN08118744, was funded by the Canadian Institutes of Health Research, Canadian Blood Services, and Health Canada. Ms. Heddle had no relevant financial disclosures.

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VIEW ON THE NEWS

Oldest blood still needs to be examined

The results of the INFORM trial should end the debate regarding whether short-term or long-term storage of blood is advantageous. However, questions remain about whether red cells transfused during the last allowed week of storage (35-42 days) pose more risk. Observational studies continue to raise concerns about the use of the oldest blood.

The INFORM trial, with its large numbers of patients, should permit researchers to analyze enough data to address this remaining issue. The transfusion medicine community needs to know whether the storage period should be reduced to less than 35 days and whether new preservative solutions should be sought.

Aaron A.R. Tobian, MD, PhD, and Paul M. Ness, MD, are with the division of transfusion medicine, department of pathology, Johns Hopkins University, Baltimore. They had no relevant financial conflicts of interest and made their remarks in an editorial (10.1056/NEJMe1612444) that accompanied the published study.

Pulmonary embolism common with syncope

BY MARY ANN MOON
Frontline Medical News


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When specifically looked for, pulmonary embolism was identified in approximately 17% of adults hospitalized for a first episode of syncope, according to a report published in the New England Journal of Medicine.

Most medical textbooks include pulmonary embolism (PE) in the differential diagnosis of syncope, but "current international guidelines, including those from the European Society of Cardiology and the American Heart Association, pay little attention to establishing a diagnostic workup for PE in these patients. Hence, when a patient is admitted to a hospital for an episode of syncope, PE – a potentially fatal disease that can be effectively treated – is rarely considered as a possible cause," said Paolo Prandoni, MD, PhD, of the vascular medicine unit, University of Padua (Italy), and his associates in the PESY (Prevalence of Pulmonary Embolism in Patients With Syncope) trial.

The investigators used a systematic diagnostic work-up to determine the prevalence of PE in a cross-sectional study involving 560 adults hospitalized for syncope at 11 medical centers across Italy during a 2.5-year period. Most of these patients were elderly (mean age, 76 years), and most had clinical evidence indicating that a factor other than PE had caused their fainting. For this study, syncope was defined as a transient loss of consciousness with rapid onset, short duration (less than 1 minute), and spontaneous resolution, with obvious causes ruled out (such as epileptic seizure, stroke, or head trauma).

PE was ruled out in 330 patients who had a low clinical probability of the disorder or a negative D-dimer assay. Of the remaining 230 patients, 135 (58.7%) had a positive D-dimer assay suggesting PE, 3 (1.3%) had a high pretest clinical probability of PE, and 92 (40.0%) had both. PE was then confirmed using CT or ventilation-perfusion scanning in 97 of these 135 patients.

The "unexpectedly high" prevalence of PE was 17.3% overall, and it was consistent, ranging from 15% to 20%, across all 11 hospitals. The prevalence was even higher, at 25.4%, in the subgroup of 205 patients who had syncope of undetermined origin, as well as in 12.7% of the subgroup of 355 patients considered to have an alternative explanation for the disorder, Dr. Prandoni and his associates wrote (N Engl J Med. 2016 Oct 20. doi: 10.1056/NEJMoa1602172).

The researchers noted that this study likely underestimates the actual prevalence of PE among patients with syncope because it did not include patients who were not hospitalized, such as those who received only ambulatory care and those who presented to an emergency department but were not admitted.

The study was supported by the University of Padua. Dr. Prandoni and his associates reported having no relevant financial disclosures.

Algorithm for suspected PE safely excluded disorder

BY BRUCE JANCIN
Frontline Medical News

ROME – A newly validated, simplified algorithm for the management of patients with suspected acute pulmonary embolism enables physicians to safely exclude the disorder in roughly half of patients without resorting to CT pulmonary angiography, Tom van der Hulle, MD, reported at the annual congress of the European Society of Cardiology.

"This is the largest study ever performed in the diagnostic management of suspected pulmonary embolism. Based on our results, I think the YEARS algorithm is ready to be used in daily clinical practice," declared Dr. van der Hulle of the department of thrombosis and hemostasis at Leiden (the Netherlands) University Medical Center.

The YEARS prospective algorithm validation study included 2,944 consecutive patients, mean age 53 years, with suspected acute pulmonary embolism (PE) at 12 Dutch academic and nonacademic hospitals. All were managed according to the YEARS algorithm. Investigators then went back and reanalyzed their data as though participants had been managed according to the standard, guideline-recommended Wells rule in order to see how utilization of CT differed.

Using the YEARS algorithm, PE was reliably ruled out without need for CT pulmonary angiography – considered the standard in the diagnosis of PE – in 48% of patients. In contrast, adherence to the Wells rule would have meant that 62% of patients would have gotten a CT scan to rule out PE with a comparably high degree of accuracy.

But that 62% figure underestimates the actual CT rate in clinical practice. The reality is that although the guideline-recommended Wells rule and revised Geneva score have been shown to be safe and accurate, they are so complex, cumbersome, and out of sync with the flow of routine clinical practice that many physicians skip the algorithms and go straight to CT, Dr. van der Hulle said. This approach results in many unnecessary CTs, needlessly exposing patients to the risks of radiation and intravenous contrast material while driving up health care costs, he added.

Only patients with a low or intermediate clinical probability of pulmonary embolism get a D-dimer test. Those with a high clinical probability of PE go straight to CT.

Using the Wells rule or revised Geneva score, the patient evaluation begins with an assessment of the clinical probability of PE based upon a risk score involving seven or eight factors. Only patients with a low or intermediate clinical probability of PE get a D-dimer test; those with a high clinical probability go straight to CT.

The YEARS algorithm is much simpler than that, Dr. van der Hulle explained. Everyone who presents with suspected acute PE gets a D-dimer test while the physician simultaneously applies a brief, three-item clinical prediction rule. These three items were

Continued on page 42

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References: 1. ProAir RespiClick Prescribing Information. Horsham, PA: Teva Respiratory, LLC; April 2016. **2.** ProAir RespiClick Patient Information Leaflet. Horsham, PA: Teva Respiratory, LLC; April 2016.

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- In controlled studies of ProAir RespiClick® in patients 12 years of age and older, adverse events that occurred at an incidence rate of at least 1% and greater than placebo included back pain (2% vs 1%), pain (2% vs <1%), gastroenteritis viral (1% vs <1%), sinus headache (1% vs <1%), and urinary tract infection (1% vs <1%)
- In controlled studies of ProAir RespiClick® in patients 4 to 11 years of age, adverse events that occurred at an incidence rate of at least 2% and greater than placebo included nasopharyngitis (2% vs 1%), oropharyngeal pain (2% vs 1%), and vomiting (3% vs 1%)

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

For more information visit **ProAir.com**

Continued from page 39

selected by the Dutch investigators because they were the three strongest predictors of PE out of the original seven in the Wells rule. They are hemoptysis, clinical signs of deep vein thrombosis such as leg swelling or hyperpigmentation, and the clinician's global impression of PE as being the most likely diagnosis.

In the YEARS algorithm, the threshold for a positive D-dimer test warranting CT pulmonary angiography depends upon whether any of the three clinical predictors is present. If none is present, the threshold is 1,000 ng/mL or above; if one or more is present, the threshold for a positive D-dimer test drops to 500 ng/mL.

Using these criteria, PE was excluded without resort to CT in 1,306 patients with none of the three YEARS items and a D-dimer test result below 1,000 ng/mL, as well as in another 327 patients with one or more YEARS items present but a D-dimer below 500 ng/mL. Those two groups were left untreated and followed prospectively for 3 months.

The 964 patients with one or more YEARS predictors present and a D-dimer score of at least 500 ng/mL underwent CT imaging, as did the 352 with no YEARS items and a D-dimer

of at least 1,000 ng/mL.

The prevalence of CT-confirmed PE in the study was 13.2%. Affected patients were treated with anticoagulants.

The primary study endpoint was the total rate of deep vein thrombosis during 3 months of follow-up after PE had been excluded. The rate was 0.61%, including a fatal PE rate of 0.20%. The rate in patients managed without CT was 0.43%, including a 0.12% rate of fatal PE. In patients managed with diagnostic CT, the deep vein thrombosis rate was 0.84%, with a fatal PE rate of 0.30%.

"I think these results are completely comparable to those in previous studies using the standard algorithms," Dr. van der Hulle commented.

The study's main limitation is that it wasn't a randomized, controlled trial. But given the tiny event rates, detecting any small differences between management strategies would require an unrealistically huge sample size, he added.

Asked if he thinks physicians will actually use the new tool, Dr. van der Hulle replied that some physicians feel driven to be 100% sure that a patient doesn't have PE, and they will probably keep overordering CT scans. But others will embrace the YEARS algorithm because it reduces wasted resources and minimizes radiation exposure, a particularly compelling consideration in young female patients.

Discussant Marion Delcroix, MD, had reservations. She said she appreciated the appeal of a simple algorithm, but she asked, "Couldn't we do better with a bit more sophistication, perhaps by adjusting the D-dimer cutoff for age and also adding some other items, like oxygen saturation and estrogen use?


Bruce Jancin/Frontline Medical News

Dr. Tom van der Hulle

"My concern is about the applicability. The age of the study cohort is relatively young, at a mean of 53 years. The peak age of PE in a very large contemporary German database is 70-80 years. We don't know if the YEARS score is any good in this older population," asserted Dr. Delcroix, professor of medicine and respiratory physiology and head of the center for pulmonary vascular diseases at University Hospital in Leuven, Belgium.

"If the aim is to decrease the number of CT pulmonary angiograms for safety reasons, why not reintroduce compression ultrasound of the lower limbs in the diagnostic algorithm?" she continued. "It has been shown to effectively reduce the need for further imaging."

Dr. Delcroix predicted that the YEARS algorithm study will prove "too optimistic" regarding the number of CT scans avoided, particularly in elderly patients.

The YEARS study was funded by the trial's 12 participating Dutch hospitals. Dr. van der Hulle reported having no financial conflicts of interest.

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No increase in CV events with tiotropium in COPD

BY BIANCA NOGRADY
Frontline Medical News

FROM CHEST

Long-acting bronchodilators, including tiotropium, do not appear to increase the risk of cardiovascular events in the first year of use, according to a study in patients with chronic obstructive pulmonary disease.

Long-acting bronchodilators are recommended as first-line maintenance therapy for chronic obstructive pulmonary disease (COPD), but they can cause cardiac complications, wrote Samy Suissa, PhD, and his colleagues at the Centre for Clinical Epidemiology, Lady Davis Institute, Montreal.

"Indeed, long-acting anticholinergics are believed to suppress parasympathetic control, while LABAs [long-acting beta2-agonists] stimulate sympathetic tone, possibly leading to tachyarrhythmia and coronary insufficiency," the authors wrote (Chest. 2016 Aug 20. doi: 10.1016/j.chest.2016.08.001). "Furthermore, these pharmacologic effects would be expected to occur immediately at initiation of therapy."

However, the observational studies and randomized trials comparing the safety of LABAs and the long-acting anticholinergic tiotropium have shown inconclusive results, possibly because of insufficient numbers, short follow-ups or "treatment-experienced" patients.

Dr. Suissa and his colleagues analyzed data from 26,442 new tiotropium users and 26,442 LABA initiators from a U.K. primary care database. Participants in each arm were matched on high-dimensional propensity scores and prior inhaled corticosteroid use, and followed for 1 year for occurrence of acute myocardial infarction, stroke, heart failure, arrhythmia, and pneumonia.

The researchers saw no significant difference between tiotropium and LABA users in the risk of acute myocardial infarction (hazard ratio, 1.10; 95% CI, 0.88-1.38), stroke (HR, 1.02; 95% CI, 0.78-1.34), arrhythmia (HR, 0.81; 95% CI, 0.60-1.09), or heart failure (HR, 0.90; 95% CI, 0.79-1.02). This was the case even when the current exposure time window was varied from 60-day periods to 30- or 90-day periods.

There was a significantly lower incidence of pneumonia in individuals treated with tiotropium (HR, 0.81; 95% CI, 0.72-0.92), which the authors suggested was likely due to the presence of inhaled corticosteroids in many LABAs.

"In our study, 78% of the LABA users were receiving a combined inhaler that included an inhaled corticosteroid, two-thirds of which were for fluticasone, which has been associated with an up to twofold increase in the risk of pneumonia," they reported.

The authors acknowledged that the presence of an inhaled corticosteroid in combination with many of the LABAs could attract criticism that the study was therefore not a strict comparison between tiotropium and a LABA. However, they noted that the study aimed to represent the real-world experience of clinical practice.

"In this real-world–setting study of the treatment of COPD, the initiation of maintenance treatment with tiotropium compared with a LABA does not increase cardiovascular risk, but reduces significantly the risk of pneumonia, albeit a likely adverse effect of the inhaled corticosteroid component present in many LABA inhalers," the authors wrote.

"This differential risk that appears to confer a safety advantage to tiotropium as the initial long-acting bronchodilator in COPD should be considered against the comparative effectiveness of these two treatments at initiation," the researchers noted.

The Canadian Institutes of Health Research, the Canadian Foundation for Innovation, and Boehringer Ingelheim supported the study.

One author disclosed ties with Boehringer Ingelheim, AstraZeneca, Novartis, and Pfizer.

No other conflicts of interest were declared.

Trial supports edoxaban for electrical cardioversion

BY BRUCE JANCIN
Frontline Medical News

ROME – Results of the largest-ever randomized clinical trial of anticoagulation for electrical cardioversion of patients with nonvalvular atrial fibrillation demonstrate that edoxaban is a safe, effective, and convenient alternative to the standard strategy of enoxaparin as a bridge to warfarin. The ENSURE-AF trial was a phase IIIb study involving 2,199 patients with atrial fibrillation who underwent electrical cardioversion at 239 sites in the United States and 19 European countries. The key finding: The edoxaban-treated group had rates of thromboembolism and major bleeding at 28-30 days follow-up similar to those of the enoxaparin/warfarin-treated controls. Edoxaban offered a major practical advantage: Because "edoxaban kicks in within 2 hours, you can do the procedure just 2 hours after initiation of therapy in a patient with a reassuring transesophageal echocardiographic exam, which is definitely not possible with warfarin," Andreas Goette, MD, observed at the annual congress of the European Society of Cardiology.

Roughly half of participants were treated at centers that don't routinely use a transesophageal echo-guided management strategy and therefore delayed cardioversion until patients were anticoagulated for at least 3 weeks. The safety and efficacy outcomes were similar regardless of whether or not transesophageal echocardiography (TEE) guidance was used, according to Dr. Goette of St. Vincenz Hospital in Paderborn, Germany.

Edoxaban (Savaysa) was prescribed at 60 mg once daily except in patients weighing 60 kg or less or having a creatinine clearance rate of 15-50 mL/min, in which case they received 30 mg once daily. In the control arm, enoxaparin (Lovenox) was used until warfarin achieved an International Normalized Ratio of 2.0-3.0. Patients in the enoxaparin/warfarin arm spent a mean of 71% of their treatment time within the target INR range.

The primary efficacy outcome was the 28-day composite of stroke or other systemic embolic events, MI, or cardiovascular mortality. The rate was 0.5% in the edoxaban arm and 1.0% in the enoxaparin/warfarin group. In patients whose management strategy was TEE-guided, the rate was 0.3% in the edoxaban group and 0.8% with enoxaparin/warfarin. In non-TEE-guided patients, the rates were 0.6% and 1.2% with edoxaban and warfarin, respectively. Although rates were consistently numerically lower in the edoxaban group, the differences did not reach statistical significance, Dr. Goette explained. The combined rate of major or clinically relevant nonmajor bleeding through 30 days was 1.5% with edoxaban and similar at 1.0% with enoxaparin plus warfarin. Three patients in the edoxaban group experienced a major bleeding event, as did five in the comparator arm.

Because anticoagulation with edoxaban is so convenient and allows cardioversion to safely be performed in short order, the ENSURE-AF investigators are in the process of calculating the potential savings in health care costs obtainable through this strategy, the cardiologist said.

ENSURE-AF provides the first prospective randomized data on the use of edoxaban as an alternative to warfarin for pericardioversion anticoagulation. There has been one other randomized trial of a novel oral anticoagulant (NOAC) in this setting, the 1,504-patient X-VeRT trial (Eur Heart J. 2014 Dec 14;35[47]:3346-55), involving rivaroxaban (Xarelto).

Riccardo Cappato, MD, first author of the X-VeRT publication, served as the designated discussant for ENSURE-AF. He noted that the results of the two trials are "completely superimposable." Rates of the composite efficacy endpoint were identical at 0.5% for both NOACs versus 1.0% for the vitamin K antagonist arms of X-VeRT and ENSURE-AF. The major bleeding rates also were identical for edoxaban and rivaroxaban in the two studies. Moreover, the major bleeding rates associated with warfarin or other vitamin K antagonists were spot-on the same in the two trials.

"It's a rather unusual situation for such large numbers of patients," observed Dr. Cappato of Humanitas Research Institute in Milan.

"These data go very clearly in the same direction. I think a good take-home message here for us today is that both of these novel oral anticoagulants can be safely and efficaciously applied to patients undergoing elective cardioversion of nonvalvular atrial fibrillation," he added.

The ENSURE-AF trial was funded by Daiichi Sankyo. The speakers reported receiving research grants from and serving as consultants to that company and other pharmaceutical and medical device manufacturers. Simultaneously with Dr. Goette's presentation in Rome, the ENSURE-AF results were published online Aug. 30 in The Lancet.

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More bleeding with rivaroxaban than dabigatran in AF

BY MARY ANN MOON
Frontline Medical News

Rivaroxaban is associated with significantly more intra- and extracranial bleeding than is dabigatran in older patients who have nonvalvular atrial fibrillation, according to a report published online Oct. 3 in JAMA Internal Medicine.

This is the principal finding of a retrospective cohort study – the only study to directly compare the two oral non–vitamin-K-antagonists – that involved more than 118,000 patients who initiated anticoagulation treatment during a 2.5-year period. The Centers for Medicare & Medicaid Services and the Food and Drug Administration jointly conducted the study.

During the study period, rivaroxaban was used 2-3 times more often than was dabigatran in AF patients in the United States, "perhaps partly because of prescriber misperceptions about bleeding risks with dabigatran, arising from FDA receipt of a large number of postmarketing case reports following its approval. Ironically, we [now find] substantially higher bleeding risks with use of rivaroxaban than dabigatran," said David J. Graham, MD, of the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, FDA, Silver Spring, Md., and his associates.

The researchers assessed Medicare beneficiaries who initiated standard oral doses of rivaroxaban (66,651 patients) or dabigatran (52,240 patients) and were followed for a mean of 110 days.

The primary outcome measure – a composite of thromboembolic stroke, intracranial hemorrhage, major extracranial bleeding events including GI bleeding, and mortality – occurred in significantly more patients taking rivaroxaban than in those taking dabigatran. When the individual components of this composite outcome were considered, rivaroxaban was associated with significant increases in intracranial hemorrhage (HR, 1.65), major extracranial bleeding (HR, 1.48), and major GI bleeding (HR, 1.40); a nonsignificant decrease in thromboembolic stroke (HR, 0.81); and a nonsignificant increase in mortality (HR, 1.15).

In a further analysis of the data, rivaroxaban was linked to 2.3 excess cases of intracranial hemorrhage, 13 excess cases of major extracranial bleeding, 9.4 excess cases of major GI bleeding, and 3.1 excess deaths per 1,000 person-years of treatment. In addition, rivaroxaban was associated with a significantly increased risk of death in two subgroups of patients: those aged 75 and older and those whose CHADS-2 scores indicated higher bleeding risk, the authors said (JAMA Intern. Med. 2016 Oct 3. doi: 10.1001/jamainternmed.2016.5954).

Of note, "the net increase in intracranial hemorrhage, the outcome with the highest case fatality rate, exceeded the net reduction in thromboembolic stroke" with rivaroxaban treatment, they added.

This study was conducted by employees or contractors of the Centers for Medicare & Medicaid Services and the FDA. The authors had no relevant financial disclosures.

VIEW ON THE NEWS

Milestone study should change practice

This "milestone" study offers real-world data for a large number of older patients with multiple comorbidities who constitute the rising tide of the AF population.

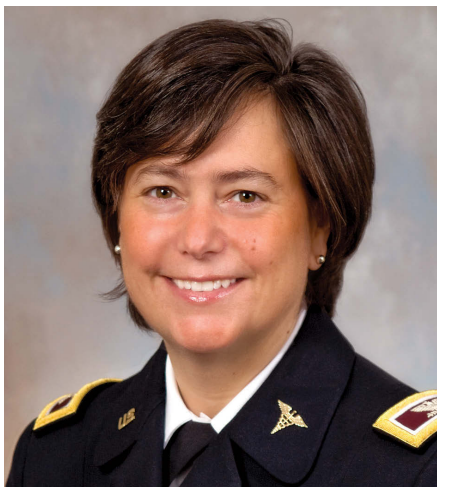
The findings should lead physicians to prescribe dabigatran over rivaroxaban in most patients with AF. Even though this was a retrospective cohort study, there are no prospective randomized trials directly comparing the two non–vitamin-K oral anticoagulants, and the few indirect comparisons derived from clinical trial data are very limited.

Anna L. Parks, MD, is at the University of California, San Francisco. Rita F. Redberg, M.D., is the editor of JAMA Internal Medicine and professor of cardiology at UCSF. Dr. Parks and Dr. Redberg made these remarks in an Editor's Note accompanying Dr. Graham's report (JAMA Intern. Med. 2016 Oct 3. doi: 10.1001/jamainternmed.2016.6429).

New slate of officers for the CHEST Foundation

The CHEST Foundation has announced Michael E. Nelson, MD, FCCP, as its new President, effective November 1. At CHEST 2016, the annual meeting of the American College of Chest Physicians (CHEST), the CHEST board also confirmed the appointments of Lisa K. Moores, MD, FCCP, as President-Elect of the CHEST Foundation; Doreen J. Addrizzo-Harris, MD, FCCP, as CHEST Foundation President-Designate; and John A. Howington, MD, FCCP, as CHEST Foundation Immediate Past President.

DR. NELSON



DR. MOORES

DR. ADDRIZZO-HARRIS

DR. HOWINGTON

Michael E. Nelson, MD, FCCP, is a private practice pulmonologist at Shawnee Mission Pulmonary Consultants, Kan., specializing in pulmonary diseases, critical care, and sleep medicine. A CHEST Foundation Trustee since 2012, Dr. Nelson has served the last 2 years as Foundation President-Elect, and has been affiliated with the American College of Chest Physicians for almost 22 years, holding a variety of roles. Dr. Nelson is board-certified in internal medicine, pulmonary disease, critical care medicine, and sleep medicine.

Lisa K. Moores, MD, FCCP, is the Associate Dean of Students and Professor of Medicine at F. Edward Hebert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Md. Currently, Dr. Moores is on active duty with the U.S. Army Medical Corps. She has been a member of the American College of Chest Physicians since 1994, and she has played a very active role in her time with the College, including serving as a CHEST Foundation Trustee-at-Large since 2011. Dr. Moores was awarded the Edward C. Rosenow III, Master FCCP/Master Teacher Honor Lecture Award at CHEST 2013. She is board-certified in critical care medicine, pulmonary disease, and internal medicine.

Doreen J. Addrizzo-Harris, MD, FCCP, is a graduate in medicine from New York University Medical Center, where she currently serves as a Professor of Medicine in the Division of Pulmonary and Critical Care. A CHEST Foundation Trustee-at-Large since 2013, she has been a Fellow of the American College of Chest Physicians for more than 20 years. Dr. Addrizzo-Harris was awarded Teacher of the Year in Pulmonary and Critical Care at NYU in 2000 and then again in 2013, showcasing her outstanding commitment and dedication to teaching.

John A. Howington, MD, FCCP, is a thoracic surgeon oncologist at St. Thomas Health, Nashville, Tenn., specializing in minimally invasive treatment options for thoracic cancer. He serves as the Chairman of Thoracic Surgery and is also the Co-Director of the Thoracic Oncology Program. A CHEST Foundation Trustee since 2012 and CHEST Foundation President for the last 2 years, he has been involved with the American College of Chest Physicians for nearly 20 years. In that time, he has held a variety of roles.

Coding Updates: EBUS, smoking cessation

BY MICHAEL NELSON, MD, FCCP
CHEST Physician Editorial Board Member

There has been some confusion about appropriate coding using the new endobronchial ultrasound codes with some of the other bronchoscopy codes.

Notably, when is CPT code **31629** *bronchoscopy with transbronchial needle aspiration biopsy(s), trachea, main stem and/or lobar bronchus(i)* appropriate to use with code **31652** *with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (e.g., aspiration[s]/biopsy[ies]), one or two mediastinal and/or hilar lymph node stations or structures* and code **31653** *with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (e.g., aspiration[s]/biopsy[ies]), 3 or more mediastinal and/or hilar lymph node stations or structures*?

Both **31652** and **31653** include needle sampling as a part of the work and therefore, if the bronchoscopy involves only one these procedures, it would be inappropriate to include **31629**.

However, mediastinal sampling is often done in conjunction with evaluation of a more peripheral lesion. If a bronchoscopy is performed with needle biopsy(ies) of a peripheral lesion and subsequently an EBUS scope is used to sample mediastinal or hilar lymph node stations, one could utilize **31629** and either **31652** or **31653**.

As an illustrative example, a 75-year-old man is found to have a 2-cm peripheral nodule in the anterior segment of the right-upper lobe with enlarged right hilar and subcarinal lymph nodes on CT scan. Bronchoscopy is performed, and, initially, the patient has a survey bronchoscopy using a non-EBUS scope, and no lesion is visible. A radial ultrasound probe is used to help identify the peripheral lesion, and multiple needle biopsies are performed as are brushings and washings. Subsequently, an EBUS scope is introduced, and right hilar, right paratracheal, and subcarinal needle biopsies were performed.

The appropriate codes to utilize to describe the work done in this procedure include **31623**, **31629**, **31653**,

Continued on following page

Continued from previous page

cedure include **31623**, **31629**, **31653**, and **31654**. Had no peripheral needle biopsies been performed, then code **31629** would NOT be used. Hopefully, this clarifies the issue further.

CMS Ceases Use of HCPCS G Codes for Smoking Cessation

Effective on or after October 1, the Centers for Medicare & Medicaid Services (CMS) will no longer allow use of Healthcare Common Procedural Coding System (HCPCS) codes **G0436** (Smoking and tobacco cessation counseling visit for the asymptomatic patient; intermediate, greater than 3 minutes, up to 10 minutes) and **G0437** (Smoking and tobacco cessation counseling visit for the asymptomatic patient; intensive, greater than 10 minutes).

Both 31652 and 31653 include needle sampling as a part of the work and therefore, if the bronchoscopy involves only one these procedures, it would be inappropriate to include 31629.

Instead, CMS will utilize the new codes developed for the Current Procedural Terminology (CPT) code set.

CMS has advised its Medicare contractors to replace code **G0436** with CPT code **99406** (Smoking and tobacco use cessation counseling visit; intermediate, greater than 3 minutes up to 10 minutes) and code **G0437** with CPT code **99407** (Smoking and tobacco use cessation counseling visit; intensive, greater than 10 minutes).

According to the Medicare National Coverage Determination Manual, tobacco cessation counseling is covered both for symptomatic and asymptomatic smokers.

CMS will allow health-care providers two attempts per 12 months to encourage Medicare patients to cease tobacco use but does not define an attempt. Rather, either of the codes may be used up to four times per attempt; so **99406** and **99407** or a combination of these codes may be used up to 8 times in a 12-month period.

These codes may be used either as a stand-alone or with an evaluation and management (E&M) service with appropriate documentation.

Remember, however, if one uses these codes during an E&M visit, a **25** modifier will need to be appended to the E&M code.

ABIM alternative assessment model

The American Board of Internal Medicine (ABIM) announced in May 2016 it would be offering an alternate option to the 10-year MOC exam, beginning in January 2018. This announcement came in response to ongoing feedback from physicians and other stakeholders regarding the high-stakes recertification exam every 10 years.

The new option will include shorter, more-frequent assessments that can be completed from a physician's office or home. These shorter assessments will identify knowledge gaps, so physicians can tailor their continuing education in order to stay current in knowledge and practice. Successful performance on the shorter assessments will allow physicians to opt out of the longer 10-year exam.

Prior to the launch of an alternative assessment model, ABIM has been soliciting input from diplomates through surveys and live conversations at society meetings.

The program will be piloted for internal medicine and select subspecialties, and based on feedback, will be extended to additional subspecialties at a later date. Physicians whose certifications expire prior to the new assessment option becoming available will need to pass the current exam in order to maintain certification, but then will not need to take another assessment for 10 years. Additional details regarding these alternative assessment options will be announced by the end of 2016 and can be tracked via ABIM's blog. They also have an FAQ document online to address common questions regarding the alternative assessment pathway, as well as other topics related to MOC.

The new option will include shorter, more-frequent assessments that can be completed from a physician's office or home.

Power of A Summit Award

The American College of Chest Physicians (CHEST) was awarded The Power of A Summit Award from the American Society of Association Executives (ASAE) in October for the China-CHEST Pulmonary and Critical Care Medicine (PCCM) Fellowship Program (**Fig 1**).

Fig 1. Accepting the Power of A Summit Award on behalf of CHEST are Stephen J. Welch, interim EVP/CEO, (center right) and Renli Qiao, MD, FCCP (center left). The award was presented by Steven C. Anderson, IOM, CAE, CEO, of the National Association of Chain Drug Stores, who served as master of ceremonies (far left); and by John H. Graham IV, FASAE, CAE, President and CEO of ASAE (far right).

CHEST is one of only six associations chosen for this honor. The Summit Award is ASAE's highest award given to associations to recognize exemplary contributions toward creating a stronger America and world.

The goal of the China-CHEST PCCM Fellowship Program is to standardize training and to equip clinicians in China to provide care to those affected by respiratory and critical care illnesses. Through collaboration among multiple international associations, CHEST has been working since 2013 to prepare physicians in the first-ever medical subspecialty of pulmonary and critical care in China.

Fig 2. Congratulations to the first four graduates of the China-CHEST Pulmonary and Critical Care Medicine Fellowship Program. Left to right: Li Huang, Xiangya Hospital, Changsha, Hunan (graduate); Chen Wang, MD, FCCP; Xianwen Sun, Ruijin Hospital, Shanghai (graduate); Robb Rabito, CHEST Director of Education Operations; Chenjuan Gu, Ruijin (graduate); Renli Qiao, MD, FCCP; and Yingmeng Ni, Ruijing (graduate).

Since the launch of China-CHEST PCCM Fellowship Program in 2013, 12 participating Chinese institutions started their PCCM training programs. By the end of 2016, 30 programs with 300 fellows and 60 faculty will be participating at institutions throughout China, with the potential to impact the care of thousands of patients. The China-PCCM Fellowship Program welcomed and congratulated its first four graduates in September 2016 (**Fig 2**).

This past spring, the Chinese Ministry of Health and the Chinese Medical Doctor Association officially recognized and adopted PCCM subspecialty training within China, while announcing the launch of subspecialty training across all medical fields in China by 2020. PCCM was selected as one of three subspecialties to pioneer fellowship training education.

The vast reach and clinical exposure of this program highlights how a CHEST and the China-CHEST PCCM Fellowship Program were recognized at the ASAE's 17th Annual Summit Awards Dinner in October.

This month in *CHEST:* Editor's picks

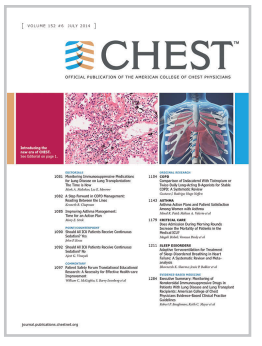
BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief, *CHEST*

Giants in Chest Medicine: Bartolome Celli, MD, FCCP. *By Dr. G. J. Criner*

Elevated Plasma Levels of sRAGE Are Associated With Nonfocal CT-Based Lung Imaging in Patients With ARDS: A Prospective Multicenter Study. *By Dr. S. Mrozek, et al.*

A Case-Control Study Assessing the Impact of Nonventilated Hospital-Acquired Pneumonia on Patient Outcomes. *By Dr. S. T. Micek, et al.*

Low Prevalence of High-Grade Lesions Detected With Autofluorescence Bronchoscopy in the Setting of Lung Cancer Screening in the Pan-Canadian Lung Cancer Screening Study. *By Dr. A. Tremblay, et al.*



CHEST Clinical Trials Registry

Are you a clinical trials investigator with unused capacity? Would you like to refer patients to participate in groundbreaking clinical trials?

The CHEST Clinical Trials Registry is a free service that connects physicians to information about clinical trials in respiratory disease conducted by participating pharmaceutical companies.

Ongoing groundbreaking research could have a measurable impact on patient care, but a lack of clinical trial participants is significantly slowing research and threatening the development of new treatments. Recruiting and retaining trial participants are the greatest challenges to developing the next generation of treatment options.

CHEST®

Participation in clinical trials provides an opportunity to advance and accelerate medical research and contribute to an improved health outlook for future generations. Use our registry to get immediate information on how you can be involved in a clinical trial.

Access this site to learn more: www.chestnet.org/Guidelines-and-Resources/Clinical-Trials/Clinical-Trials-Registry.

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.

gsk | Theravance

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

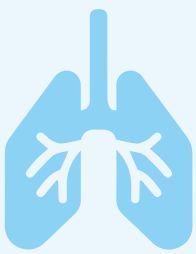
BREO offers patients proven efficacy with just one daily dose

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.

BREO ELLIPTA was developed in collaboration with Theravance

Visit **BREOhcp.com** today for clinical videos and formulary information

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
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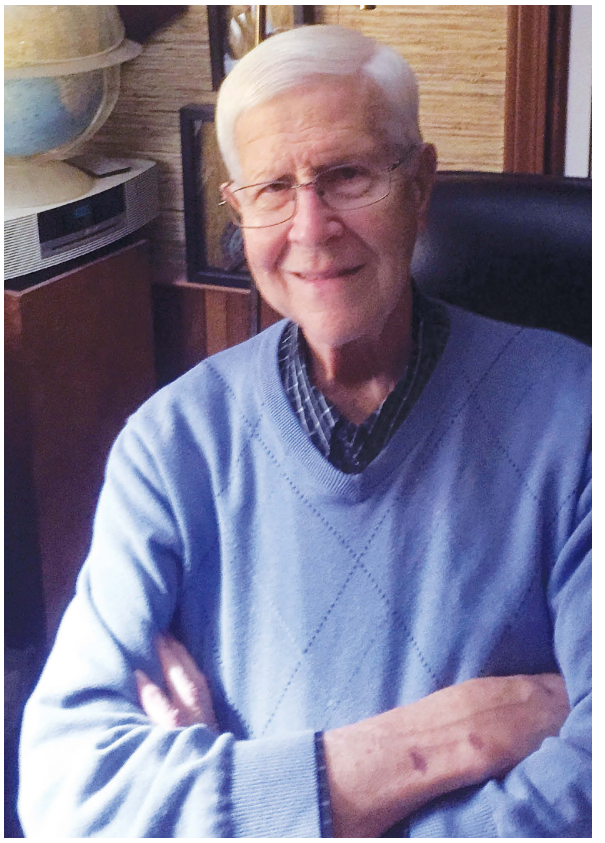
Catching up with our Past Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to give us a look at what's new.

Paul Stein, MD, Master FCCP
President 1992-1993

It is now 24 years since I was president of the American College of Chest Physicians (CHEST). Dr. Al Soffer had just retired, and it was Al Lever's first year. Dr. Roger Bone preceded me as President and Dr. Ron George followed me.

I have been at Michigan State University since 2011, in the College of Osteopathic Medicine. It has been great. I work out of my home office and drive to East Lansing, 87 miles from greater Detroit, only about once or twice a month. My research in the last 30 years has been primarily on pulmonary embolism, which is where I started when training with Dr. Lewis Dexter at Peter Bent Brigham Hospital, 1964-1966. Most of the research is based on administrative data from large publicly available government databases, typically with about 2 million patients with pulmonary embolism. Also, we have a consortium of five or so regional EDs, which collaborates on obtaining cohort data. I stray occasionally from pulmonary



Dr. Paul Stein

embolism, however. For example, I wrote in the *Journal of Anatomy*, how the sinuses of Valsalva are shaped as converging nozzles, which would contribute to stabilization of flow in the proximal portion of the coronary arteries.

Getting back to pulmonary embolism, with distinguished collaborators throughout the United States, and some in Canada, we did the PIOPED II investigation of the accuracy of multidetector CT pulmonary angiography and PIOPED III, the accuracy of magnetic resonance imaging for the diagnosis of pulmonary embolism. I have written three editions of the book, "Pulmonary Embolism" (1998, 2007, 2016).

So that's how I spend most of my time, working and doing research, which I love. I feel blessed to be able to continue being productive at age 82. Janet and I just celebrated our 50th wedding anniversary. We have three children and two grandchildren.

My main hobby is playing the clarinet. I particularly enjoy playing classical sonatas and meet monthly with a superb pianist who had been a professional organist. We are hoping to make a CD. In addition, I play in a "swing band" and a concert band that hopefully will go to a national contest.

Another hobby is collections, which include fossils, old books, rocks, masks, tribal art, and musical instruments, to name a few. It is a thrill to hold the fossil of an animal that lived 400 million years ago or an arrowhead made by someone 10,000 years ago.

I appreciate this opportunity to provide an update for my many friends who are in this great CHEST organization. Bottom line, I am living and active.

Influenza vaccine beneficial for type 2 diabetics

BY DEEPAK CHITNIS
Frontline Medical News

Individuals with type 2 diabetes should receive the seasonal influenza vaccines annually, as doing so significantly mitigates their chances of being hospitalized for – or dying from – cardiovascular complications such as stroke, heart failure, and myocardial infarction.

"Studies assessing influenza vaccine effectiveness in people with diabetes are scarce and have shown inconclusive results," wrote Eszter P. Vamos, MD, PhD, of Imperial College London and her coauthors in a study published in the Canadian Medical Association Journal. "None of the previous studies adjusted for residual confounding, and most of them reported composite endpoints such as admission to hospital for any cause."

The retrospective cohort study looked at adult patients with type 2 diabetes in the Clinical Practice Research Datalink, one of the largest databases of primary care records in England. Ultimately, 124,503 adults with type 2 diabetes were enrolled in the study, representing 623,591 person-years of observation that occurred over the course of the 7 years covered by the study. For this period, the dominant strains of influenza were A(H3N2) in 2003-2004, 2004-2005, 2006-2007, and 2008-2009, with A(H1N1) being dominant during the 2007-2008 and 2009-2010 seasons and strain B in 2005-2006 (CMAJ. 2016 Jul 25. doi: 10.1503/cmaj.151059).

Each year included was divided into four seasons: preinfluenza season (Sept. 1 through the date of influenza season starting); influenza season (date of season onset as defined by national surveillance data through 4 weeks after the determined date of season ending); postinfluenza season (from the end of influenza season through April 30); and summer season (May 1 through Aug. 31). The primary outcomes were defined as hospital admissions for acute myocardial infarction, stroke, heart failure, pneumonia or influenza, and all-cause death, comparing between those who received their seasonal influenza vaccines and those who did not.

Following adjustment to account for any possible residual confounding, individuals who received their influenza vaccines were found to have a 19% reduction in their rate of hospital admissions for acute myocardial infarction (incidence rate ratio, 0.81; 95% confidence interval, 0.62-1.04), a 30% reduction in admissions for stroke (IRR, 0.70; 95% CI, 0.53-0.91), a 22% reduction in admissions for heart failure (IRR, 0.78; 95% CI, 0.65-0.92), a 15% reduction in admissions for either pneumonia or influenza (IRR, 0.85; 95% CI, 0.74-0.99), and a 24% lower death rate than those who had not been vaccinated (IRR, 0.76; 95% CI, 0.65-0.83). "These findings underline the importance of influenza vaccination as part of comprehensive secondary prevention in this high-risk population," the authors said.

The study was supported by National Institute of Health Research. The authors did not report any relevant financial disclosures.

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Chest physician perceptions of e-cigarettes mixed

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Chest physicians in the United States are likely to encounter electronic cigarette users in clinical practice, yet there is no consensus regarding how to advise them, results from a survey suggest.

"There is controversy in the community of physicians we surveyed on whether e-cigarettes would be useful for smoking cessation and whether they can reduce harm from tobacco smoking," lead study author Stephen R. Baldassarri, MD, said in an interview in advance of the annual meeting of the American College of Chest Physicians. "Our results suggest that we need more high quality scientific data regarding potential harms and benefits of e-cigarettes in order to inform both health professionals and the general public."

Dr. Baldassarri, a pulmonary and critical care medicine fellow at the Yale University, New Haven, Conn., and his associates e-mailed a brief, online questionnaire to members of the American College of Chest Physicians in an effort to assess practice patterns and perceptions regarding e-cigarette (EC) use and tobacco smoking among their patients. As an incentive to participate, respondents were entered into a lottery to win $500. He reported results from 994 members who completed the survey. Fewer than half of respondents (44%) reported asking patients about EC use either most of the time or always, 88% reported that patients had asked their opinion of ECs, and 31% reported EC use among at least 10% of their patients. More than two-thirds reported believing that ECs are harmful (69%) and that daily EC use is not safe (72%).


DR. BALDASSARRI

When asked if ECs promote tobacco cessation, respondents were split (33% agreed or strongly agreed while 32% disagreed or strongly disagreed); only 13% believed that ECs were at least as effective as Food and Drug Administration–approved treatments to promote smoking cessation, and 11% reported that ECs should be used in an initial quit attempt. Dr. Baldassarri also reported that 6% of respondents thought ECs are more harmful than smoking, 21% thought switching from daily tobacco smoking to EC use would improve a patient's health, and 55% reported feeling comfortable discussing health effects of ECs with their patients.

"In light of the fact that the long-term health risks of ECs remain unknown, we were surprised to find that more than half of the survey respondents reported feeling comfortable discussing health effects of ECs," Dr. Baldassarri commented. "This proportion was higher than we expected given the current state of the scientific evidence."

He acknowledged certain limitations of the survey, including its low response rate, "which limits the degree to which we can generalize our findings to account for the perceptions of all chest physicians," he said. "We surveyed providers only within CHEST, and opinions and experiences of physicians outside of the organization and in other specialties may vary. And finally, since knowledge regarding e-cigarettes is rapidly evolving, the perceptions and opinions here are likely subject to change over the next few years as more becomes known."

Dr. Baldassarri reported having no financial disclosures.

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Inhaled antibiotic regimen reduces exacerbations

BY TED BOSWORTH
Frontline Medical News

LONDON – In patients with non–cystic fibrosis bronchiectasis (NCFB), use of inhaled ciprofloxacin on a schedule of 14 days on and 14 days off significantly reduced the rate of exacerbations, in a multicenter placebo-controlled trial. The results were presented at the annual congress of the European Respiratory Society.

"At last, an antibiotic intervention trial [in NCFB] with a positive outcome," reported Anthony De Soyza, MBChB, PhD, senior lecturer in respiratory medicine, Newcastle (England) University. Dr. De Soyza was the study's principal investigator.

In this study, called RESPIRE 1, the researchers conducted two placebo-controlled arms simultaneously. In one, patients randomized to inhaled ciprofloxacin or placebo took their assigned treatment twice daily for 14 days on and then 14 days off. In the other, patients took their assigned treatment of ciprofloxacin or placebo twice daily, but for 28 days on and then 28 days off. The on-off schedules were maintained for 48 weeks. The ratio of randomization of active therapy to placebo was 2:1.

There were two coprimary endpoints. One was the number of exacerbations over the 48 weeks of follow-up. Exacerbations were strictly defined as the worsening of at least three respiratory symptoms (dyspnea, wheezing, cough, increased sputum volume over 24 hours, or increased sputum purulence) plus fever with malaise or fatigue, and systemic antibiotic use. The other endpoint was the time to first exacerbation.

When the 111 patients randomized to the 14-day on-off regimen of inhaled ciprofloxacin were compared to 49 placebo patients, the mean number of exacerbations over 48 weeks of follow-up was 0.6 in the active treatment group, versus 1.0 in the placebo group (adjusted hazard ratio of 0.61, $P = .0061$), according to Dr. De Soyza.

The mean time to first exacerbation approached 1 year in those randomized to the 14-day on-off schedule of inhaled ciprofloxacin. In the two placebo arms (pooled for this analysis), the mean time to first exacerbation was 186 days. This difference was highly significant (HR = 0.53; $P = .0005$).

On the 28-day schedule, for 174 patients, there was a trend for a delay in the time to first exacerbation (HR 0.73; $P = .0650$) for those randomized to inhaled ciprofloxacin relative to placebo. The difference in the mean number of exacerbations between patients in the experimental group and the placebo group did not approach significance, which Dr. De Soyza said may have been caused by a lack of protection from antibiotics during the off period.

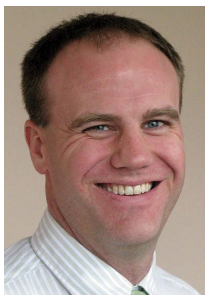
Ciprofloxacin, which was delivered in a dose of 32.5 mg in a proprietary dry powder inhalation device, was well tolerated. The overall rate of adverse events was similar across the study arms. The rates of discontinuation for adverse events in the 14-day and 28-day arms of ciprofloxacin were 12.5% and 10.6%, respectively. These rates were numerically lower than the 13.9% rate of adverse events that occurred among the patients receiving placebos.

According to previously published data cited by Dr. De Soyza, the proportion of NCFB patients with chronic lung infections is 70%, and approximately 40% of these patients have at least two exacerbations per year. In patients with at least two exacerbations per year, the 4-year mortality rate is 15%, Dr. De Soyza reported.

In this study, enrolled patients had relatively advanced NCFB. About 30% had a baseline forced expiratory volume in one second of less than 50% of predicted, about 55% had experienced two or more exacerbations in the past 12 months, 20% had been hospitalized in the last year, and more than 15% were on long-term oral macrolides, Dr. De Soyza reported.

Dr. De Soyza has financial relationships with several companies.

VIEW ON THE NEWS



Eric Gartman, MD, FCCP, comments: Patients with advanced non-CF bronchiectasis experience significant impairment in their daily quality of life and utilize significant health care resources. Many strategies have been attempted to improve their symptoms and keep them from having exacerbations – and this has proven difficult – especially in those with more advanced disease. The data from this trial are extremely encouraging, and as suggested in the article, will be taken together with the results of ongoing studies to potentially change practice. In any chronic antibiotic regimen, the issue of microbial resistance must always be discussed as it may be an inevitable consequence – but in this specific group of severe bronchiectasis patients, the risk of this occurrence is likely worth the reported benefit.

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Benefits of lebrikizumab in asthma inconsistent

BY TED BOSWORTH
Frontline Medical News

LONDON – Two large phase III trials with lebrikizumab, a monoclonal antibody that blocks the activity of interleukin-13 (IL-13), produced inconsistent evidence of benefit in patients with uncontrolled asthma, according to a presentation of both sets of data at the annual congress of the European Respiratory Society.

The two phase III studies compared lebrikizumab in doses of 37.5 mg and 125 mg to placebo, each administered subcutaneously every 4 weeks. The results were mixed not only for the primary endpoint, which was a reduction in the rate of exacerbations, but also for several secondary outcomes.

"The discrepancies across the studies preclude a definitive conclusion with respect to dose response and treatment benefit," reported Nicola A. Hanania, MBBS, associate professor in the pulmonology division of Baylor College of Medicine, Houston.

Evenly randomized into three treatment arms, 1,081 patients were enrolled in LAVOLTA I and 1,081 in LAVOLTA II. For entry, patients were required to have a forced expiratory volume in 1 second (FEV_1) between 40% and 80% of predicted. Lebrikizumab was added on top of stable background therapy. For the efficacy analyses, patients were divided into those who were biomarker high, defined as having levels of periostin greater than 50 ng/mL or blood eosinophils greater than 300 mcg/L, or biomarker low, defined as having lower levels of periostin and blood eosinophils.

In the biomarker high patients enrolled in LAVOLTA I, the rate of exacerbations was 51% lower among those randomized to the 37.5 mg dose (P less than .001) and 30% lower (P = .0232) among those randomized to the 125-mg dose relative to placebo. In the biomarker low group, a statistically significant 45% reduction in exacerbations was achieved with the 37.5 mg dose relative to placebo (P = .0318). In the biomarker high patients enrolled in LAVOLTA II, both the 37.5-mg and the 125-mg doses reduced the rate of exacerbations by 26% relative to placebo, but neither reduction reached statistical significance. In the biomarker low patients, the 37.5-mg dose was associated with a 46% increase in exacerbations and the 125-mg dose was associated with a 6% increase in exacerbations relative to placebo.

In LAVOLTA I, lung function improved in biomarker high patients in both active treatment arms relative to placebo. The relative advantage of taking lebrikizumab was seen only in the biomarker low patients who took the 125-mg dose. In LAVOLTA II, a similar advantage was observed in biomarker high patients who took both doses of lebrikizumab over biomarker high patients who took the placebo. Changes in time to first exacerbation was significantly increased by lebrikizumab in LAVOLTA I but not in LAVOLTA II.

Dr. Hanania reports financial relationships with several companies.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: The treatment of difficult-to-control asthma is extremely challenging and watching the development of novel treatments targeting new pathways is always encouraging. The data from these trials are disappointing, and similar to other complex conditions, most likely reflects the etiologic heterogeneity of asthma symptoms and phenotypes. The inconsistency in the data of these two trials demonstrates how much we don't know about the varied processes leading to the common endpoint of "asthma" – and more importantly, how to choose which treatments will benefit a given patient.

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Findings suggest new phenotype for ever smokers

BY TED BOSWORTH
Frontline Medical News

LONDON – Recent evidence of ever smokers having measurable deficits in activity even when lung function is preserved has been further expanded by findings suggesting a different phenotype for patients in this group with radiologic evidence of emphysema, according to data from SPIROMICS (Subpopulations and Intermediate Outcome Measures In COPD Study). The most recent data were presented at the annual congress of the European Respiratory Society.

Earlier this year, published data drawn from SPIROMICS demonstrated that current and former smokers with preserved lung function (forced expiratory volume in 1 second:forced vital capacity greater than or equal to 0.70) had activity limitations, respiratory symptoms, and exacerbations even though they did not meet the current definition of chronic obstructive pulmonary disease (COPD) (N Engl J Med. 2016;374:1811-21). In the new analysis, further distinctions could be made for patients in this subgroup who also had emphysema on computed tomography (CT).

"Among smokers with preserved lung function, emphysema on CT was associated with reduced activity levels and desaturation on the 6-minute walk test (6MWT)," reported Christian M. Lo Cascio, MD, Columbia University, New York. Compared with smokers with preserved lung function without CT evidence of emphysema, the patients with emphysema on CT did not have more symptoms or exacerbations.

"These and prior findings suggest two distinct but overlapping phenotypes in ever smokers with preserved lung function: an airway disease with respiratory symptoms and frequent exacerbations and emphysema characterized by activity limitation and increased mortality," Dr. Lo Cascio said.

SPIROMICS, an observational study supported by the National Heart, Lung, and Blood Institute, has enrolled current and former smokers at six centers in the United States to prospectively analyze biomarker, genetic, and clinical data. In the previously published analysis, the focus was on the difference between 849 ever smokers with preserved lung function and 963 patients with mild to moderate COPD.

In the data presented by Dr. Lo Cascio, 901 SPIROMICS patients with preserved lung function were analyzed with the focus on the difference between the 66 (7%) who had radiologic evidence of emphysema and the 835 (93%) who had undergone CT indicating that they did not have emphysema.

As measured on the activity component of the St. Georges Respiratory Questionnaire, there was about a 10-point (*P* less than .001) greater reduction in reported activity levels among those with emphysema on CT relative to those without. In addition, the odds ratio (OR) for significant oxygen desaturation, defined as a 4% fall in oxygen saturation of hemoglobin during the 6MWT, was approximately two times greater (*P* less than .001) for the patients with CT evidence of emphysema. Overall, when ever smokers with preserved lung function were subdivided into those with and without CT evidence of emphysema, several similarities were found between the two groups, including their mean pack-years of smoking and average body mass indexes.

The percentage of patients who had a COPD Assessment Test score of greater than or equal to 10 was 61% among those with CT evidence of emphysema, vs. 50% among those patients without CT evidence of emphysema.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: In the last few years, there has been a significant re-visitation of the concept that smoking patients may have early predictive signs of significant smoking-related morbidity and mortality – albeit with normal spirometry. The entity of "GOLD stage 0" was lost several years ago, but it seems it may be reincarnated with much greater definition and data-support. It has been demonstrated repeatedly for decades that a significant percentage of smoking patients with airways symptoms will have more exacerbations and accelerated lung function loss; and with the addition of CT scanning, it is clear that the presence of emphysema - especially at a certain percentage of total lung - is associated with decreased function, quality of life, and mortality. These data particularly are important in the age of ubiquitous lung cancer screening – as it will be important to educate those ordering these tests that one not only has to look out for lung nodules, but know the prognostic importance of finding lone emphysema.

Depression drops COPD medication adherence

BY M. ALEXANDER OTTO
Frontline Medical News

Chronic obstructive pulmonary disease (COPD) patients with depression are less likely to take their maintenance medications, according to a review of Medicare claims by the University of Maryland, Baltimore.

"Clinicians who treat older adults newly diagnosed with COPD should be aware of the development of depression, especially during the first 6 months. As such, clinicians should consider the need to monitor their patients with COPD for … depression [treatment], as well as use of and adherence to prescribed COPD medications. Close management of these and other aspects of newly diagnosed older adults with COPD will help to ensure optimal clinical outcomes," said the investigators, led by Jennifer Albrecht, PhD, of the department of epidemiology and public health at the University of Maryland.

Depression is common but underrecognized in COPD, with a prevalence of 17%–44%. Depression is also well known to decrease drug adherence in diabetes and other chronic conditions, but few studies have analyzed its effect on drug adherence in COPD (Ann Am Thorac Soc. 2016 Sep;13[9]:1497-504. doi: 10.1513/AnnalsATS.201602-136OC).

The researchers ran a random sampling of Medicare data and identified 31,033 beneficiaries diagnosed with COPD between 2006 and 2010; 6,227 patients (20% of the study sample) were diagnosed with depression within 2 years of being diagnosed with COPD.

The investigators found that depression reduced the likelihood of chronic obstructive pulmonary disease patients filling their prescriptions. Maintenance medication adherence was low overall, peaking at 57% in the month after the first fill and decreasing every month for the next 9 months for both the patients with depression and those patients who had not been diagnosed with the condition.

Depression made things worse; 20% of depressed patients filled 80% or more of their medications at the pharmacy, vs. 22% of nondepressed patients. Patients with newly diagnosed depression were about 7% less likely to have good adherence (odds ratio, 0.93; 95% confidence interval, 0.89-0.98). Women – 65% of the study sample and 75% of those with depression – were less likely than men to fill their scripts.

Meanwhile, adherence to COPD maintenance medication was more likely among patients on short-term inhalers and supplemental oxygen, as well as among nursing home patients and those with low-income subsidies.

Patients were 83% white. Those diagnosed with depression were slightly younger on average than those who were not (67 vs. 69 years old) and were more likely to have more than three comorbid conditions (33% vs. 23%). With the exception of asthma, comorbid conditions made adherence worse. Depressed patients also had more severe COPD symptoms, based on their higher rates of oxygen use (10% vs. 8%).

Dr. Albrecht reported receiving grants from the National Institutes of Health during the conduct of the study.

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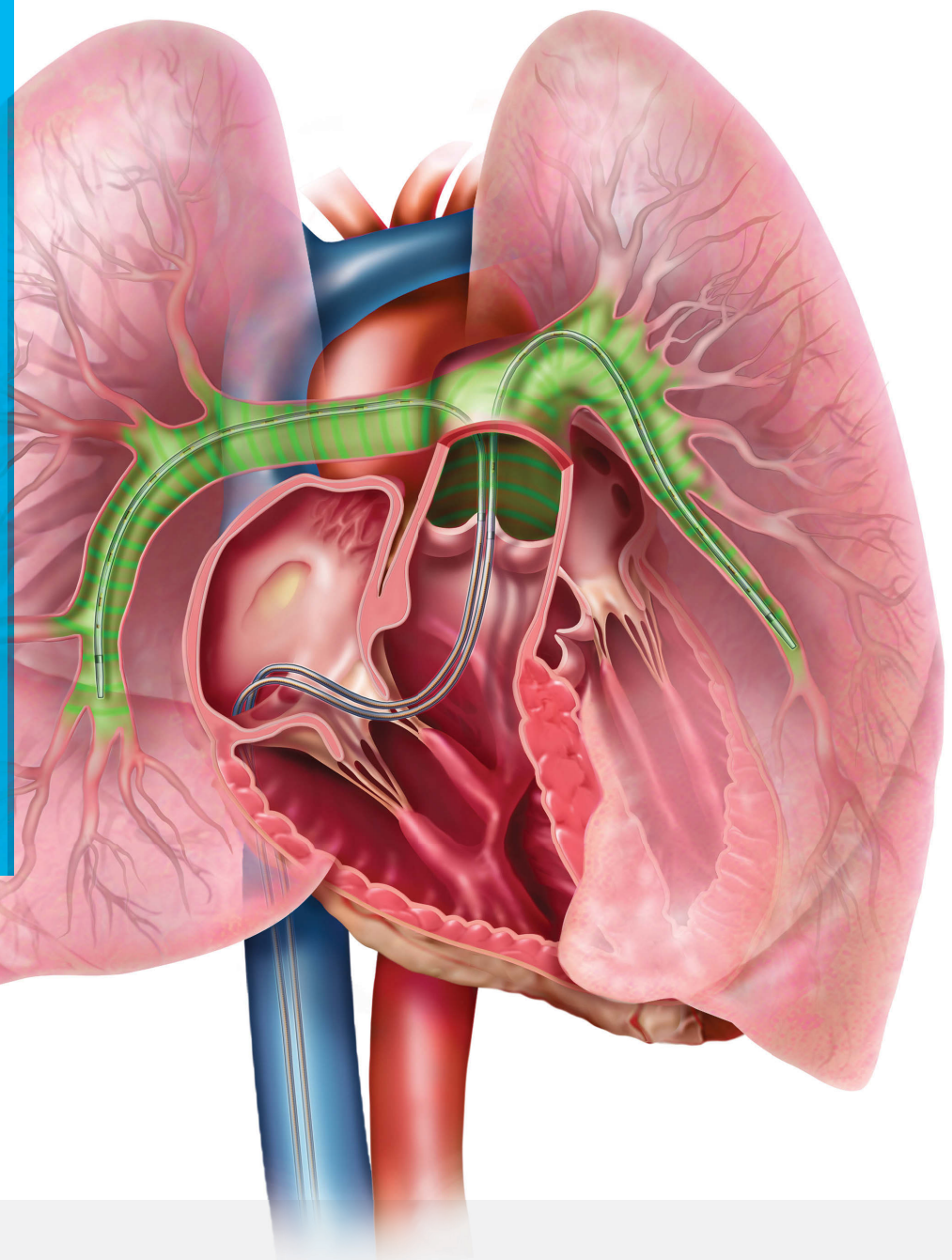

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2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

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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