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"DNR/DNI patients were less likely to receive many invasive procedures," the researchers said.

DNRs affect residents' patient care decisions

BY ELI ZIMMERMAN
Frontline Medical News

Internal medicine residents reported being less likely to consider certain aggressive interventions outside of CPR on patients with do not resuscitate (DNR) and do not intubate (DNI) orders, according to a study.

These findings have researchers worried about a trend of doctors ignoring patient preferences, especially those who may have DNRs but do not want to ignore other treatment options, according to Elizabeth K. Stevenson, MD, of the Division of Pulmonary and Critical Care Medicine, North Shore Medical Center, Salem, Mass., and her colleagues.

"DNR/DNI patients were less likely to receive many invasive procedures, surgical consultations, or transfer to the ICU," wrote the researchers. "[D]ecisions to withhold many types of care not specified in DNR/DNI orders is concerning, given that the majority of patients with a DNR/DNI status in registry studies indicated they would accept other interventions beyond CPR and intubation."

Researchers surveyed 553 internal medicine residents in the United States using an In-

See **DNRs** • *page 4*

Postop oxygen reduced number of AHI events

Carbon dioxide retention a concern.

BY JIM KLING
Frontline Medical News

FROM CHEST

Postoperative oxygen therapy in patients with previously undetected obstructive sleep apnea (OSA) led to a reduction in apnea-hypopnea index (AHI) events per hour with no increase in apnea-hypopnea event duration.

The results suggest that postoperative oxygen could be useful in patients with OSA who refuse continuous positive airway pressure (CPAP) therapy, those with newly diagnosed OSA, and those with suspected OSA.

The researchers set out to determine if postoperative oxygen therapy could improve oxygenation in patients with previously undiagnosed OSA, reasoning that the intervention could reduce adverse events.

The study, published in CHEST (2017 March;151[3]:597-611), provided generally good news, but with a caveat: "Essentially we are saying, yes, if you give supplemental oxygen, you improve oxygenation of the patient. But overall we have to be careful because a significant

See **Postop O_2** • *page 7*

INSIDE

In sepsis patients, death risk rises 9% for each hour of antibiotic delay

BY HEIDI SPLETE
Frontline Medical News

Hospital mortality for sepsis patients was 9% more likely with each hour of delayed administration of antibiotics, and the mortality rates increased with the severity of sepsis, based on data from 35,000 randomly selected sepsis patients.

Early administration of antibiotics in sepsis cases has become accepted as a way to improve outcomes, but the benefits have not been well studied, wrote Vincent X Liu, MD, MS, of Kaiser Permanente Division of Research, Oakland, Calif., and his colleagues.

To quantify the impact of antibiotic timing on mortality rates in different types of sepsis patients, the researchers reviewed data from 35,000 adults treated for sepsis at 21 emergency de-

See **Antibiotic delay** • *page 7*

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IPF=idiopathic pulmonary fibrosis.

*Baseline characteristics (including clinical characteristics, demographics, and select comorbidities) were well balanced across treatment groups, with 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624).[1,2]

†The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).[2] In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide (%DL_{CO}) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[3] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{CO} ≥35%. 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%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[4] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[2,3] Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).[1,4] 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]

‡In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[2]

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Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. In some cases 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.

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 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.

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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 diseases 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. 2016. **2.** Esbriet Prescribing Information. Genentech, Inc. January 2017. **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.

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ICU transfers tied to code status

DNRs *from page 1*

ternet survey that presented four vignettes describing clinical situations. Participants were asked to rank how likely they would be to employ listed intervention methods, from "strongly agree" to "strongly disagree," in each scenario (Ann Am Thorac Soc. 2017, Apr;14[4]:536-42). Two different versions of the survey were randomly assigned, varying only in terms of which vignettes included patients with a DNR/DNI order.

Of the interventions listed for each scenario, decisions to transfer patients to the intensive care unit and suggest surgery consultations showed the strongest association with code status.

"Residents were significantly less likely to indicate they would provide invasive procedures (including central venous catheter placement, esophagogastroduodenoscopy, colonoscopy, bronchoscopy, dialysis, and surgery consultation) to patients who had a status of DNR/DNI compared with Full Code," the investigators noted. "In contrast, decisions to pursue noninvasive diagnostic or therapeutic interventions

(CT scans, administration of oxygen or intravenous fluids, blood cultures, and initiation of anticoagulation) did not significantly differ by patient code status, with high levels of use across all vignettes."

In one vignette involving surgical consultation for an 80-year-old woman with septic shock secondary to *Clostridium difficile* infection, 89.1% of residents recommended a consult for full-care patients, while 77.7% recommended one for a patient with a DNR/DNI ($P = .0008$).

Despite these findings, 94%-96% of participants reported willingness to consult with patients on their preferences before treatment decisions.

The study was limited by the size of the sample, which numbered approximately 2% of the active internal medicine residents in the United States. The researchers recognized that these scenarios were theoretical, and that practicing physicians may act differently when faced with a medical situation in real life. The study also was limited by the concentration of respondents within a single program, they wrote.

One of the study's authors reports grants from the National Institutes of Health. The other investigators report no relevant financial disclosures.

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VIEW ON THE NEWS

Patient care = patient's cares

End-of-life treatment usually should be based on the preferences of the patients and how aggressive they want their physicians to be. Yet the study by Dr. Stevenson et al. shows that decisions in types of care are more often being based on the preferences of the doctors, which is very concerning. Engaging patients in a high-quality discussion of options and care preferences is an essential part of end-of-life treatment, and this trend of physician-attributable variation shows a level of paternalism that has no place in this type of care, and could lead to dire results for patients. For example, 72% of residents in one of the theoretical situations chose to intervene with dialysis in a full-code patient, while only 38% chose to do so for patients with a DNR. While the situations are theoretical, these findings uncover a disregard for patients' autonomy in decisions about their own care. Since patients are unable to choose their own residents and many residents will not have the opportunity to consult with every patient, DNR patients are certainly vulnerable to the possibility of being assessed for treatment based on their code status. Residents are the future of medicine, and must be trained out of this habit so that patients' preferences are not overlooked.

Joanna L. Hart, MD, is a research fellow in the Pulmonary, Allergy, and Critical Care Division, and the Palliative and Advanced Illness Research Center, University of Pennsylvania, Philadelphia. Meeta Prasad Kerlin, MD, MSCE, is the associate program director at the same institution. They had no disclosures. Their comments are in an editorial (Ann Am Thorac Soc. 2017 Apr;14[4]:491-2).

Anti-TNF agents show clinical benefit in sarcoidosis

BY BIANCA NOGRADY
Frontline Medical News

Around two-thirds of patients with severe or refractory sarcoidosis show a significant clinical response to tumor necrosis factor (TNF) antagonists, according to findings from a retrospective, multicenter cohort study.

Biologic agents targeting TNF, such as etanercept, infliximab, and adalimumab, have been introduced as a third-line option for patients with disease that is refractory to other treatments. However, Yvan Jamilloux, MD, of the Hospices Civils de Lyon (France) and his coauthors reported that there are still insufficient data available on efficacy and safety of these drugs in the context of sarcoidosis.

Dr. Jamilloux and his colleagues analyzed data from 132 sarcoidosis patients who received TNF antagonists, 122 (92%) of whom had severe sarcoidosis (Semin Arthritis Rheum. 2017 Mar 8. doi: 10.1016/j.semarthrit.2017.03.005).

Overall, 64% of patients showed clinical improvements in response to TNF antagonists; 18% had a complete response, and 46% had a partial response. However, 33 (25%) patients showed no change, and 14 (11%) had continued disease progression despite treatment with TNF antagonists. In another 16 patients who received a second TNF antagonist, 10 (63%) had a complete or partial clinical response. The investigators could find no differences in response between anti-TNF agents or between monotherapy and a combination with an immunosuppressant.

Pulmonary involvement was associated with a significantly lower clinical response, but none of the other factors examined in a multivariate analysis (sex, age, ethnicity, organ involvement, disease duration, steroid dosage, or prior immunosuppressant use) distinguished responders and nonresponders.

The authors noted that these response rates were lower than those seen in the literature and suggested this may be attributable to the multicenter design, more patients with longer-lasting and more refractory disease, and longer times under biologic therapy (median 12 months).

The researchers reported significant improvements in central nervous system, peripheral nervous system, heart, skin, and upper respiratory tract involvements based on declines in Extrapulmonary Physician Organ Severity Tool (ePOST) scores. There were also improvements in the eye, muscle, and lung, but these were not statistically significant.

TNF-antagonist therapy was associated with a high rate of adverse events. Around half of all patients (52%) experienced adverse events,

Continued on following page

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: This uncontrolled, unblinded retrospective observational study reports the outcomes of anti-TNF therapy in a heterogenous group of refractory sarcoid patients, with only 12% of the severe sarcoidosis population studied having the indication for treatment based on lung involvement. Further, it is notable that the patients with primarily pulmonary involvement had a poorer response to anti-TNF therapy. Over half of the patients had an adverse event related to the treatment, with nearly a quarter having to discontinue therapy. Given the limitations of this type of study, the low numbers of pulmonary sarcoid patients included, the lack of an efficacy signal in pulmonary sarcoid, and the high rate of serious adverse events – the role of anti-TNF agents for pulmonary sarcoid remains unclear and limited. However, in a larger way it should be questioned if the timing of administration of these agents is important – i.e., if they are given only after significant pulmonary damage has been seen and the disease is "refractory," this significantly may limit their potential beneficial clinical effect.

IN THIS ISSUE

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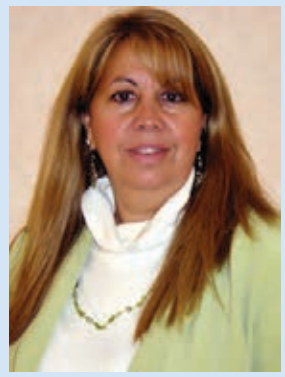

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such as pneumonia, urinary tract infections, bacterial sepsis, and herpes zoster. In 31 patients (23%), these led to treatment cessation.

Nine patients also had severe allergic reactions, four had paradoxical granulomatous reactions, three developed neutralizing antibodies against anti-TNF agents, two patients had demyelinating lesions, and one had a serum sickness–like reaction. All of these events led to discontinuation.

Overall, 128 (97%) of the patients in the study had received corticosteroids as first-line therapy, and 125 (95%) had received at least one second-line immunosuppressive drug over a median duration of 16 months. Most were treated with infliximab (91%) as the first-line TNF antagonist, followed by adalimumab (6%), etanercept (2%), and certolizumab pegol (1%).

Treatment with TNF antagonists was associated with significant reductions in corticosteroid use; the mean daily prednisone dose decreased from 23 mg/day to 11 mg/day over the median 20.5-month follow-up. This was seen even in the 33 patients who showed no change in their disease course after TNF-antagonist therapy.

No conflicts of interest were declared.

Septic shock mortality rate was 26%

Antibiotic delay *from page 1*

partments in northern California between 2010 and 2013. The time from registration at the emergency department to administration of the first antibiotics was less than 6 hours (Am J Respir Crit Care Med. 2017 Mar 27. doi: 10.1164/rccm.201609-1848OC).

The overall mortality rates were 3.9%, 8.8%, and 26.0% for sepsis, severe sepsis, and septic shock, respectively. Absolute mortality increased by 0.3% for sepsis, 0.4% for severe sepsis, and 1.8% for septic shock patients after an hour's delay in the administration of antibiotics, and the adjusted odds ratio for hospital mortality was 1.09 for each hour between patient registration and antibiotic administration.

The median time to the first administration of antibiotics was 2.1 hours, ranging from 1.7 hours for septic shock patients to 2.3 hours for sepsis patients, with ceftriaxone having been the most commonly used antibiotic across all groups.

Approximately 42% of patients received one antibiotic and 43% received two antibiotics. The odds of receiving two or more antibiotics were significantly higher for septic shock patients compared with sepsis patients (72% vs. 52%, respectively).

The findings were limited by several factors, including the inability to adjust for concomitant sepsis treatments and preexisting antibiotic treatments, the researchers said.

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: In medicine, we strive to increase our understanding of disease states and improve outcomes for patients. This study supports the belief that timing of the administration of antibiotics and mortality in septic shock patients are linked.

The study results do not resolve all questions about the timing of antibiotic administration for sepsis patients, such as whether there is additional benefit to giving the medications at 2 hours rather than 3 hours or 4 hours after ED admission, the researchers noted. However, "our findings support currently held beliefs that administering early antibiotics to infected patients with systemic inflammation is beneficial for reducing mortality," they said.

The study was supported in part by the Permanente Medical Group and Kaiser Foundation Hospitals, the National Institute of General Medical Sciences, and the Veterans Affairs Health Services Research and Development Service. The researchers reported no conflicts of interest.

Some experienced substantial CO_2 retention

Postop O_2 *from page 1*

number of patients have significant carbon dioxide retention when receiving supplemental oxygen. So we have to monitor patients – not just oxygen, but we may have to monitor carbon dioxide levels, too," said lead study author Frances Chung, MBBS, professor of anesthesiology at the University of Toronto and Toronto Western Hospital.

The researchers randomized 123 patients with an AHI of at least five events per hour to postoperative oxygen (3 L/min for 3 nights via nasal prongs) or no postoperative oxygen.

On the third night, the oxygen group had a higher average oxygen saturation than controls (95.2% plus or minus 3.2% vs. 91.4% plus or minus 3.5%; *P* less than .0001) and a lower oxygen desaturation index (median, 2.3 vs. median, 18.5; *P* less than .0001).

A lower number of AHI events per hour occurred in the oxygen group (median, 8.0) than in the control group (median, 15.6; $P = .016$).

On average, the longest apnea-hypopnea event (median, 33.8 seconds) was shorter for a patient on oxygen, compared with a patient who did not receive oxygen (median, 49.6 seconds; $P = .002$).

But one finding surprised the researchers and led to some concern: Across both groups, 11.4% of patients experienced substantial CO_2 retention. Specifically, for at least 10% of 1 of the nights, these patients had a partial pressure of CO_2 of at least 55 mm Hg, according to measurements taken with a transcutaneous CO_2 monitor. Of the 14 patients who experienced this event, 13 were receiving oxygen.

Dr. Chung said the results argue strongly for postsurgical oxygen in patients with OSA, who are known to be at increased risk for complications. "We are not doing something about it, and we should be doing something. Because one death from a complication is too many," she said.

The study was funded by the University Health Network Foundation, Toronto, and the University of Toronto.

Dr. Chung reported receiving research grant support from Ontario Ministry of Health Innovation Grant, University Health Network Foundation, ResMed Foundation, Acacia, and Medtronic.

Genetic variant in COPD tied to more antibiotic use

BY BIANCA NOGRADY
Frontline Medical News

A genetic variant associated with a poorer therapeutic response in patients with asthma may also be linked to more severe chronic obstructive pulmonary disease, researchers have found.

The polymorphisms at codons 16 and 27 of the beta-2-adrenoreceptor (ADRB2) gene are responsible for enhanced down-regulation of the beta$_2$-adrenoreceptor, and research suggests that Arg/Arg homozygosity at position 16 is associated with worse control of disease in patients with bronchial asthma.

However, the results of studies exploring the impact of this variant on the clinical response to the administration of the beta$_2$-adrenoreceptor agonists in COPD patients are "parse and inconclusive," according to Justyna Emeryk-Maksymiuk and colleagues at the Medical University of Lublin (Poland).

In a study published in the April issue of Pulmonary Pharmacology & Therapeutics, the researchers looked for variants of the ADRB2 gene in blood samples taken from 92 patients with stable grade COPD.

They collected data on each patient's disease course during the previous 12 months, including the frequency of exacerbations requiring hospitalization, and antibiotic and systemic corticosteroid use.

They found significant differences between patients with either the Arg/Arg (n = 18), Arg/Gly (n = 61), and Gly/Gly (n = 13) polymorphism at codon 16 of the ADRB2 gene (Pulm Pharmacol Ther. 2017. doi: 10.1016/j.pupt.2017.01.005).

Those who were Arg/Arg homozygotes were significantly more likely to require two or more courses of antibiotic therapy: 33% of this group required two courses of antibiotics compared to 16.4% of those with the Arg/Gly polymorphism and none of those with the Gly/Gly polymorphism.

Those with the Arg/Arg polymorphism also required significantly more corticosteroid therapy; 16.7% needed three or more courses of

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systemic corticosteroid therapy, compared to none of the patients with the other polymorphisms.

However there were no significant differences among the three groups in the number of hospitalizations over the prior 12 months.

The researchers did not see any significant effects on hospitalizations, courses of corticosteroids, or antibiotic use from polymorphisms at codon 27 of the ADRB2 gene.

"The majority of researchers focus on the bronchodilator effect brought by the activation of the beta-2-adrenoreceptors, with less emphasis on the facts that these receptors are also involved in the inhibition of mast cell degranulation, chemotaxis, adhesion and activation of leukocytes, as well as in the improvement of mucociliary clearance of respiratory epithelium," the authors wrote.

"The results of these studies confirmed that the Arg/Arg genotype at codon 16 predisposes patients to clinically more severe manifestation of obstructive respiratory disorders."

The authors noted that the differences in the effect of genetic polymorphisms in the ADRB2 gene could also be the result of differences in the use of inhaled glucocorticoids, as these can prevent the desensitization of the beta$_2$-adrenoreceptor.

Previous research has found that nonusage of inhaled glucocorticoids in asthma patients with the Arg/Arg phenotype is associated with a twofold greater odds of uncontrolled asthma, when compared with patients with the Gly/Gly phenotype.

While patients with asthma are recommended to have inhaled glucocorticoids in conjunction with beta$_2$-mimetics, a considerable fraction of patients with COPD would not be administered glucocorticoids.

"Therefore, it cannot be excluded that a more severe course of asthma and COPD in patients with [the] Arg/Arg genotype of [the] *ADRB2* gene at codon 16 does not result solely from the polymorphism itself, but also from the lack of [inhaled glucocorticoids]," the researchers said.

"The phenotypic variation seen in our COPD patients is extraordinary, and the results from this study likely represent one small facet of the background of why this is the case," said Eric Gartman, MD, FCCP, assistant professor of medicine at Brown University, Providence, R.I., in an interview. "As this type of information becomes more available and refined, a composite picture of a given patient's risk and potential therapies can be made more personalized – maximizing benefit and minimizing harm. Further work such as this, involving larger populations, will allow clinicians to care for a given patient with much more precision."

The Ministry of Science and Education supported the study. No conflicts of interest were declared.

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: This study demonstrates that the pulmonologist's "bread and butter" disease, COPD, continues to be very complex and gives us an understanding of why patients may not respond as we expect them to.

Survey eyes severe pediatric asthma care trends

BY DOUG BRUNK
Frontline Medical News

ATLANTA – The treatment of pediatric severe acute asthma has changed over the past 21 years, but interspecialty differences in the management of these patients persist, results from a national survey suggest.

"I think it's good for every ER and ICU department to have a conversation with providers about what to do when these kinds of patients come in," lead study author Roua Azmeh, MD, said in an interview at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. "A lot of ERs are establishing protocols. I think that's going to be the wave of the future."

The National Heart, Blood, and Lung Institute Asthma Guidelines, first published in 1991, were most re-

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Continued from previous page

cently revised in 2007. In an effort to observe changes in asthma management in pediatric EDs and ICUs over the past 21 years, and to compare common management strategies, Dr. Azmeh and her associates distributed a 16-question online survey to 144 current program directors of U.S. training programs in pediatric emergency medicine and pediatric critical care. Results were compared to a similar survey that was sent by snail mail to program directors of U.S. training programs in pediatric emergency medicine and pediatric critical care in 1995.

Dr. Azmeh, a fellow in allergy and immunology at the Saint Louis University, reported results from 62 respondents who completed the 2016 questionnaire (43%). For initial management of pediatric acute severe asthma, a greater proportion of program directors in pediatric critical care reported using parenteral corticosteroids, compared with their counterparts in pediatric emergency medicine (85% vs. 32%, respectively; *P* less than .0001), as well as continuous beta$_2$-agonists (73% vs. 56%; *P* less than .05). A majority of overall respondents (98%) did not use theophylline for initial management, but more program directors in pediatric critical care reported using it for treatment failure, compared with their counterparts in pediatric emergency medicine (56% vs. 20%, respectively; *P* less than .0071). There was a trend among all respondents for more use of heliox for treatment failure than for initial management (13% vs. 6%).

When the researchers compared current survey responses to responses from the 1995 survey, they observed that program training directors across both specialties increased the use of nebulized ipratropium bromide in initial management and treatment failure (17% vs. 69%; *P* less than .0001 and 33% vs. 42%; *P* less than .05) and decreased use of theophylline for initial management of severe acute asthma (17% vs. 3%; *P* less than .05). However, theophylline is still used in treatment failure.

Among respondents to the 2016 survey, program directors in pediatric emergency medicine were less likely than were those in pediatric critical care to use continuous nebulized beta$_2$ agonists for initial management or to add parenteral selective beta$_2$ agonists (56% vs. 73% and 12% vs. 21%, respectively; *P* less than .05). They also were less likely to use theophylline in treatment failure (20% vs. 56%; *P* less than .05).

Dr. Azmeh reported having no relevant financial disclosures.

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Surveys are interesting to establish a trend for what

residents and fellows are being taught in emergency rooms and critical care units. The parenteral steroid use difference for the two groups in 2016 may be related to the fact that the emergency room hasn't decided to admit their patients yet. Also, theophylline is not something I see any more in our practice!

Study nixed Mg for infants with acute bronchiolitis

BY AMY KARON
Frontline Medical News

FROM CHEST

Intravenous magnesium does not benefit, and may harm, infants with moderate to severe acute bronchiolitis, investigators reported.

Compared with placebo, adding a single intravenous dose of magnesium sulfate (100 mg/kg) to usual care did not reduce time to medical readiness for discharge, even when patients had eczema or a family history of asthma, and was tied to more than a threefold rise in the rate of short-term readmissions, Khalid Al Ansari, MD, of Hamad Medical in Doha, Qatar, and his associates wrote in Chest. "To our knowledge, this is the first randomized study to investigate the effect of intravenous magnesium in a bronchiolitis population," they added.

Bronchiolitis lacks new, inexpensive, readily available treatments, despite being a common reason for hospital admission, the researchers noted. For older children with moderate to severe exacerbations of asthma, a meta-analysis found that the addition of magnesium to usual care appeared to cut readmissions and shorten lengths of stay, compared with placebo. To explore magnesium therapy in younger children, the investigators enrolled 162 previously healthy infants up to 18 months old who had been admitted to the short-stay unit of a pediatric emergency center with a diagnosis of moderate to severe viral bronchiolitis. Patients received usual care with oral dexamethasone and nebulized 5% hypertonic saline in 1 mL of 1:1,000 epinephrine, plus an intravenous 60-minute infusion with a blinded syringe of either 0.9% saline placebo or magnesium sulfate (100 mg/kg) (Chest. 2017 Mar 9. doi: 10.1016/j.chest.2017.03.002).

The primary endpoint, time to medical readiness for discharge, did not statistically differ between groups, averaging 24.1 (95% confidence interval, 20.0-29.1) hours with magnesium and 25.3 (95% CI, 20.3-31.5) hours with placebo ($P = .91$). Among patients with a history of eczema or a family history of asthma, mean times to readiness for discharge resembled those for the entire cohort and did not statistically differ based on treatment. Average Wang bronchiolitis severity scores also were similar between groups, as were rates of outpatient clinic visits (33.8% with magnesium and 27.2% with placebo).

Strikingly, 2-week readmission rates were 19.5% with magnesium (95% CI, 11.3-30.1) and 6.2% with placebo (95% CI, 0.02-13.8; $P = .016$). Among patients with eczema or a family history of asthma, 2-week readmission rates also were significantly higher with magnesium (26.3%; 95% CI, 13.4-43.1) than with placebo (7.5%; 95% CI, 1.6-20.4; $P = .034$) These might have been chance findings, or magnesium might have masked worse bronchiolitis, prolonged the disease course, or interacted with 5% hypertonic saline or systemic corticosteroids, the investigators said. Intravenous magnesium might contribute to secondary relapse, especially among patients with eczema or a family history of asthma, they added.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: The study authors are correct that there isn't a "new" treatment for infant bronchiolitis. But the American Academy of Pediatrics published a Clinical Practice Guidelines in 2014 (Pediatrics. Vol 134, Number 5, November 2014). In the guidelines, it was recommended not to do nebulized hypertonic saline in the emergency room and to not administer systemic corticosteroids to infants with a diagnosis of bronchiolitis in any setting. This study included patients admitted to a short-stay unit within the emergency room and they were receiving both of these therapies as "usual care." Therefore, it is difficult to say if this may have confounded the results. In any case, intravenous magnesium sulfate doesn't make sense as an intervention for bronchiolitis.

Patients in this study, which was sponsored by Hamad Medical, had a median age of 3.7 months, about half had eczema or a family history of asthma, and 86% had positive nasopharyngeal virus swabs. Cardiopulmonary monitoring revealed no acute events during treatment. Of 16 readmissions in the magnesium group, 11 entered the infirmary and 4 entered the hospital. The five placebo readmissions included four to the infirmary and one to the hospital.

Death risk drop tied to vaccine

BY DAN WATSON
Frontline Medical News

Influenza vaccination was associated with reduced risk of laboratory-confirmed influenza-associated death in children, a case-cohort analysis found.

"These results support current recommendations for annual influenza vaccination for all children 6 months of age" and older, wrote Brendan Flannery, PhD, and his coauthors at the Centers for Disease Control and Prevention, Atlanta. "To our knowledge, this is the first study to use laboratory-confirmed outcomes to investigate influenza vaccine effectiveness against influenza-associated deaths."

"Best estimates based on [National Health Interview Survey] data suggested that vaccination reduced the risk of influenza-associated death by half among children with high-risk conditions and by nearly two-thirds among children without high-risk conditions," Dr. Flannery and his coauthors reported.

Of 358 cases of pediatric death (aged 6 months to 17 years) confirmed to be associated with influenza, 75 (26%) had been vaccinated prior to their disease onset. The case-cohort analysis compared the 358 cases against three cohorts of U.S. children and adolescents: a telephone survey, a household survey, and a health insurance claims database.

The researchers had examined cases that were reported to the U.S. Influenza-Associated Pediatric Mortality Surveillance System from July 2010 to June 2014. They excluded cases of children not yet eligible to be vaccinated or whose disease onset may have occurred before their vaccine had 14 days to take full effect (Pediatrics. 2017 Apr. doi: 10.1542/peds.2016-4244).

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This information screams at all providers and parents regarding the critical importance of yearly influenza vaccinations for all children 6 months of age and older!

Low flu vaccine rates seen in chronically ill children

BY LUCAS FRANKI
Frontline Medical News

Poor influenza vaccination rates in children with chronic diseases is primarily due to poor parental understanding of influenza risk and vaccination benefits, according to Janita Pak Chun Chau, PhD, of the Chinese University of Hong Kong, and associates.

Studies show that children with chronic conditions "are at a disproportionately higher risk for severe influenza-associated complications, causing increased visits to outpatient or emergency departments, longer hospital stays, and higher mortality," the researchers said.

A total of 623 parents of children with chronic conditions in Hong Kong were included in the study. The most common chronic condition was asthma, followed by chronic respiratory disease and cardiomyopathy. Only 33% of children had received an influenza vaccination in the previous 12 months, and 57% of children had ever received one.

Just under 40% of parents indicated intent to have their children vaccinated in the next 12 months. Parents who had their children vaccinated were more aware of vaccination benefits and considered vaccination a social norm, compared with parents who had not had their children vaccinated. Television was by far the most common source of information about influenza, followed by health professionals, and newspapers and magazines.

"Development of community-based influenza vaccination programs by health care professionals targeted to promote awareness and communicate the benefits and effectiveness of the vaccines in children with chronic conditions, as well as clarifying safety issues concerning the vaccination, may be able to promote the uptake of influenza vaccination," the investigators wrote.

Find the study in the Pediatric Infectious Disease Journal (doi: INF.0000000000001550).

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What do doctors want from health reform?

BY ALICIA GALLEGOS
Frontline Medical News

With the demise of Republican repeal and replace legislation, analysts say the landscape is ripe for repairs to the Affordable Care Act or for additional legislation that both political parties could support. So what do physicians want from health reform?

The first step should be stabilizing the health insurance marketplaces by strengthening and perhaps extending risk mitigation measures such as the risk adjustment, risk corridors, and reinsurance provisions of the law, said Patricia Salber, MD, an internist and health care consultant and the founder of TheDoctorWeighsIn.com. Those three ACA provisions were intended to promote insurer competition on the basis of quality and value and promote insurance market stability.

"Stabilization of the marketplaces would benefit physicians as well as patients, providers, and plans, ensuring payment for services instead of returning to the bad old days of cost-shifting to pay for [uninsured] and underinsured," Dr. Salber said in an interview.

Keeping premiums at manageable levels for patients should also be addressed, said William J. Burke, DO, dean of Ohio University Heritage College of Osteopathic Medicine.

"Without a doubt increased premium costs and high deductibles for patients insured through the system have become a challenge," Dr. Burke said in an interview. "I do think we need to rein in, to the best of our ability, those increases in premium costs. To be fair, in many markets, we have seen some stabilization, but in other markets, we have seen substantial increases."

That was echoed in a poll taken by this news organization. Of 390 respondents, fully half (50%) said they would repair the ACA by stabilizing premiums and out-of-pocket costs for patients as of April 2. About 11% stated they would increase payment rates for care provided to Medicaid patients, and 10% said they would return the primary care incentive payment. About 9% of those surveyed would address workforce issues exacerbated by more patients in the system.

Other priorities cited by respondents ranged from allowing insurers to compete across state lines to tighter regulation of drug prices to permitting balance billing by physicians. Some respondents expressed the need for a complete repeal and replace of the ACA, while others said health care needs to move to a single-payer system. Changing the ACA's individual mandate was frequently recommended, with some respondents wanting the mandate eliminated and others suggesting that the cost of noncompliance with the mandate be increased and the mandate itself better enforced.

"Stabilization of the marketplaces would benefit physicians as well as patients, providers, and plans ... "

DR. SALBER

Improving reimbursement for Medicaid services is a necessary health reform change, agreed Diane J. Horvath-Cosper, MD, an obstetrician-gynecologist and reproductive health advocacy fellow for Physicians for Reproductive Health, a reproductive rights advocacy organization.

"Reimbursement rates are so low that sometimes [physicians] have to limit the number of Medicaid patients to be able to pay staff," Dr. Horvath-Cosper said in an interview. "That's a terrible position to put physicians in because we want to be able to see as many people who want to see us."

Speaking of Medicaid, Dr. Salber adds that governors should be encouraged to continue expanding Medicaid to eliminate the coverage gap for the "near poor" that exists in states that did not participate in the expansion.

"Now that the [American Health Care Act] has failed, I think we will see some expansion take place organically even in states that were deeply opposed before," she said.

Reducing the administrative burden of prior authorizations should be considered a top health reform priority, added Michael L. Munger, MD, president-elect of the American Academy of Family Physicians. He said the AAFP would like to see all plans – public and private – use a standard form and standard process for all prior authorizations. In addition, the need for prior authorizations should be examined and eliminated in some areas, such as for generic medications for Medicare patients or for patients with chronic disease who are on an established treatment regimen.

"The volume of prior authorizations that all physicians face, but especially primary care physicians, is huge," Dr. Munger said in an interview. "In many cases, we're having to hire extra staff just to handle all of the prior authorizations. Every patient may not just have one prior authorization, but they may require two or three or four prior authorizations each month or quarterly. It really detracts from meaningful time you can spend with the patient."

Keeping premiums at manageable levels for patients should also be addressed.

DR. BURKE

Meanwhile, Jane Orient, MD, executive director for the conservative Association of American Physicians and Surgeons, said health reform efforts should include a complete revamping of how physicians are paid. The AAPS is opposed to the ACA and would like to see repeal and replace legislation enacted.

For starters, doctors should provide care to patients based on mutually agreed terms and without the interference of insurers, Dr. Orient said in an interview. In such a private medicine system, patients would pay doctors for services, and patients would then file claims with their insurer for reimbursement. Similarly, physicians should not be at the mercy of Medicare for payment, Dr. Orient said.

"Doctors can sign away their rights if they want in a Medicare participation agreement," she said. "Doctors who do not sign the agreement to take assignment in all cases doctors should be freed of price controls and coding demands. Their patients should be allowed to file their own simple claims to Medicare with an itemized bill as they did before the 1990s law that requires physicians to submit the claims. Nonparticipating doctors should be exempted from MACRA [the Medicare Access and CHIP Reauthorization Act], and without the price controls, there is no need for [Recovery Audit Contractors] and other auditors."

While contraceptive care was strengthened by the ACA, Dr. Horvath-Cosper said further efforts should be made to improve coverage and level the playing field for reproductive medicine. In addition, she said that abortion should be treated as a valid medical procedure, rather than parsed out, and both public and private insurers should be required to pay for the procedure, she said.

"I would love to see strengthened provisions for contraception coverage," Dr. Horvath-Cosper said. "[We need to] make sure that doesn't get bargained away. The other thing is to expand coverage and make sure every method is covered, not just one method in each category."

Addressing the opioid epidemic and achieving innovative medical liability reform are top issues that should be included in any new health reform legislation, Nitin Damle, MD, president of the American College of Physicians, said at a March 31 press conference. The ACP also supports reform legislation that builds on existing requirements that insurers and Medicare cover essential benefits, lowers deductibles, makes premiums more affordable, and preserves the existing federal commitment to Medicaid, while allowing for state innovation.

However, Robert Doherty, ACP senior vice president of governmental affairs and public policy, said the college is concerned that the current administration may fail to maintain the ACA.

Without aggressively pushing ACA enrollment for younger patients and continued support for the individual mandate, more insurers may pull out of the marketplaces, and the ACA could implode, Mr. Doherty said.

"There are a number of ways that Republicans could either make things better or worse with action or inaction," Mr. Doherty said during the press conference. "The insurance [companies] have gone to this administration with a wish list of things that will help keep them in the market. What remains to be seen is whether this administration is going to be receptive. If they don't aggressively enforce the requirement that people buy coverage, more younger people will opt out and stay out until they get sick. That would make the problem of adverse selection even worse and could create the death cycle for insurance."

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Gregory Twachtman contributed to this report.

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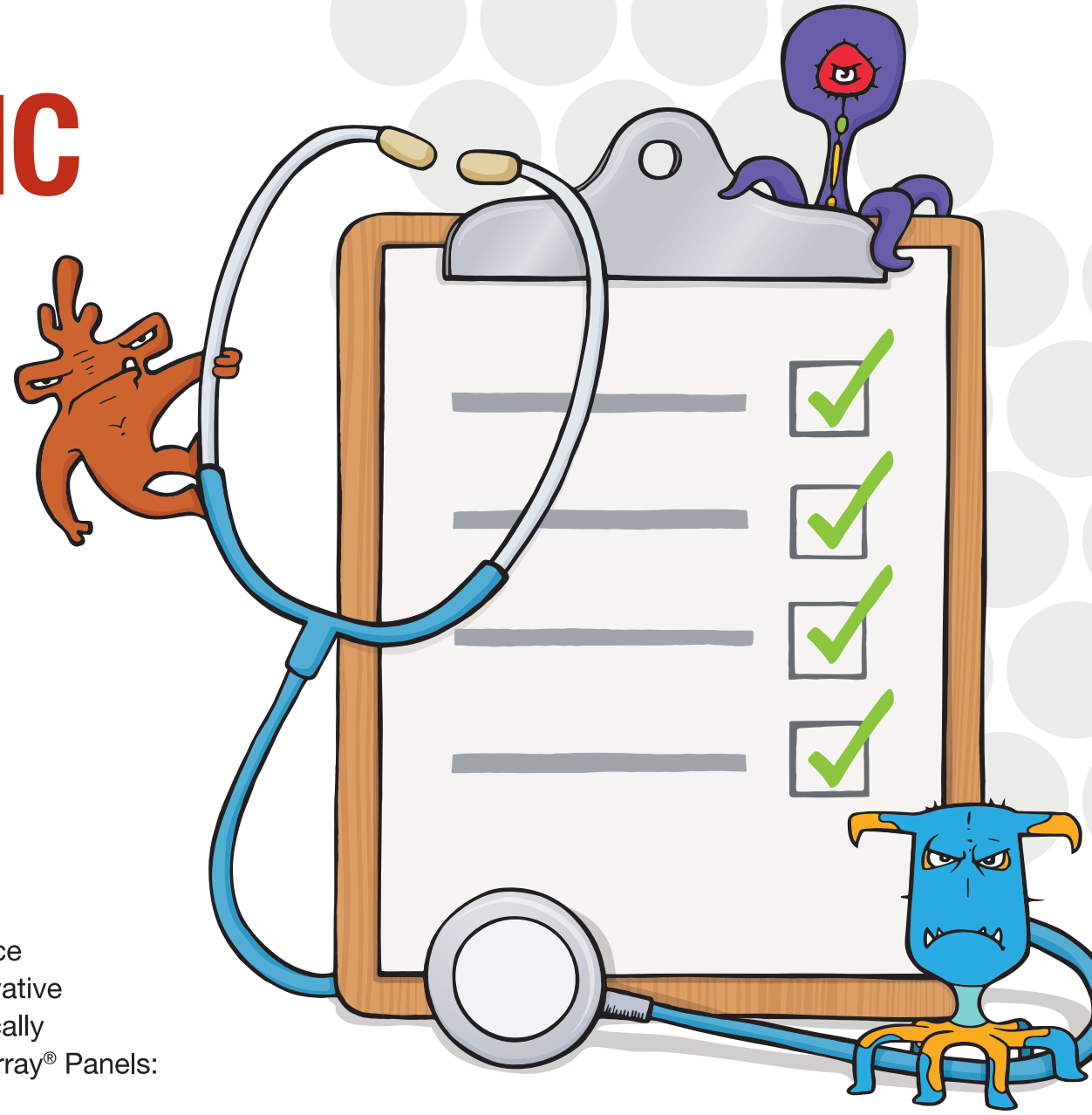

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MedPAC says their proposal could save billions

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – Reducing the amount physicians are paid for drugs administered in their offices and introducing shared savings could save Medicare up to $5 billion over 5 years, according to recommendations from the Medicare Payment Advisory Commission.

Those MedPAC recommendations to Congress include cutting physicians' average sales price add-on percentage, as well as an alternative purchasing initiative called the Drug Value Program that would allow shared savings through more effective pharmaceutical utilization.

"It is our obligation to deal with the escalation of the cost of drugs, including in this case those that are paid through Medicare Part B," MedPAC Chairman Francis J. Crosson, MD, said during a MedPAC meeting April 6. "We have come up with a recommendation, and it consists necessarily of a set of parts that we believe are balanced in a number of ways."

Physicians should not be in a position to provide Part B drugs at a financial loss, Dr. Crosson noted. But the current 6% add-on to average sales price (ASP) "overpays many physicians and institutions, and is inherently a cost-ineffecient payment system for the Medicare program."

If implemented, the proposals could save Medicare between $250 million and $750 million in the first year, and between $1 billion and $5 billion within 5 years. MedPAC staff said.

The first part of the recommendation, which would start in 2018, would alter the current Part B drug payment process. Currently, doctors receive ASP plus 6%, or wholesale acquisition cost (WAC) plus 6% for drugs without sufficient ASP history. The proposal would enhance ASP reporting, including requiring more manufacturers to submit data and increasing fines by an unspecified amount for those that fail to meet reporting standards. The WAC add-on percentage would be reduced to 3%. A to-be-determined inflation index would be applied to ASP and would trigger automatic rebates if ASP climbs faster than inflation. Finally, billing codes for biosimilars and their reference products would be combined.

Under the second part of MedPAC's recommendation, in 2022 providers would face a choice: Continue to have Part B drugs paid for under the ASP scheme with a reduced add-on percentage of 3%, or take part in the Drug Value Program.

Under the Drug Value Program, physicians would sign up with one of several vendors that would be charged with negotiating prices for Part B drugs. Physicians would pay the negotiated prices for the drugs. Vendors would have standard formulary tools, such as prior authorization, tiering, and step-therapy. For a very small subset of drugs with no competition in the marketplace, the proposal includes a binding arbitration process, the specific details to be determined later. The proposal will be included in MedPAC's June 2017 report to Congress.

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CMS rule will be ineffective without subsidies

BY GREGORY TWACHTMAN
Frontline Medical News

New final regulations designed to bring stability to the individual health insurance market may not matter if the White House follows through on a threat to kill subsidies paid to insurers to help reduce deductibles and other out-of-pocket costs for low-income patients.

The final rule from the Centers for Medicare & Medicaid Services grants a number of wishes sought by the insurance industry to help bring a level of predictability and flexibility when designing plans for the individual market. Specifically, it does the following:

- Shortens the open enrollment period for the 2018 plan year to 6 weeks running from Nov. 1 to Dec. 15, so that open enrollment closely aligns with Medicare and other pri-

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vate insurance.
- Requires individuals to submit documentation when seeking coverage through a special enrollment period.
- Allows insurers to collect past-due premiums before issuing coverage for a future year.
- Provides more actuarial flexibility to allow for different plan designs.
- Returns network adequacy oversight to states.

The new rules are not expected to alter the existing market dynamic, according to Kelly Brantley, vice president at Avalere Health.

"I would say the rule is nominally helpful, but it's really unlikely to persuade anyone, particularly those insurers who are already on their way out. I don't think this a game-changer for them," she said in an interview.

The American Medical Association, in comments to the CMS when the rule was proposed as a draft, said that if finalized, the rule "would raise premiums, out-of-pocket costs, or both for millions of moderate-income families and would make it more difficult for eligible individuals to enroll in health coverage and access needed care."

The potential impact of these regulatory changes could be moot

DNDAVIS/THINKSTOCK

if President Trump makes good on his threat to withhold cost-sharing subsidies to insurers. The subsidies already are the subject of a lawsuit brought by the House of Representatives against the Obama administration; they continue to be paid while the suit makes its way through the judicial process. President Trump has threatened to cut off the subsidies in an effort to force Congressional Democrats to the negotiating table regarding the repeal and replacement of the Affordable Care Act.

"My take on this is that the [market stabilization] rule as written is not likely to shift the market, really, in terms of access," Ms. Brantley said. "The bigger question is whether the cost-sharing reductions are going to be paid. I think that has a bigger likelihood of influencing issuer participation and robustness of the market in 2018."

Even with the changes made by the market stabilization rule, "there is still too much instability and uncertainty in this market," Marilyn Tavenner, president and CEO of the industry group America's Health Insurance Plans, said in a statement. "Most urgently, health plans and the consumers they serve need to know that funding for cost-sharing reduction subsidies will continue uninterrupted."

"My take on this is that the [market stabilization] rule as written is not likely to shift the market, really, in terms of access," Ms. Brantley said.

Ms. Tavenner noted that, without the subsidies, more plans are likely to drop out of the health insurance exchanges, leading to premium increases, and "doctors and hospitals will see even greater strains on their ability to care for people."

The AMA, in an April 12 letter to President Trump, cosigned by America's Health Insurance Plans, the American Benefits Council, the American Academy of Family Physicians, the American Hospital Association, Blue Cross Blue Shield Association, the Federation of American Hospitals, the and the U.S. Chamber of Commerce, stated that the "most critical action to help stabilize the individual market for 2017 and 2018 is to remove uncertainty about continued funding for cost sharing reductions."

Ms. Brantley added that, if the subsides were cut, "it makes it more challenging to bring any kind of money back into the system at a later point. I think it would be hard for those cost-sharing reductions to go away at this point and then ever come back, but I do think that it's a possibility that that could happen."

The CMS released the final rule April 13, 2017, and it was published in the Federal Register on April 18, 2017.

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Medicaid reform: Work-based waivers may not fly

BY BARBARA BOLAND
Frontline Medical News

The Trump administration may not be able to successfully implement the work requirements and other Medicaid eligibility caveats proffered by Health & Human Services Secretary Tom Price, MD, according to Jane Perkins, legal director for the National Health Law Program.

In March, Secretary Price and Seema Verma, administrator of the Centers for Medicare & Medicaid Services, wrote to state governors, letting them know that the HHS would support states' efforts to increase employment, community engagement, and work requirements for Medicaid recipients. The letter also was supportive of aligning Medicaid benefits with private insurance via alternative benefits, cost sharing, and premium payments.

High mandatory premiums, cost sharing, lifetime limits, and drug testing "are of concern to us," Ms. Perkins said at an April 13 press briefing. "They really change the complexion of Medicaid and Medicaid coverage for low-income people."

These requirements "are not typically seen in Medicaid programs," she said.


MS. VERMA

While Section 1115 of the Social Security Act "allows states to test novel approaches to providing medical assistance" via Medicaid waivers, it does not allow the HHS or the states to "ignore congressional mandates; to cut eligibility, services, or provider payments; or to use section 1115 to save money," according to an issue brief by Ms. Perkins.

Kentucky submitted a Medicaid waiver request to the Obama administration in August 2016; it was not acted upon and is still awaiting action by the HHS. Other states that are looking into waivers include Indiana, Arizona, Florida, Maine, and Montana.

When asked how work requirements harm people, Ms. Perkins responded that adding a work requirement to Medicaid eligibility gets things "backwards," because a sick person needs health care before being able to return to work.

The work requirement would not save states much money, as nearly 8 in 10 adults on Medicaid are in a household that includes a worker and 59% of recipients work themselves, according to a Kaiser Family Foundation study. The adults affected by the work requirement would make up only a drop in the ocean of Medicaid spending. About two-thirds of that spending goes toward senior citizens, people with disabilities, children, and people in long-term care, according to projections from the Congressional Budget Office.

There's also a question of whether Medicaid waivers would hold up when subjected to legal challenges. Heads of federal agencies are given broad rule-making authority; however, courts have previously rejected the argument that they have unlimited discretion. Secretaries must adhere to the Administrative Procedures Act, a federal law that limits how they implement regulations, requires time for public comment, and provides specific guidelines on the rule-making process. The law denies departments the ability to engage in rule making that is arbitrary or capricious.

The National Health Law program, which advocates for low-income Medicaid recipients, is following the waivers state-by-state with a network of lawyers who work with people with disabilities in each state.

"With this new openness to flexibility, we are certainly watching what is going on in the states," Ms. Perkins said.

ABIM turns MOC page with open-book 2-year exams

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – The way the president of the American Board of Internal Medicine, Richard J. Baron, MD, sees it, maintenance of certification is more important than ever, because trust in the medical profession "is under assault right now in all kinds of ways."

So, to help "bring clarity to uncertainty," ABIM is continuing its makeover of the maintenance of certification (MOC) process. Beginning in 2018, an open-book option to test every 2 years will be available for physicians who are certified in internal medicine and for those in the subspecialty of nephrology.

Both the 10-year long-form assessment and the shorter 2-year assessment options will be open book, "meaning physicians will have access to an online reference while they're taking the exam," said Yul D. Ejnes, MD, who is a member of ABIM's board of directors and serves on the ABIM's internal medicine specialty board.

Similar maintenance of certification changes are scheduled to be rolled out to other medical specialties by 2020.

Known as the "Knowledge Check-In," the 2-year assessment is a shorter, "lower stakes" option that can be taken at home, in an office, or at a testing facility. The check-ins will be scheduled four to six times per year, with 10-year exams remaining available twice per year. The open-book 2-year assessments will be about 3 hours in length.

"It's a more continuous way of learning and assessing, because the way we'll do feedback is going to change," explained Dr. Ejnes, who practices in Cranston, R.I. "Specifically, you'll know right away whether you were successful or not with the assessment, as opposed to having to wait a couple of months, which happens with the 10-year assessment. Then you'll get more feedback later helping to identify areas where you may be a little weaker and need to work out things."

In general, physicians will need to either take the 2-year assessments or pass the 10-year assessment within 10 years of their last pass of the 10-year exam. Those who fail two successive 2-year assessments will have to take the 10-year exam. However, unsuccessful performance on the 2-year assessment in 2018 will not have a negative impact on certification or MOC participation status.

"It won't count as one of the two opportunities you have before you have to go to the 10-year exam," Dr. Ejnes said. "It allows people to try it out and lets us learn from what happens and do whatever we need to do to make things better."

Why a 2-year period instead of a 5-year option, for example? A shorter time frame will allow the ABIM to move to a more modular approach to test material, Dr. Ejnes explained. For now, the 2-year assessments will be breadth-of-discipline exams.

Physicians whose certification expires in 2017 will need to take the 10-year exam – as Dr. Ejnes noted he himself was forced to do. "You cannot wait until 2018," he cautioned. "That's important, because if you let your certification lapse, you can't enter the certification pathway. The prerequisite is that you need to be in good standing with your certification."

The open-book Knowledge Check-Ins and 10-year assessments are slated to expand to eight subspecialties in 2019 and nine more in 2020.

CHEST Physician's Medical Editor in Chief, Vera A. De Palo, MD, MBA, FCCP, applauded the changes.

"The increasing pressures of the practicing physician's workday continue to erode the personal time which may be dedicated to other activities, including the lifelong learning necessary for our profession. Having different paths for maintenance of certification available to the physician, with multiple timing and location options, offers more degrees of freedom for the physician in the recertification process," she said.

The American Thoracic Society had little to say about the changes themselves, but expressed appreciation of ABIM's reexamining of the MOC process. "The ATS supports the efforts of the ABIM to continue to reassess the issues of Maintenance of Certification. We appreciate the efforts to add some flexibility to the system and would also advocate that the ABIM continue to reassess their new system to determine if it is effectively meeting all goals," said Debra Boyer, MD, MPHE, Education Committee Chair of the ATS, in an interview.

During a question and answer session at the annual meeting of the American College of Physicians, Anne Cummings, MD, an internist who practices in Greenbrae, Calif., asked the ABIM for support in educating the general public about what it means to be treated by a board-certified physician. Other attendees recommended that ABIM expand the number of ways physicians can earn MOC points, and they expressed concern about the time MOC takes away from their daily practice.

For regular updates on the MOC process, physicians can subscribe to the ABIM's blog at transforming.abim.org.

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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.

Routine U.S. mitral clip use found reassuring

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – U.S. heart teams have used the mitral valve transcatheter clip repair device for fixing leaky mitral valves exactly the way it was designed to be used once the device hit the U.S. market in 2013.

In the first review of periprocedural and 1-year outcomes of U.S. patients treated with the MitraClip repair device and entered in the national device registry, the results showed "acute effectiveness and safety of transcatheter mitral valve repair," Paul Sorajja, MD, said at the annual meeting of the American College of Cardiology.

Although 1-year outcomes, gleaned from Medicare records, showed a high, 1-year mortality rate of 22% among patients who achieved a low mitral regurgitation grade of 0 or 1 (none or mild) following their procedure, and even higher mortality among patients with higher residual valvular regurgitation, this high mortality is attributable to the patients advanced age, frailty, and high prevalence of comorbidities rather than any apparent failures of the valve repair procedure, he said.

"We need to be keenly aware of the impact of comorbidities on the prognosis of these patients. The data show that untreated comorbidities really impact prognosis," said Dr. Sorajja, an interventional cardiologist and director of the Center of Valve and Structural Heart Disease of the Minneapolis Heart Institute.

"The clip is for the no-option patient, meaning patients at high risk who have no surgical option. The data show that these are the patients who are being treated" in routine U.S. practice. "The data show that, even for these patients, you can still get pretty good results," Dr. Sorajja said in an interview. "These are the first data on clip use in routine U.S. practice, and they are really reassuring. The data show that the clip is being used in the correct way, without risk creep, on patients with prohibitive surgical risk based on their STS [Society of Thoracic Surgeons] predicted mortality and frailty scores."

The data he and his associates reviewed came from the 2,952 U.S. patients who underwent a transcatheter mitral valve clip repair following the devices premarketing approval from the Food and Drug Administration in November 2013, and through September 2015 at any of 250 U.S. sites offering the procedure.

The data on patient demographics and clinical status came from the STS/American College of Cardiology Transcatheter Valve Therapy registry, and data on 1-year outcomes came from Medicare records for 1,867 (63%) of the patients.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Paul Sorajja

The mitral valve repair patients averaged 82 years old, 85% had a New York Heart Association functional class of III or IV, 93% had a mitral valve regurgitation grade of 3 or 4, half were judged frail, and their STS predicted mortality risk from mitral valve repair was about 6% and from valve replacement about 9%.

Immediately after their procedure, 93% of patients had a valve regurgitation grade of 2 or less, the periprocedural mortality rate was just under 3%, and 86% of patients were discharged home following a median length of stay of 2 days. Acute procedural success occurred in 92% of patients, Dr. Sorajja reported.

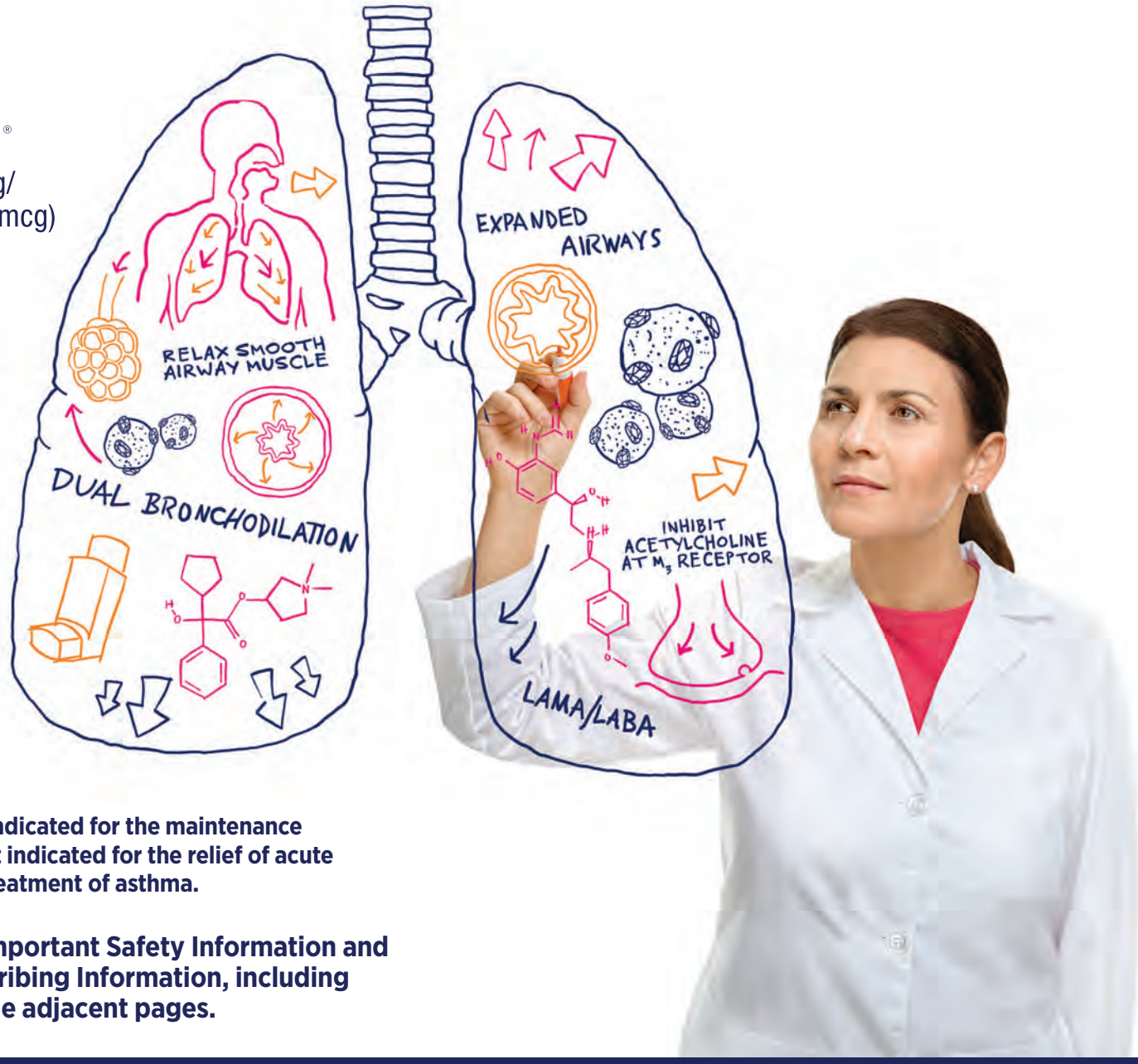
At 1 year, the mortality rate among the patients followed through their Medicare records showed that 26% of patients had died, 20% had been hospitalized at least once for heart failure, and 38% had at least one of these two outcomes. In addition, 6% underwent a repeat procedure of transcatheter mitral repair, and 2% had mitral valve replacement surgery.

Although patients who had a successful repair with a residual regurgitation grade of 0 or 1 still had a substantial mortality rate of 22% during 1-year follow-up, survival was worse in patients with higher grades of residual mitral regurgitation. One-

Continued on page 26

BEVESPI AEROSPHERE®

(glycopyrrolate 9 mcg/
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting $beta_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, 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 LABAs, including formoterol fumarate.

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

CONTRAINDICATION: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. BEVESPI is contraindicated in patients with a hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product.

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BEVESPI 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
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions, including angioedema, urticaria, or skin rash, occur, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- 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
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI (≥2% and more common than placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

INTELLIGENT FORMULATION*

Intelligent formulation for a pMDI using patented CO-SUSPENSION™ Delivery Technology[1]

MAXIMIZE BRONCHODILATION†

Improved lung function‡ vs placebo including[1]

- 150-mL improvement in predose FEV_1 at 24 weeks
- Nearly a 300-mL improvement in peak FEV_1 at 24 weeks
- Nearly a 200-mL improvement in FEV_1 at 5 minutes on Day 1

In a separate study vs placebo

- Achieved a 381-mL improvement in peak inspiratory capacity on Day 29[2§‖]

Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.[1]

BEVESPI AEROSPHERE is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. It is not for the treatment of asthma.

* BEVESPI AEROSPHERE is a pMDI containing the LAMA glycopyrrolate and LABA formoterol fumarate, along with phospholipid porous particles that form the co-suspension with the micronized drug crystals.[1]

† Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials (n=3699).[1,3]

§ Results from a separate Phase IIIb trial (n=35). There was a significant mean improvement in primary endpoint FEV_1 $AUC_{0\text{-}24}$ on Day 29 vs placebo.[2¶] Peak inspiratory capacity after the evening dose on Day 29 was a secondary endpoint.[#] Similar results seen in a second Phase IIIb trial (n=75).[2‖]

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- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

LIMITATION OF USE: Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

‡ Demonstrated in two 24-week efficacy and safety studies in patients with moderate to very severe COPD (n=3699). Inclusion criteria: A clinical diagnosis of COPD; between 40-80 years of age; history of smoking ≥10 pack-years; post-albuterol FEV_1 of <80% of predicted normal values, and FEV_1/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; P<0.0001 for all treatment comparisons.[1,3] Statistically significant results were also seen in Trial 2.[1,3]

‖ Two Phase IIIb crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI AEROSPHERE compared with placebo in subjects with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and Study B). Inclusion criteria were consistent with the two 24-week pivotal trials. Adverse events were numerically similar across treatment arms.[2]

¶ Primary endpoint, FEV_1 $AUC_{0\text{-}24}$: Study A – BEVESPI AEROSPHERE (n=35) vs placebo (n=31) = 249 mL (baseline FEV_1 1.382 L and 1.345 L, respectively); Study B – BEVESPI AEROSPHERE (n=65) vs placebo (n=65) = 265 mL (baseline FEV_1 1.328 L and 1.333 L, respectively); both P<0.0001.[2]

Secondary endpoint, Peak IC (evening): Study A – BEVESPI AEROSPHERE (n=34) vs placebo (n=30) = 381 mL (baseline IC [evening], 1.980 L and 1.939 L, respectively); Study B – BEVESPI AEROSPHERE (n=62) vs placebo (n=63) = 312 mL (baseline IC [evening] 1.877 L and 1.913 L, respectively); both P<0.0001.[2]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2016. **2.** Data on File, 3270300, AZPLP. **3.** Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357.

AstraZeneca

BEVESPI AEROSPHERE™

(glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) 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 all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication *[see Warnings and Precautions (5.1) in the full Prescribing Information]*. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs 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 LABAs.

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; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE 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 BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, 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 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 BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled medicines containing beta$_2$-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, 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) in the full Prescribing Information]*. If such effects occur, BEVESPI AEROSPHERE 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, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

BEVESPI AEROSPHERE, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

BEVESPI AEROSPHERE 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 should any of these signs or symptoms develop.

Worsening of Urinary Retention

BEVESPI AEROSPHERE 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 should any of these signs or symptoms develop.

ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma *[see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information]*.

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Hypersensitivity reactions *[see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10) in the full Prescribing Information]*

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 BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

Additional Adverse Reactions**:** Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of $beta_2$ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

Pregnancy Category C. There are no adequate and well-controlled trials of BEVESPI AEROSPHERE or its individual components, glycopyrrolate and formoterol fumarate, in pregnant women. Because animal reproduction studies are not always predictive of human response, BEVESPI AEROSPHERE 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 BEVESPI AEROSPHERE.

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m^2 basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m^2 basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

Pediatric Use

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

Geriatric Use

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

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE 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 medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Glycopyrrolate

High doses of glycopyrrolate, a component of BEVESPI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

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Preoperative variables can predict prolonged air leak

BY RICHARD MARK KIRKNER
Frontline Medical News

Prolonged air leak is a well-known complication after lung cancer surgery that can worsen patient outcomes and drive up costs, and while international authors have developed tools to calculate the risk of PAL, their use has been limited in the United States for various reasons. Researchers at the University of Pittsburgh have reported on a predictive model that uses easy-to-obtain patient factors, such as forced expiratory volume and smoking history, to help surgeons identify patients at greatest risk for complications and implement preventative measures.

"An accurate and generalizable PAL risk stratification tool could facilitate surgical decision making and patient-specific care ... ," the researchers noted.

Adam Attaar and his coauthors reported that their nomogram had an accuracy rate of 76% for predicting PAL after surgery (J Thorac Cardiovasc Surg. 2017 March;153[3]:690-9). "Using readily available candidate variables, our nomogram predicts increasing risk of prolonged air leak with good discriminatory ability," noted Mr. Attaar, a student at University of Pittsburgh, and his coauthors.

Previously published reports put the incidence of PAL complications at 6%-18%, they noted. In the University of Pittsburgh series of 2,317 patients who had pulmonary resection for lung cancer or nodules from January 2009 to June 2014, the incidence was 8.6%.

In this series, patients with PAL were more likely to be older, men, and smokers, and to have a lower body mass index, peripheral vascular disease, chronic obstructive pulmonary disease, a history of steroid use, a high Zubrod score and lower forced expiratory volume."They were less likely to have diabetes or to be hospitalized before surgery," the researchers said. Surgical factors that characterized patients with PAL were resection for primary lung cancer rather than benign or metastatic tumors; lobectomy/segmentectomy or bilobectomy rather than wedge resection; a right-sided resection; thoracotomy; and a surgeon with higher annual caseloads.

Not all those factors made it into the nomogram, however. The nomogram scores each of these 10 variables to calculate the risk of PAL, in order of their weighting: lower forced expiratory volume, procedure type, BMI, right-sided thoracotomy, preoperative hospitalization, annual surgeon caseload, wedge resection by thoracotomy, reoperation, smoking history, and Zubrod score. A second nomogram drops out surgeon volume to make it more generalizable to other institutions.

In explaining higher surgeon volume as a risk factor for PAL, the researchers said that high-volume surgeons may be operating on patients with variables not accounted for in the Society of Thoracic Surgeons General Thoracic Surgery Database. "These unmeasured variables … could reveal modifiable technical factors to reduce the incidence of PAL and require further study," the researchers said.

Fast-track discharge has gained acceptance in recent years as a way to spare patients a prolonged hospital stay and cut costs, but in this series the median hospital stay for patients with PAL was 10 days vs. 4 days for non-PAL patients (*P* less than 0.001).

"An accurate and generalizable PAL risk stratification tool could facilitate surgical decision making and patient-specific care" and aid in the design of trials to evaluate air-leak reduction methods such as sealants, buttressed staple lines, and pneumoperitoneum the researchers wrote.

In the future, further development of the model would involve a multicenter study and inclusion of risk factors not accounted for in the thoracic surgery database, they noted.

The researchers had no relevant financial relationships to disclose.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: Prolonged air leak (PAL) following pulmonary resection is a common complication associated with increased hospital length of stay and cost. The work by the University of Pittsburgh group is a welcome addition to previous work by several international groups on coming up with a predictive model for PAL following pulmonary resection. The nomogram developed is based on rigorous analyses of a large data set on 2,317 patients that underwent lung resection for lung cancer/nodules and has a good discriminatory accuracy of 76%. Would this nomogram gain widespread use in clinical practice? This remains to be seen and it may depend on the ease of use and implementation possibly through creation of an app with tech companies or potentially a risk calculator for general thoracic surgery within the Society of Thoracic Surgery framework.

Continued from page 21

year mortality among those with residual grade 2 regurgitation was 29%, and for those with residual grade 3 or 4 regurgitation, 1-year mortality was 49%.

Many patients also had at least one comorbidity, and when these were present, 1-year survival was significantly worse. In a multivariate model, patients on dialysis had twofold greater mortality than did those not on dialysis, patients with severe tricuspid valve regurgitation had twice the mortality of those with lesser or no tricuspid regurgitation, and patients with moderate or severe lung disease had a 50% higher mortality, compared with those with milder or no lung disease.

The study was supported in part by Abbott Vascular, the company that markets the MitraClip. Dr. Sorajja has been a consultant to and speaker on behalf of Abbott Vascular. He has also been a consultant to Integer, Lake Region Medical, and Medtronic, and a speaker on behalf of Boston Scientific.

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PAP sensor may cut real-world heart failure hospitalization

BY MARY ANN MOON
Frontline Medical News

Implantation of a pulmonary artery pressure sensor to guide care in chronic heart failure was associated with a significant 45% reduction in HF hospitalization and its attendant substantial costs in a real-world patient population, Akshay S. Desai, MD, said at the annual meeting of the American College of Cardiology.

The PAP sensor is used to monitor pulmonary artery filling pressure, which rises in many HF patients during the weeks preceding an HF exacerbation. This early detection of progressing congestion allows clinicians to intervene earlier and head off hospitalization for the exacerbation.

In a manufacturer-sponsored retrospective observational study using Medicare claims data, investigators compared the rate of HF hospitalizations during the 6 months preceding sensor implantation against that during the 6 months following implantation in 1,114 patients.

Their intention was to determine whether the positive results of the CHAMPION clinical trial, which prompted Food and Drug Administration approval of the device as a means to reduce HF-associated hospitalizations, could be replicated in a real-world population, said Dr. Desai of Brigham and Women's Hospital, Boston.

The results of their study were presented March 19 at the annual meeting of the American College of Cardiology and simultaneously published online in the Journal of the American College of Cardiology (2017 Mar 19. doi: 10.1016/j.jacc.2017.03.009).

The mean age of the study cohort was 71 years, and 40% of the participants were at least 75 years of age. Women composed 40% of the cohort. There was a high burden of comorbid illness, including diabetes, hypertension, and chronic obstructive pulmonary disease. This represents a broader sample than

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was enrolled in the CHAMPION trial, he noted.

There were 1,020 HF hospitalizations before implantation and 381 afterward. A total of 59% of patients had at least one HF hospitalization before the PAP implantation, compared with 22% afterward. The median number of HF hospitalizations was 0.92 per patient before implantation and 0.37 per patient afterward.

Further analysis showed that the cumulative rate of HF hospitalization was 45% lower during the 6 months after implantation than during the 6 months preceding it (hazard ratio, 0.55). This finding remained robust across several subgroups of patients.

These reductions were associated with a corresponding decline in costs related to HF care, which dropped by $7,433 per patient.

In addition to HF-related hospitalizations, all-cause hospitalizations also declined by roughly 30% after implantation of a PAP sensor (HR, 0.69).

These findings suggest that the reduction in hospitalizations, along with attendant reductions in the costs of care, may be achievable in real-world practice. The 45% drop in HF hospitalizations in this study "compares favorably with the 28% reduction seen with PAP-guided therapy over the same time period in the randomized CHAMPION study that supported the initial FDA approval," Dr. Desai said.

Moreover, a subgroup of 480 patients had data for 12 months preceding and 12 months following implantation. Analysis of those data showed that the benefits of PAP monitoring to guide HF care "were consistent over longer-term follow-up, with a 34% reduction in HF hospitalizations sustained at 12 months," he added.

The study had several limitations. It excluded Medicare Part D data, so medication changes related to implantation could not be examined and may have exerted substantial influence on study outcomes.

It also didn't include the actual PAP-sensor data, "which makes it challenging to confirm that physicians intervened to treat elevated PAPs" and that intervention is the reason for the study outcomes.

"We were unable to definitively ascertain whether reduced HF hospitalizations are related to undertreatment in the preimplant period or improved treatment in the postimplant period," Dr. Desai said.

The study was sponsored by Abbott, maker of the CardioMEMS PAP sensor. Dr. Desai and his associates reported ties to Abbott and St. Jude Medical.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: This retrospective study based on administrative Medicare Claims data on 1,114 elderly patients in NYHA class III who received a pulmonary artery pressure sensor (PAP sensor) confirms the findings of the original Champion trial (Lancet. 2011; 377: 658-66) that the use of this wireless device is significantly reducing the rate of heart failure hospitalization and is reducing costs. As compared to the Champion trial, the sample size was almost twice that of that trial and patients were older and with more comorbidities. The results of this study are encouraging for both the practitioners engaged in the management of patients with advanced heart failure and the hospital administrators.

Pathways cut costs without compromising outcomes

BY SUSAN LONDON
Frontline Medical News

ORLANDO – Implementation of clinical pathways aimed at improving appropriate, evidence-based care for patients with metastatic non–small-cell lung cancer (NSCLC) reduces costs without negatively affecting survival, the Dana-Farber Cancer Institute's experience suggests.

"At Dana-Farber ... we have looked toward pathways as a potential tool to help manage complexity and resource utilization," senior author David M. Jackman, MD, explained at a symposium on quality care sponsored by the American Society of Clinical Oncology. "We see pathways as a patient-centered platform that provides real-time decision-making support across the continuum of cancer care. We think that these should be based on preemptive decision making, reflect current standards of care, incorporate feedback from which we can learn from our practice patterns, and support clinical research."

SUSAN LONDON/FRONTLINE MEDICAL NEWS

Dr. David M. Jackman: "[We hope] pathways can be an area for innovation."

After the customized Dana-Farber Lung Pathways were implemented in 2014, the cost of outpatient care per patient in the first year after diagnosis fell by about $17,000, or 25%, primarily driven by reduced use of antineoplastic agents, according to data reported at the symposium and simultaneously published (J Oncol Pract. 2017 Mar 4. doi: 10.1200/JOP.2017.021741). Meanwhile, median survival remained at about 11 months, even trending slightly upward.

"Frankly, I'd like to think that we were delivering reasonable and expert care prior to 2014, so I did not anticipate that we were going to see a major change in terms of improvement in survival. But it is important for us to make sure that, as we implemented pathways, there was certainly no decrease in such care," said Dr. Jackman, medical director of clinical pathways at Dana-Farber and an assistant professor of medicine, Harvard Medical School, Boston.

He and his colleagues plan to expand pathways to cover the full spectrum of cancer care at their center, encompassing medical, radiation, and surgical oncology, he said.

"We also think that pathways can have a major impact on things like symptom management and survi-

vorship care," he added. "And as we work to embed all of our trials within our pathways system, and as we push to have our trials in our satellites and in our network affiliates, we hope that this combination of activity can help move us from being not just a good care network, but also a research network."

The pathways will still have to address some of the thornier issues related to the value of care, Dr. Jackman acknowledged "It's incredibly easy for us to look at two equivalent therapies in terms of toxicity and efficacy and pick the cheaper one. The harder conversations are to come, that is, what if something is x dollars more expensive and only improves things by a small number of months, is it really worth it?

"Finally, we hope that pathways can be an area for innovation, not used solely to manage costs and to make decisions based on yesteryear, but also to help us move forward and to be the watering hole where everybody comes, as we build out our system that is looking granularly at genomics in order to help match patients with trial opportunities, and for researchers, to help them find specific patients for their trials," he said. "Pathways can potentially be the nexus where everyone comes and

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where doctors are informed in real time about opportunities for their patients."

More evidence of benefit

The Dana-Farber study adds to others showing that the benefits of pathways are real and reproducible, according to invited discussant Thomas J. Smith, MD, professor of oncology and palliative medicine at Johns Hopkins Medicine in Baltimore.

"We need to know how much the intervention costs. The fact that you can purchase it from a vendor is a great idea, but it has to then be less than the cost of the savings that you will have," he said. "We also have to be cognizant that it reduces costs, also known as income to the center that administers these. So as a former service-line manager in oncology, I'd be very interested to know what impact this had on our total bottom line."

Susan London/Frontline Medical News

Dr. Thomas J. Smith: "We need to know [what] the intervention costs."

"More importantly, I think, for patients, who are getting hit with these bills and might have a 20% copay, it's going to reduce their copays and for all the right reasons," Dr. Smith concluded.

Pathways development

In developing the pathways, Dana-Farber began with lung cancer in part because the center sees a high volume of patients with the disease. In addition, decision making for this malignancy is complex, and there was considerable variation in oncologists' practices.

"Our platform exists as an independent web-based system that currently lives outside of our EMR. Physicians can access this in real time, in the clinic room with the patient if they so choose," Dr. Jackman explained. "From our EMR, we are flagged every time a provider orders a new start [of therapy], whether it's IV chemo, oral chemo, or hormonal therapy. From our vendor, we receive granular treatment decision information made within the pathways system – information about the provider and site, information about the patients, their disease, and the line of therapy, as well as other important factors that drive decision making. Finally, from our clinical trials system interface, we can confirm trial enrollment data."

Oncologists are free to leave the suggested pathway if their clinical judgment favors an alternative course, according to Dr. Jackman.

"We always want our physicians to feel comfortable treating the patients in front of them however they see best fit. If that means an off-pathway therapy, we want them to have the freedom to do that," he said. "But we think one of the major tools of the pathways is to help capture the reasons why. So if they think it's warranted and appropriate, go ahead, go off pathway, but tell us why you are doing it so we can learn from it."

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Real-world EGFR and ALK testing of NSCLC falls short

BY SUSAN LONDON
Frontline Medical News

ORLANDO – A large proportion of patients with advanced non–small cell lung cancer (NSCLC) are not being tested for tumor associated–epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations according to national guidelines. This situation may be leading to suboptimal treatment, a large retrospective cohort study suggests.

Guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend testing before first-line therapy for all treatment-eligible patients with nonsquamous histology and for those patients with squamous histology who are nonsmokers or who have mixed cell types or small tumor samples. Additionally, the guidelines recommend that results be made available within 2 weeks of the lab's receipt of the sample so that they can be used to inform treatment decisions.

However, the analysis of more than 16,000 community-oncology patients with advanced NSCLC treated in real-world practice found high variation in EGFR and ALK testing rates across clinics, with some not testing any patients and others testing all of them, according to findings reported at a symposium on quality care sponsored by the American Society of Clinical Oncology.

Overall, 22% of patients with nonsquamous tumors had no evidence of EGFR and ALK testing in their records. The large majority of patients with squamous tumors did not have any evidence of testing either, and it was unclear how well testing corresponded with the criteria.

In roughly a third of cases in which testing was done, the time between diagnosis of advanced disease and availability of test results exceeded 4 weeks. Among patients with positive test results, those whose results came back after the start of first-line therapy, were about half as likely to appropriately receive a therapy that targeted their tumor's molecular aberration.

"We observed variation in adherence to [the American Society of Clinical Oncology] and [the National Comprehensive Cancer Network]

Continued on following page

Susan London/Frontline Medical News

"If we had done this for PD-L1 [programmed death ligand 1] testing, perhaps we might have thought about some lag in adoption," Jay Rughani said.

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Using pathways has not proved burdensome, according to Dr. Jackman. Navigating through the system requires about a minute or two, and use is required only when a patient is starting a new therapy, which typically occurs less than once per half-day clinic session.

Study details

In the study, he and colleagues compared costs of care in the first year after diagnosis of stage IV NSCLC between 160 patients treated at Dana-Farber in 2012 (before pathways implementation) and 210 patients treated there in 2014 (after pathways implementation).

"It should be noted that, because we are a free-standing outpatient cancer center, all of the costs that we were able to gather are intramural and therefore related only to outpatient activities," he pointed out.

The total annual costs of care per patient, adjusted for potential confounders (age, sex, race, distance to the institute, clinical trial enrollment, and epidermal growth factor receptor and anaplastic lymphoma kinase status) fell by $17,085 after implementation of pathways, from $69,122 to $52,037 ($P = .01$), he reported.

The largest source of cost savings by far, accounting for 73% of the total, was reduced use of antineoplastic agents (chemotherapy, biologics, and other anticancer agents). Cost for this component fell from $44,237 per patient to $31,846 ($P$ less than .01).

"The majority of this savings came through a reduction in the use of what we considered unwarranted use of combination chemotherapy," Dr. Jackman said. "In the first-line setting, we specifically went after the regimen of carboplatin, pemetrexed, and bevacizumab; based on our interpretation of the PointBreak study, we felt that that regimen did not bring additional efficacy but did essentially double drug costs. In going after that, we reduced not only use of that but also the subsequent use of pemetrexed plus bevacizumab maintenance. In the second-line setting, with the implementation of pathways, we saw a decrease in the use of inappropriate platinum-based doublet therapy in those patients who had previously progressed on a platinum-based doublet."

Median overall survival did not decrease and in fact increased slightly, from 10.7 months before pathways implementation to 11.2 months afterward ($P = .08$). Corresponding 1-year rates of survival were 52% and 64%.

"We stand on the shoulders of those who came before us, who have also shown savings associated with implementation of pathways," concluded Dr. Jackman. "But we hope that we add our voice and our data to this argument that pathways, I think, are a reasonable tool as we try to manage complexity and resource utilization. In addition, we do so without impinging upon clinical outcomes."

Dr. Jackman disclosed that he is an adviser or consultant to Bayer, Celgene, CVS Caremark, Genentech, and Lilly.

Age and disease stage predict long-term survival in elderly lung cancer patients

BY DOUG BRUNK
Frontline Medical News

HOUSTON – Although certain medical factors predict long-term survival in patients over age 65 years with lung cancer, advanced age and disease stage are especially strong predictors, results from a large analysis of national data demonstrated.

The findings, which were presented by Mark Onaitis, MD, at the annual meeting of the Society of Thoracic Surgeons, come from a novel effort to pair Medicare data with files from the STS General Thoracic Surgery Database (GTSD).

"Surgeons in the STS database do an excellent job taking care of these patients," Dr. Onaitis, a thoracic surgeon at the University of California, San Diego, said in an interview. "The current survival model will allow surgeons to better estimate long-term survival of each individual patient. In addition, future analyses will identify subgroups of patients that may benefit from specific surgical approaches and procedures."

For the current study, he and his associates linked GTSD data to Medicare data on 29,899 patients who underwent lung cancer resection from 2002 to 2013. They used Cox proportional hazards modeling to create a long-term survival model and used statistically significant univariate factors and known clinical predictors of outcome to perform variable selection.

"The deleterious effects of sublobar operations and open approach were more pronounced than expected."

DR. ONAITIS

Dr. Onaitis reported that the median age of patients was 73 years and that 52% were female. Of the 29,899 patients, 805 had a missing pathologic stage. Of the 29,094 patients not missing a pathologic stage, 69% were stage I, 18% stage II, 11% stage III, and 2% stage IV. Two-thirds of patients (66%) underwent lobectomy, followed by wedge resection (17%), segmentectomy (7%), bilobectomy (3%), pneumonectomy (3%), and sleeve lobectomy (1%). A thoracoscopic approach was performed in nearly half of resections (47%).

Cox analysis revealed the following strong negative predictors of long-term survival: having stage III or IV-V disease (hazard ratio, 1.23 and 1.37, respectively), and being age 70-74 (HR, 1.19), 75-80 (HR, 1.40), or 80 and older (HR, 1.90).

After disease stage was controlled for, the following procedures were associated with increased hazard of death, compared with lobectomy: wedge resection (HR, 1.22), segmentectomy (HR, 1.10), bilobectomy (HR, 1.30), and pneumonectomy (HR, 1.58). In addition, video-assisted thoracoscopic surgery was associated with improved long-term survival, compared with thoracotomy (HR, 0.86).

"Given the large number of patients and the excellent quality of the data, it was not surprising that age and stage and known medical conditions affect long-term survival," Dr. Onaitis commented. "The deleterious effects of sublobar operations and open [as opposed to thoracoscopic or VATS] approach were more pronounced than expected."

Other modifiable predictive factors include being a past or current smoker (HR, 1.35 and HR, 1.54, respectively) and having a body mass index below 18.5 kg/m^2 (HR, 1.58).

Dr. Onaitis acknowledged certain limitations of the study, including its retrospective design. "Because the study involves linkage of STS data to Medicare data, the findings may not be applicable to patients less than 65 years of age," he added. He reported having no financial disclosures.

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guidelines around biomarker testing in advanced NSCLC, and we saw significant variation in testing in the squamous population and the nonsquamous population across practices," presenting author Jay Rughani, manager of Life Sciences at Flatiron Health, New York, commented in an interview. Observed delays in availability of test results were mainly driven by delays between diagnosis and submission of samples to the lab for testing.

"There may be an opportunity to educate the oncology community around testing, certainly for all nonsquamous patients, because this is a case where they all should have been tested," he said. "And there is also an opportunity to ensure testing of the appropriate squamous cell patients, while discouraging the testing of the majority who aren't candidates, so there may be an opportunity for education around smoking status."

Slow uptake of the national guidelines is unlikely to explain the observed variations in testing, according to Mr. Rughani. "Since we looked at patients diagnosed after Jan. 1, 2014, our impression was that the guidelines were sort of disseminated enough and widely known enough by that point, particularly around EGFR and ALK, that we wouldn't expect any lag there. If we had done this for PD-L1 [programmed death ligand 1] testing, perhaps we might have thought about some lag in adoption."

The impact of variations in testing and receipt of inappropriate initial therapy on clinical outcomes is yet to be determined. "As a follow-on, some of the work we have been doing is trying to understand, for these separate cohorts of patients, depending on what they received in the front line, what their overall survival was and what their surrogate endpoints were," Mr. Rughani concluded.

Study details

For the study, the investigators identified 16,316 patients with advanced NSCLC from 206 community clinics across the United States participating in the Flatiron Network. All patients were treated between 2014 and 2016.

Cross-checking of the total Flatiron population against the National Program of Cancer Registries and Surveillance, Epidemiology, and End Results databases suggested that it is a good national representation, according to Mr. Rughani.

A record review showed that the rate of EGFR and ALK testing among study patients ranged widely across clinics, from 0% to 100% for both the nonsquamous cases and the squamous cases, according to results reported in a poster session. The median was 79% for the former and 16% for the latter.

Overall, 22% of the nonsquamous cohort and 79% of the squamous cohort did not have any evidence of testing in their records. For the latter, a sampling of records was unable to verify whether testing was appropriately matched to eligibility criteria.

"The delays were mostly attributed to nonlab factors. When we isolated the time that the lab took to turn [test results] around, it was under 2 weeks for the vast majority of patients," noted Mr. Rughani.

When testing was performed, 35% of EGFR test results and 37% of ALK test results were not available to the treating clinician until more than 4 weeks after the date of the advanced cancer diagnosis.

"The delays were mostly attributed to nonlab factors. When we isolated the time that the lab took to turn it around, it was under 2 weeks for the vast majority of patients," Mr. Rughani reported. Possible nonlab culprit factors include clinic work flows, insurance-related issues, and families' and patients' hesitancy to be tested, he said.

Delays in receipt of positive test results appeared to influence choice of first-line therapy. Among patients in whom these results were available before first-line therapy, 80% of those found to have an EGFR-mutated tumor received an EGFR–tyrosine kinase inhibitor, and 77% of those found to have ALK-rearranged tumors received an ALK inhibitor.

In sharp contrast, among patients in whom positive test results did not become available until after the start of first-line therapy, respective values were just 43% and 42%.

"Anecdotally, we saw that some patients would go on to Avastin [bevacizumab] in the front line when the results were delayed, and then, ultimately, they would have the opportunity to receive an EGFR[–tyrosine kinase inhibitor] or something like that in later lines," commented Mr. Rughani. "So, that impacted treatment decisions there."

Mr. Rughani disclosed stock and other ownership interests in Flatiron Health.

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

For appropriate adult patients

CONSIDER MAKING **24-HOUR BREO** YOUR GO-TO ICS/LABA OPTION

BREO 100/25 is for maintenance treatment of airflow obstruction in patients with COPD, and for reducing COPD exacerbations in patients with a history of exacerbations. BREO 100/25 is the only strength indicated for COPD.

BREO is 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.

BOXED WARNING CONTINUED ON NEXT PAGE

Please see additional Important Safety Information for BREO on pages 2–4.
Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

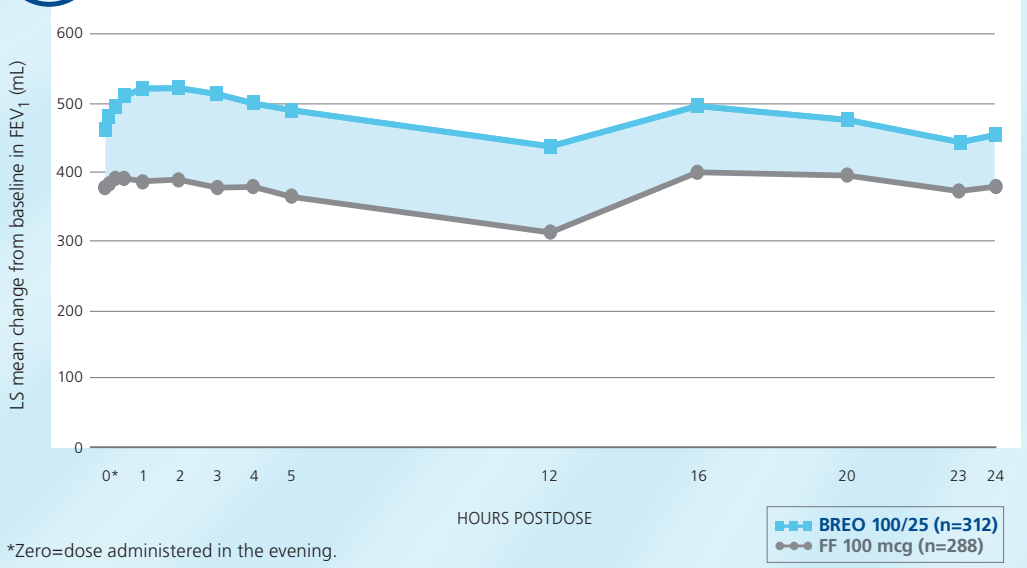
BREO:
CONTINUOUS LUNG FUNCTION IMPROVEMENT

In patients with **asthma** uncontrolled on an ICS

BREO 100/25 (n=312) provided a 108-mL improvement from baseline in weighted mean (wm) FEV_1 (0-24 hours) vs fluticasone furoate (FF) 100 mcg (n=288) at Week 12 (*P*<0.001).[1]

BREO 100/25

SERIAL FEV_1 (0-24 HOURS) AT WEEK 12[1]



*Zero=dose administered in the evening.

Study description

Design: 12-week, randomized, double-blind study that evaluated the safety and efficacy of BREO 100/25, BREO 200/25, and FF 100 mcg (each administered once daily in the evening). Patients who reported symptoms and/or rescue $beta_2$-agonist use during a 4-week run-in period on mid- to high-dose ICS (≥250 mcg fluticasone propionate [FP] twice daily or equivalent) were randomized to treatment.

Patients: 1039 patients with asthma aged 12 years and older[††] (mean age: 46 years). At baseline, patients had a mean percent predicted FEV_1 of 62%.

[††] BREO is approved for use in patients ≥18 years of age.

Primary endpoint: wm FEV_1 (0-24 hours) at Week 12.

Weighted mean FEV_1 (0-24 hours) was calculated from predose FEV_1 (within 30 minutes of dose) and postdose FEV_1 after 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours.

FEV_1=forced expiratory volume in 1 second; LS=least squares.

In a placebo-controlled 12-week study[2]:

- **wm FEV_1:** in a subset of patients, BREO 100/25 (n=108) demonstrated a numerically greater improvement in change from baseline in wm FEV_1 (0-24 hours) compared with FF 100 mcg (n=106) of 116 mL (95% CI: –5, 236; *P*=0.06) and a statistically significant 302-mL improvement (*P*<0.001) compared with placebo (n=95) at Week 12.

Study description: 12-week, randomized, double-blind, placebo-controlled study of 609 patients aged 12 years and older[†] (mean age: 40 years) with asthma, symptomatic on low- to mid-dose ICS (FP 100 mcg to 250 mcg twice daily or equivalent) during a 4-week run-in period (mean baseline percent predicted FEV_1 of 70%) randomized to BREO 100/25, FF 100 mcg, or placebo (each administered once daily in the evening). The co-primary endpoints were weighted mean FEV_1 (0-24 hours) (in a subset of patients) and trough FEV_1 at Week 12.

[†] BREO is approved for use in patients ≥18 years of age.

Important Safety Information (cont'd)

WARNING: ASTHMA-RELATED DEATH
(BOXED WARNING cont'd)

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

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.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

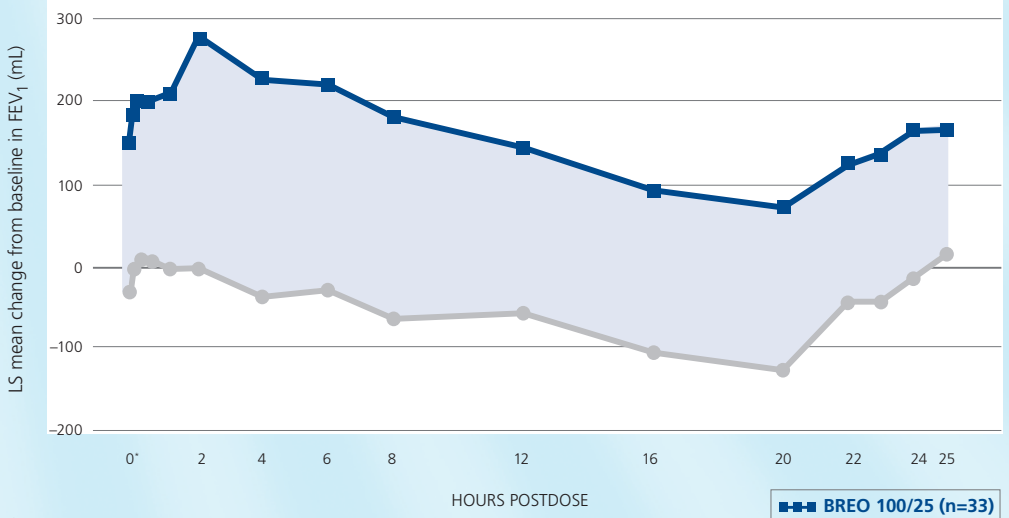
FOR A FULL 24 HOURS, WITH JUST ONE DAILY INHALATION

In patients with COPD

BREO 100/25 (n=33) provided a 220-mL improvement from baseline in wm FEV_1 (0-24 hours) vs placebo (n=51) at end of the 28-day treatment period (*P*<0.001).[3,4]

BREO 100/25

SERIAL FEV_1 (0-25 HOURS) ASSESSED OVER 1 FULL DAY AT DAYS 28 AND 29[3,4]



*Zero=dose administered in the morning.

Study description

Design: randomized, double-blind, crossover study compared the effect of 28 days of treatment with BREO 100/25 and placebo (each administered once daily in the morning) on lung function over 24 hours.

Patients: 54 patients (mean age: 58 years) with COPD who had a mean percent predicted postbronchodilator FEV_1 of 50% and a mean postbronchodilator FEV_1/FVC ratio of 53%.

Primary endpoint: wm FEV_1 (0-24 hours) at end of 28-day treatment period.

Secondary endpoint: serial FEV_1 (0-25 hours) assessed over 1 full day at Days 28 and 29.

FVC=forced vital capacity.

BREO 100/25 is the only strength indicated for COPD.

In a separate 6-month lung-function study: a randomized, double-blind, parallel-group study compared the effect of BREO 100/25 vs FF 100 mcg and vs placebo (each administered once daily) on lung function in 1030 patients (mean age: 63 years) with COPD.[§] For the co-primary endpoints, BREO significantly improved wm FEV_1 (0-4 hours) postdose on Day 168 by 120 mL vs FF[‖] and 173 mL vs placebo (*P*<0.001 for both); and BREO demonstrated a greater difference in LS mean change from baseline in trough FEV_1 at Day 169 of 115 mL vs placebo (95% CI: 60, 169; *P*<0.001); the 48-mL difference vs vilanterol (VI) 25 mcg[¶] did not achieve statistical significance (95% CI: –6, 102; *P*=0.082).[3,5]

[§]At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 48% and a mean postbronchodilator FEV_1/FVC ratio of 48%.
[‖]The wm comparison of BREO with FF, the ICS component, evaluated the contribution of VI to BREO. ICS are not approved as monotherapy for COPD.
[¶]The trough FEV_1 comparison of BREO with VI, the LABA component, evaluated the contribution of FF to BREO. VI is not approved as monotherapy.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- 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.
- An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal.
  - In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO 100/25 (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and BREO 200/25 (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (<1% for each treatment group).

References: 1. Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. *J Asthma*. 2015;52(10):1073-1083. **2.** Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract*. 2014;2(5):553-561. **3.** Data on file, GSK. **4.** Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clin Ther*. 2012;34(8):1655-1666. **5.** Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. *Respir Med*. 2013;107(4):560-569.

Please see additional Important Safety Information for BREO on pages 1, 2, and 4.

Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

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

CONSIDER **24-HOUR BREO** TODAY

Important Safety Information (cont'd)
WARNINGS AND PRECAUTIONS (cont'd)

- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- 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 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. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter.
- 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: BREO 100/25 FOR COPD

- The most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).
- In addition to the events reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects with COPD treated with BREO in two 1-year studies included back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

ADVERSE REACTIONS: BREO FOR ASTHMA

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

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- 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 additional Important Safety Information for BREO on pages 1–3.
Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

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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; 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

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease:
BREO 100/25 is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/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. BREO 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 once daily is the only strength indicated for the treatment of COPD.
Important Limitation of Use: BREO is NOT indicated for the relief of acute bronchospasm.

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. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

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.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO 100/25 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 reevaluation of the patient and the COPD treatment regimen should be undertaken at once. For COPD, increasing the daily dose of BREO 100/25 is not appropriate in this situation.

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.

5.5 Pneumonia:
An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO 100/25 in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

In replicate 12-month trials in 3,255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving fluticasone furoate/vilanterol 50 mcg/25 mcg: 6% (48 of 820 subjects); BREO 100/25: 6% (51 of 806 subjects); or BREO 200/25: 7% (55 of 811 subjects) than in subjects receiving vilanterol 25 mcg: 3% (27 of 818 subjects). There was no fatal pneumonia in subjects receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (less than 1% for each treatment group).

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,

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

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)]*; Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; 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.

6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:
The clinical program for BREO included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects with COPD received at least 1 dose of BREO 100/25, and 1,087 subjects received a higher strength of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6- and 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 BREO 100/25 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n=1,224 and n=1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were white. They had a mean age of 62 years and an average smoking history of 44 pack-years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%). Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

In Trials 1 and 2, adverse reactions (≥3% incidence and more common than placebo) reported in subjects with COPD taking BREO 100/25 (n=410) (vilanterol 25 mcg [n=408]; fluticasone furoate [n=410]; or placebo [n=412]) were: nasopharyngitis 9% (10%, 8%, 8%); upper respiratory tract infection 7% (5%, 4%, 3%); headache 7% (9%, 7%, 5%); and oropharyngeal candidiasis 5% (2%, 3%, 2%). Oropharyngeal candidiasis includes oral candidiasis, candidiasis, and fungal oropharyngitis.

12-Month Trials: Long-term safety data is based on two 12-month trials (Trials 3 and 4; n=1,633 and n=1,622, respectively). Trials 3 and 4 included 3,255 subjects, of which 57% were male and 85% were white. They had a mean age of 64 years and an average smoking history of 46 pack-years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 12% to 91%), and the mean postbronchodilator FEV_1/FVC ratio was 46% (range: 17% to 81%), indicating that the subject population had moderate to very severely impaired airflow obstruction. Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, or vilanterol 25 mcg. In addition to the reactions previously mentioned, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO 100/25 (n=806) for 12 months included back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

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

Continued on next page

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 COPD included 2,508 subjects aged 65 and older and 564 subjects aged 75 and older. 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.

Pneumonia:
Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

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.

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App may improve PAP adherence

BY KATIE WAGNER LENNON
Frontline Medical News

Use of a mobile app may help sleep apnea patients adhere to positive airway pressure (PAP) therapy, a small study suggests.

The app – SleepMapper (SM) – has interactive algorithms that are modeled on the same theories of behavior change that have improved adherence to PAP when delivered in person or through telephone-linked communication, wrote Jordanna M. Hostler of Walter Reed National Military Medical Center, Bethesda, Md., and her coinvestigators in the Journal of Sleep Research (2017;26:139-46).

"Despite our small sample size, patients in the SM group were more than three times as likely to meet Medicare criteria for [PAP] adherence (greater than 4 hours per night for 70% of nights), a trend that just missed statistical significance (P = .06)," the researchers noted.

"The magnitude of the increase [in PAP use] indicates likely clinical benefit," they added.

SleepMapper allows patients to self-monitor the outcomes of positive airway pressure therapy by providing information on their adherence, Apnea-Hypopnea Index, and mask leak. The app also includes training modules on how to use PAP. The system, owned by Phillips Respironics, will sync with the Encore Anywhere software program.

The study comprised 61 patients who had been diagnosed with obstructive sleep apnea (OSA) via overnight, in-lab polysomnography. The patients were initiating PAP for the first time at Walter Reed National Military Medical Center's Sleep Disorders Center in Bethesda, Md., through the center's program. This program included group sessions with instruction on sleep hygiene and training in the use of PAP, an initial one-on-one meeting with a physician, and a follow-up appointment with a physician 4 weeks after initiating the therapy. Thirty of the program's participants used SleepMapper in addition to the center's standard education and follow-up. The researchers analyzed 11 weeks of data for all 61 study participants.

Patients in the SleepMapper group used their PAP machines for a greater percentage of days and achieved more than 4 hours of use on more days of participation in the program, compared with patients who did not use the app. The patients using the app also showed a trend toward using PAP for more hours per night overall. Specifically, nine of the patients in the app group used their PAP machines greater than 4 hours per night for 70% of nights, versus three of the patients in the control group (P = .06). SleepMapper usage remained significantly associated with percentage of nights including greater than 4 hours of PAP use, in a multivariate linear regression analysis.

Some additional advantages to use of SleepMapper over simply participating in the center's educational program are that the app provides ongoing coaching and immediate access to Apnea-Hypopnea Index and PAP use data, according to the researchers. They touted the app's educational videos about OSA and PAP therapy and "structured motivational enhancement techniques such as feedback and goal setting, which have shown benefit when delivered by health care professionals in other studies."

The researchers observed many similarities between patients in both groups, including Apnea-Hypopnea Index scores, central apnea index scores, and percentages of time spent in periodic breathing.

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VIEW ON THE NEWS

David A. Schulman, MD, FCCP, comments: Feedback to patients regarding their clinical status is rarely a bad thing. I'm a big fan of tools that give patients information on their CPAP adherence and outcomes, of which several now exist, including some that are not affiliated with any particular respiratory device company, and are able to read a number of different device downloads. The referenced study by Hostler et al. showed a statistically significant improvement in the number of nights adherent (defined as greater than 4 hours of CPAP use) at 54% for the intervention group versus 37% for the standard group (P = .02), even though improvement in the percentage documented as adherent by Medicare standards did not reach statistical significance. While this latter finding is an important outcome for economic purposes, any improvement in adherence at all should be looked upon as a favorable endpoint.

In the end, the use of technology for monitoring CPAP adherence is here to stay, and the incremental cost of making it available to our patients is low. Taking the time to educate patients who are newly prescribed CPAP about interpreting their outcome data is likely to be time well spent.

OSA tool uncovers risks of postoperative complications

BY ELI ZIMMERMAN
Frontline Medical News

High scores on the symptomless multivariable apnea prediction index (sMVAP) showed a strong correlation with increased risk for postsurgery complications, according to a study approved by the University of Pennsylvania, Philadelphia.

This validation helps assert the benefits of using the sMVAP as a tool to screen for obstructive sleep apnea (OSA) before elective inpatient surgeries, a test that is highly underutilized but very important, wrote M. Melanie Lyons, PhD, of the Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, and her colleagues.

"Most patients having elective surgery are not screened for obstructive sleep apnea, even though OSA is a risk factor for postoperative complications," wrote Dr. Lyons and her colleagues. "We observe that sMVAP correlates with higher risk for OSA, hypertension, and select postoperative complications, particularly in non-bariatric groups without routine preoperative screening for OSA."

In a retrospective study of 40,432 patients undergoing elective surgery, high sMVAP scores were strongly correlated with postoperative complications including longer hospital stays (odd ratio, 1.83), stays in the ICU (OR, 1.44), and respiratory complications (OR, 1.85) according to the researchers (Sleep. 2017 Jan 6. doi: 10.1093/sleep/zsw081).

Researchers separated participants into 10 categories according to the type of procedure: bariatric, orthopedic, cardiac, gastrointestinal, genitourinary, neurological, otorhinolaryngology/oral-maxillofacial/ear-nose-throat, pulmonary/thoracic, spine, and vascular.

The sMVAP calculates risk factors for OSA based on gender, age, and body mass index, the researchers noted. Those in the highest sMVAP score quintile were predominantly male (58%), with average age of 61 years, and average BMI of 40.9 kg/m^2 (indicating morbid obesity). These patients reported the highest prevalence of having been previously diagnosed with OSA (26%). Comparatively, those patients in the lowest sMVAP quintile reported the lowest prevalence of an OSA diagnosis prior to undergoing their surgeries (9.3%). Among non–bariatric surgery patients, those undergoing orthopedic procedures showed the highest correlation between complications and sMVAP scores. The orthopedic surgery category reported a higher percentage of ICU-stay compared with bariatric surgery (14.3% vs 5.4%, P less than .0001), despite 23% of the patients who underwent an orthopedic surgery reporting previous OSA, compared with 50% of those who underwent surgery in the bariatric category.

This difference in previously reported OSA, according to Dr. Lyons and her colleagues, shows another example of the need for sMVAP in non–bariatric surgery preoperative procedure as a way to catch potentially undiagnosed OSA.

"[W]ork by Penn Bariatrics suggests that it is logical that the benefits of rigorous preoperative screening and diagnosis for OSA followed by a tailored team approach toward ensuring compliance toward treatment postoperation ... may be effective in limiting the likelihood of select postoperative complications," the researchers wrote.

With 9.3% of all patients diagnosed with OSA, and a projected 14%-47% increase in specialty surgeries, there is an urgency in implementation of sMVAP and in conducting further studies, they noted. Two of the study's authors reported receiving grants.

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SLEEP STRATEGIES Sleep in adults with Down syndrome

BY FIDAA SHAIB, MD, FCCP, FAASM

Down syndrome (DS) is the most common chromosomal disorder with an estimated 250,700 children, teens, and adults living with DS in the United States in 2008 (CDC.gov). The life expectancy for individuals with DS has increased due to improved medical care, educational interventions, and identification and management of underlying psychiatric and behavioral problems. This has resulted in increased median age to 49 years, and the life expectancy of a 1-year-old child with DS to more than 60 to 65 years (Bittles et al. *Dev Med Child Neurol.* 2004;46[4]:282).


DR. SHAIB

Sleep medicine specialists have been very involved in the care of the pediatric DS population but with the improved survival, more adult patients with DS are presenting to sleep clinics for their care. The complexity of caring for adult patients with DS poses a challenge to sleep specialists, especially with the paucity of literature and clinical guidelines.

OSA is more prevalent in children with DS (30% to 55%) compared with control subjects (2%). This high OSA prevalence further increases to 90% in adults with DS and is associated with more oxygen desaturation, hypoventilation, and sleep disruption (Trois et al. *J Clin Sleep Med.* 2009;5[4]:317). Childhood risk factors for OSA in DS are mostly related to hypotonia, relatively large tongue, tonsillar and adenoid hypertrophy, and the small airway. Obesity, hypothyroidism, and, more importantly, advancing age contribute to the increased risk of OSA in adults with DS. Central sleep apnea is relatively rare in adults with DS (Esbensen. *Int Rev Res Ment Retard.* 2010;39(C):107).

A bidirectional relationship exists between sleep disorders and mood and cognitive problems in this population. The frequency of OSA diagnosis is increased in adults with DS who present with new-onset mood disorder or declining adaptive skills (Capone et al. *Am J Med Genet A.* 2013;161A[9]:2188). OSA in DS is associated with sleep disruption, decreased slow wave sleep, and intermittent hypoxemia that are thought to contribute to the mechanism of declining cognitive function and memory. Given that individuals with DS are genetically at increased risk for diffuse senile plaque formation in the brain (a characteristic pathologic finding in Alzheimer's disease brain), the super-imposed sleep fragmentation and intermittent hypoxia may accelerate the cognitive decline (Fernandez et al. *J Alzheimers Dis Parkinsonism.* 2013;3[2]:124).

In addition, sleep in adults with DS is characterized by a high incidence of sleep fragmentation and circadian misalignment with delayed sleep onset and early morning

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awakenings (Esbensen. *J Intellect Disabil Res.* 2016;60[1]:68). The DS population is also at increased risk for developing depression, anxiety, obsessive-compulsive tendencies, and behavioral issues. It is also worth noting that there is a tenfold increase in autism spectrum disease in this population, and a rare condition of developmental regression in adolescents with DS has recently been recognized. Patients usually present with rapid, atypical loss of previously attained skills in cognition, socialization, and activities of daily living that may further complicate their care. The regression occurs with maladaptive behaviors that develop in relation to new transitions, hormonal or menstrual changes, or major life events (Jensen et al. *Br Med J.* 2014;349:g5596). As a result, new behavioral sleep problems may emerge, or challenges to the treatment of existing sleep disorders may ensue.

All of the aforementioned conditions alone or in combination pose additional challenges for the management of sleep problems in this population.

Adults with DS continue to manifest the same spectrum of health problems as children with DS. Adults with DS also tend toward premature aging, which puts them

at risk for additional health problems seen in the geriatric population (Covelli et al. *Int J Rehabil Res.* 2016;39[1]:20). Adults with DS will age earlier and two times faster than control subjects (Nakamura et al. *Mech Ageing Dev.* 1998;05:89). Coexisting obesity and worsening cognitive function that further increase after the age of 40 will make multiple aspects of medical management very challenging (Carfi et al. *Front Med.* 2014;1:51).

The care of the adult patient with DS can be best delivered through a multidisciplinary team, led by physicians well informed about the specific needs of this population. The role of the sleep specialist is essential, given the implications of sleep on health and cognitive and behavioral function. The approach to diagnosing disorders of sleep timing, quality, and duration includes a focused history. Incorporating actigraphic monitoring provides additional information that can be relevant and useful. The value of the parent-reported sleep diary becomes less and less reliable as patients enter adolescence and adulthood. Attended sleep studies are widely utilized for diagnosing sleep-disordered breathing, but their value in guiding therapy is debatable. There are mul-

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tiple factors that can affect the validity of a single night of sleep testing for the individual patient. Such factors include poor sleep achieved in a strange environment and sleep position variations when compared with sleep at home. There is no evidence yet to support the use of portable sleep testing in this population.

Establishing and maintaining routines are critical in different aspects of the care of this special population, particularly in relation to behavioral sleep problems. Success is dependent on the caregiver's approach and level of involvement in their care, the individual's intellectual ability, and the presence of other comorbidities. Management of obesity with counseling on healthy diet and participation in exercise programs are also integral parts of their care.

Although treatment with positive airway pressure (PAP) is thought to be effective in treating OSA in DS, little data are available to support its efficacy and benefits. Treatment of OSA with PAP can be very challenging. Our sleep center experience incorporates a personalized approach with gradual PAP desensitization in addition to positive feedback and a reward system to encourage and maintain use. We also utilize behav-

ioral therapy to encourage avoidance of supine sleep in order to decrease the severity of OSA in patients who do not accept or tolerate PAP. Surgical interventions based on assessment of the upper airway during sleep through dynamic imaging or sleep endoscopy may also be considered. A recent report of hypoglossal nerve stimulation therapy in an adolescent with severe OSA suggests a potentially new alternative option for therapy (Diercks et al. *Pediatrics*. 2016;137(5). doi: 10.1542/peds.2015-3663.

It seems intuitive that the management of sleep disorders in adult patients with DS positively contributes to their care and promotes their overall wellbeing. Adult patients with DS continue to present particular diagnostic and therapeutic challenges that have become even more complex as their life expectancy has increased. Further research and clinical guidelines are momentously needed in order to guide the management of sleep disorders for this particularly challenging patient population.

Dr. Shaib is Associate Professor of Medicine, Medical Director, Baylor St Luke's Center for Sleep Medicine, Department of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, Baylor College of Medicine, Houston, Texas.

Chronic rhinosinusitis tied to poor sleep quality

BY DOUG BRUNK
Frontline Medical News

ATLANTA – Answers on a popular self-reported sleep questionnaire correlated positively with sinonasal inflammation, suggesting that patients with chronic rhinosinusitis should be assessed for sleep-related problems, results from a single-center study showed.

"We need to be recognizing the symptoms of chronic rhinosinusitis patients more in order to help them improve their quality of life," lead study author Jessica Hui, MD, said in an interview at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. "Asking them about sleep is important."

DOUG BRUNK/FRONTLINE MEDICAL NEWS

Jessica Hui: Asking chronic rhinosinusitis patients about sleep is important.

In an effort to identify the chronic rhinosinusitis (CRS)–related factors associated with poor sleep quality, Dr. Hui and her associates at Rush University Medical Center, Chicago, administered the Pittsburgh Sleep Quality Index (PSQI) to a cohort of 125 CRS patients with refractory disease and 41 controls. Patients with obstructive sleep apnea were excluded from the study. A self-report questionnaire that contains 19 items, the validated PSQI, assesses sleep over a 1-month time period. Scores below 5 indicate normal sleep quality. The researchers reviewed patient charts for CRS characteristics, including nasal polyps, histopathology of the sinus tissue (such as neutrophilic inflammation, eosinophilic inflammation, fibrosis, edema, and basement membrane thickening), Lund-Mackay Score (a radiographic score of CRS severity), a pain index measured on a visual scale from 0 to 6, the Sino-Nasal Outcome Test (SNOT-22), a subjective measure of CRS severity and outcome, and comorbid diseases including asthma, aspirin-exacerbated respiratory disease, allergic rhinitis, and gastroesophageal reflux disease. They compared the association of PSQI scores with these variables in order to determine factors associated with poor sleep in CRS.

Dr. Hui, a pediatrics resident at Rush University Medical Center, reported that CRS patients had significantly worse sleep quality, compared with controls (a mean PSQI score of 7.44 vs. 3.31, respectively) and that a higher Lund-Mackay Score correlated with greater PSQI (Pearson correlation coefficient of 0.25; $P = .03$).

The researchers also observed that CRS patients without nasal polyps trended toward a higher PSQI, compared with controls.

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Sepsis survivors may have high risk for seizures

BY JEFF EVANS
Frontline Medical News

BOSTON – Survivors of sepsis face a significantly increased risk of seizures following an index hospitalization, regardless of any previous history of seizures or seizures occurring during hospitalization, according to findings from a retrospective, population-based cohort study.

The risk for having subsequent seizures was highest for patients younger than 65 years but was still elevated above the general population for those aged 65 years or older, Michael Reznik, MD, reported at the annual meeting of the American Academy of Neurology.

Seizures are already a well-known complication of sepsis, and they also can occur alongside sepsis-associated encephalopathy, stroke, and neuromuscular disease. The frequency of sepsis-associated encephalopathy also has led to the recognition of post-sepsis cognitive dysfunction, said Dr. Reznik, a neurocritical care fellow in the department of neurology at Weill Cornell Medicine and Columbia University Medical Center in New York. It is unclear, however, how much of the risk for cognitive impairment after sepsis is due to pre-existing cognitive impairment, frailty, or lingering sedation effects, he said.

It's possible, he noted, that "seizures may be more specific for structural brain injury, and I think our findings may support the hypothesis that sepsis could be associated with pathways leading to long-lasting brain injury that's independent of other primary injuries that we have controlled for."


DR. REZNIK

Dr. Reznik and his coinvestigators used administrative claims data from all discharges from nonfederal emergency departments and acute care hospitals in California, New York, and Florida during 2005-2013 that had been collected as part of the federal Healthcare Cost and Utilization Project (HCUP). The HCUP assigns each patient a unique number that can be used to follow them anonymously through all subsequent hospitalizations. At each encounter, HCUP also tracks up to 25 discharge diagnoses that were present before hospital admission or developed during hospitalization, based on ICD-9-CM codes.

The investigators excluded patients with an ICD-9-CM diagnosis of seizures either before or during the index hospitalization for sepsis.

Overall, the 842,735 adult sepsis survivors in the study had a 6.67% cumulative rate of seizures over the 8-year period, compared with 1.27% in the general population. This translated to an incidence of about 1,288 per 100,000 patient-years in sepsis survivors, compared with 159 per 100,000 patient-years in the general population. The overall incidence rate ratio (IRR) for seizures among sepsis survivors was about 5, but was higher for those who also had neurologic dysfunction (such as encephalopathy, delirium, coma, or stupor) during their index hospitalization than in those without it (7.52 vs. 4.53). Sepsis survivors also had an elevated IRR of 5.42 for status epilepticus.

Sepsis survivors also had an elevated IRR of 4.35 for seizures when compared against control patients who were hospitalized for diagnoses other than sepsis and matched for age, sex, race, insurance, length of stay, discharge location, year of hospitalization, state, and the presence of codes for organ dysfunction.

The investigators confirmed the findings from the state-based HCUP analysis through inpatient and outpatient Medicare claims during 2008-2014 in a nationally representative sample of 5% of Medicare beneficiaries. These patients had an IRR for seizures of 2.72, and the IRR remained elevated (2.18) relative to patients who were hospitalized with diagnoses other than sepsis even when they excluded patients with ICD-9-CM codes for conditions that confer risk for seizures, including stroke, traumatic brain injury, CNS infection, or brain neoplasm. The seizure outcome in this analysis was defined as one or more inpatient claims for epilepsy or two or more outpatient claims within 3 months of each other.

The study was supported by a grant from the National Institute for Neurological Disorders and Stroke to one of the investigators and also by the Michael Goldberg Research Fund.

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Cutting back on ICU antibiotics could limit MDRO transmissions

BY DEEPAK CHITNIS
Frontline Medical News

Cutting back on antibiotic courses in intensive care unit settings can significantly reduce the number of multidrug-resistant organism (MDRO) transmissions, according to the findings of a modeling study.

"Significant opportunities exist to optimize and reduce antibiotic usage, [but] the impact of reducing overall antibiotic usage on antibiotic resistance is not known and would be difficult to assess using traditional study designs," wrote Sean L. Barnes, PhD, of the University of Maryland, College Park, and his colleagues. "Therefore, we applied mathematical modeling to estimate the effect of reducing antibiotic usage on antibiotic resistance."

Using an agent-based model – which allows for a realistic prediction of interactions between patients and health care workers, while also allowing for heterogeneity in the characteristics of each distinct "person" – Dr. Barnes and his coinvestigators simulated the transmission of MDROs from health care workers to patients.

Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci were deemed "high-prevalence pathogens;" carbapenem-resistant *Enterobacteriaceae*, multidrug-resistant *Acinetobacter baumannii*, and multidrug-resistant *Pseudomonas aeruginosa* were deemed low-prevalence pathogens. These designations were based on transmission rates found in existing literature.

Patients on antibiotic courses were set at 75% (0.75) at baseline, which was then adjusted to determine its effect on overall MDRO transmission. The number of patients at baseline was 18, with nine nurses, two physicians, and six other health care workers. Mean length-of-stay was 3.5 days, hand hygiene rates were set at 80% for nurses and 50% for physicians, with a 0.83 (83%) efficacy rate when followed. The probability of worker-to-patient transmission was set at 0.025 (2.5%), and set at 0.075 (7.5%) for transmission going the other way.

"We simulated the transmission of the high- and low-prevalence MDROs for 1 year [and] performed 200 replications each for 33 parameter-based scenarios," the authors said.

When the number of patients on an antibiotic course was dropped from 75% to 65% (a drop of 10%), the rate of high-prevalence MDRO transmission dropped by 11.2% ($P < .001$). When reduced from 75% to 50% (a drop of 25%), the high-prevalence MDRO transmission rate fell by 28.3% ($P < .001$), according to the model.

Low-prevalence MDROs also reduced by significant amounts when antibiotic regimens were cut back by the same percentages, with transmission rates falling by 14.3% ($P < .001$) and 29.8% ($P < .001$), respectively.

In terms of microbiome effects, the 10% reduction in antibiotics lowered high-prevalence rates by an effect of 1.5, and low-prevalence rates by 1.7; those numbers were 1.2 and 1.4, respectively, when antibiotics were dropped by 25%.

"These reductions are statistically significant and proportionally similar for both high- and low-prevalence MDROs," the authors concluded, "and they can potentially decrease MDRO acquisition among patients who are receiving antibiotics, as well as among patients who are not receiving antibiotics."

The National Institutes of Health and the Department of Veterans Affairs' Health Services Research and Development Department funded the study. Dr. Barnes and his coauthors reported no relevant financial disclosures.

Three factors linked to rhinovirus pneumonia in HCT patients

BY KARI OAKES
Frontline Medical News

ORLANDO – For patients who have received hematopoietic cell transplants, a rhinovirus infection can become much more than a cold.

"It holds true that rhinovirus is just as likely to be associated with mortality as are other respiratory viruses" among HCT recipients, Alpana Waghmare, MD, said at the combined annual meetings of the Center for International Blood & Marrow Transplant Research and the American Society for Blood and Marrow Transplantation.

In a new retrospective study, Dr. Waghmare and her coinvestigators found that the median time for a rhinovirus infection to progress from an upper to a lower respiratory tract infection was about 2 weeks among post-HCT patients.

Clinical and demographic risk factors for progression to lower respiratory tract infection included higher levels of steroid use (2 mg/kg per day or more) before developing the upper respiratory infection, a low white blood cell count, and a low monocyte count, said Dr. Waghmare, an infectious disease specialist and professor of pediatrics at the University of Washington, Seattle.

Of 3,445 HCT patients treated at the university center during the 6-year study, 732 patients (21%) were positive for human rhinovirus. Patients were classified as having upper respiratory infections if they had a polymerase chain reaction–positive nasal swab.

Patients were classed in one of three categories for potential lower respiratory infections: Proven lower respiratory infections were those detected by bronchoalveolar lavage or biopsy in patients who had a new radiographic abnormality. Probable lower respiratory infections were those with positive findings on bronchoalveolar lavage or biopsy but without radiographic changes. In possible lower respiratory infections, patients had upper tract virus detected on nasal swabs but did have a new radiographic abnormality.

Among the patients positive for human rhinovirus, 85% (665 patients) presented with upper respiratory infections and 15% (117 patients) with lower respiratory tract infections. By day 90, 16% of patients progressed from upper to lower respiratory tract infections. The median time to progression was 13.5 days. Progression to proven lower respiratory tract infection affected 5% of the HCT recipients.

In multivariable analytic models, a minimum white blood cell count of 1,000 or

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Hospital floors are an overlooked reservoir for pathogens

BY MARY ANN MOON
Frontline Medical News

Floors in hospital patients' rooms are frequently contaminated with pathogens such as *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci, which are easily transmitted to the hands of patients, care providers, and visitors, according to a report published in the American Journal of Infection Control (2017 Mar 1;45[3]:336-8).

Disinfection usually focuses on surfaces that are frequently touched by patients' or health care workers' hands, such as bed rails and call buttons. Floor disin-

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ANDREI MALOV/THINKSTOCK

HCT patients *Continued from previous page*

less was associated with a hazard ratio (HR) of 2.21 for progression to lower respiratory tract infection. A minimum monocyte count of 1,000 or less was associated with a HR of 3.66 for progression to lower respiratory tract infection.

The model also found a HR of 3.37 for lower respiratory tract infection with steroid use of 2 mg/kg per day or more. The patient's conditioning regimen and donor type were not significantly associated with risk of progression to lower respiratory infection.

Viral copathogens, prior respiratory virus episodes, and the duration of time since HCT were not associated with risk of progress to lower respiratory infections. Neither were patient age, baseline lung function, and the year the transplant occurred.

"These data provide an initial framework for patient risk stratification and the development of rational prevention and treatment strategies in HCT recipients," she said.

Dr. Waghmare reported receiving research funding from Aviragen, the maker of vapendavir, an investigational drug for human rhinovirus infection, and Gilead Sciences.

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Floors *Continued from previous page*

fection has received limited attention. However, floors are frequently touched by objects that are then handled, such as shoes and socks, said Abhishek Deshpande, MD, PhD, of the Cleveland Clinic, and his associates.

To examine the extent of floor contamination and the potential for transfer of pathogens to hands, the investigators surveyed five Cleveland-area hospitals. They collected samples from 1-square-foot areas of floors adjacent to beds and in bathrooms in *C. difficile* isolation rooms, and in two to three randomly selected nonisolation rooms on the same wards. At least 30 rooms at each hospital were cultured for *C. difficile*, MRSA, and VRE, either during a patient stay or after the rooms had been cleaned at patient discharge. The researchers also performed a point-prevalence survey of the number and type of high-touch objects contacting floors in 10-25 randomly selected occupied patient rooms at each hospital. After they handled these objects, their hands were cultured.

Floor contamination was common with all of the pathogens, particularly with *C. difficile*. The frequency of contamination was similar across the five hospitals, in both bedroom and bathroom sites, and even in the 50 rooms that had been cleaned at the last patient discharge. *C. difficile* spores were recovered from the floors of 47%-55% of rooms, MRSA was recovered from the floors of 8%-32% of rooms, and VRE were recovered from the floors of 13%-30% of rooms.

Forty-one of 100 occupied rooms had one to four "high-touch" objects in direct contact with the floors, including personal items such as clothing, canes, or cellphone chargers; medical supplies or devices such as pulse oximeters, call buttons, heating pads, urinals, blood pressure cuffs, and wash basins; and linens. Of the 31 cultures taken from both bare and gloved hands that handled these items, MRSA was recovered from 18%, VRE were recovered from 6%, and *C. difficile* was recovered from 3%.

The Agency for Healthcare Research and Quality and the U.S. Department of Veterans Affairs funded the study. Two of the authors reported receiving grants from various sources.

FDA clears procalcitonin test to hone antibiotic use

BY DEEPAK CHITNIS
Frontline Medical News

The Food and Drug Administration has cleared the expanded use of a procalcitonin test to help determine antibiotic use in patients with lower respiratory tract infections (LRTI) and sepsis.

The Vidas Brahms PCT Assay (bioMérieux) uses procalcitonin levels to determine whether a patient with a lower respiratory tract infection should begin or remain on antibiotics and when antibiotics should be withdrawn in a patient with sepsis.

"Unnecessary antibiotic use may contribute to the rise in antibiotic-resistant infections [and] this test may help clinicians make antibiotic treatment decisions," Alberto Gutierrez, PhD, director of the FDA's Office of In Vitro Diagnostics and Radiological Health, said in a statement.

The test will be used primarily in hospital settings and emergency departments, according to the FDA. Test levels that are high levels suggest bacterial infection and the need for antibiotics while low levels indicate viral or noninfectious processes. However, concerns exist regarding false-positive or false-negative test results, which can prompt clinicians to prematurely stop or unnecessarily continue an antibiotic regimen in certain patients.

"Health care providers should not rely solely on PCT test results when making treatment decisions but should interpret test results in the context of a patient's clinical status and other laboratory results," according to the FDA statement.

The expanded use of the test was approved based on promising data from clinical trials that was presented at an FDA advisory committee meeting in November 2016. The Vidas Brahms test was already approved by the FDA for use in determining a patient's risk of dying from sepsis. The test was cleared via the FDA 510(k) regulatory pathway, which is meant for tests or devices for which there is already something similar on the market.

Support for the test's expanded usage comes from published prospective, randomized clinical trials that compared PCT-guided therapy with standard therapy.

Digoxin definitively dissed for AF

BY BRUCE JANCIN
Frontline Medical News

WASHINGTON – In what could prove to be the final word in the clinical controversy over the safety of prescribing digoxin in patients with atrial fibrillation, a secondary analysis of the roughly 18,000-patient ARISTOTLE trial has come down emphatically on the side of avoiding the venerable drug.

"The clinical implications of our analysis are that in the absence of randomized trial data showing its safety and efficacy, digoxin should generally not be prescribed for patients with atrial fibrillation, particularly if symptoms can be alleviated with other treatments. And in patients with atrial fibrillation already taking digoxin, monitoring its serum concentration may be important, targeting blood levels below 1.2 ng/

mL," Renato D. Lopes, MD, PhD, said at the annual meeting of the American College of Cardiology.

The new ARISTOTLE analysis is potentially guideline changing. Dr. Lopes noted that both the current American College of Cardiology/American Heart Association and European Society of Cardiology atrial fibrillation guidelines recommend digoxin for rate control in patients with AF, and neither set of guidelines contains any specific recommendation about serum monitoring.

A randomized clinical trial of digoxin in AF is extremely unlikely, added Dr. Lopes, professor of medicine at Duke University in Durham, N.C.

ARISTOTLE was a randomized trial of apixaban (Eliquis) versus warfarin for stroke prevention in AF. The results of this landmark study, previously reported (N Engl J Med. 2011 Sep 15;365[11]:981-92), demonstrated that apixaban was the superior oral anticoagulant in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

ARISTOTLE had some unique features that rendered the study database an exceptional resource for use in a large observational study of digoxin's safety in patients with AF. It included a detailed serial assessment of concomitant medications as well

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as measurements of serum digoxin levels, left ventricular ejection fraction, creatinine clearance, and biomarkers including vasoactive intestinal peptide, troponins T and I, N-terminal pro–brain-type natriuretic peptide, and growth differentiation factor 15. These were among the 48 clinical variables included in multivariate adjusted analyses of mortality risk.

One-third of ARISTOTLE participants were on digoxin at study entry, a prevalence typical of what's seen in clinical practice. Among the 5,824 subjects with AF already on digoxin at the start of the trial, the risk of death during follow-up proved independently related to baseline serum digoxin concentration. Patients with a level from 0.9 ng/mL to less than 1.2 ng/mL had a 16% increased risk of death during study follow-up, compared with digoxin nonusers, a trend that didn't reach statistical significance. However, the 11% of AF patients with a serum concentration of 1.2 ng/mL or above were at a significant 56% increased risk for death.

When serum digoxin concentration is looked at as a continuous, rather than dichotomous variable, for each 0.5-ng/mL increase in drug concentration, the adjusted risk of all-cause mortality at 1 year of study follow-up climbed by 19%.

Moreover, among 781 AF patients who initiated digoxin during the study, the risk of death was increased by 78%, compared with that of 2,343 extensively matched controls. The most common cause of this excess mortality was sudden death, and in a closer look at that endpoint, the investigators found that the risk of sudden death was increased fourfold in new users of digoxin. This increased risk occurred early: Most sudden deaths occurred within the first 6 months after going on the drug, suggesting a causal relationship, although not providing definitive proof, Dr. Lopes noted.

Forty-three percent of ARISTOTLE participants had heart failure at enrollment. Interestingly, the increased risk of death associated with on-study initiation of digoxin was of similar magnitude, regardless of whether comorbid heart failure was present. The mortality risk was 58% greater in new users with heart failure, compared with matched nonusers with heart failure, and twofold greater in new users without heart failure than in their matched controls.

The benefits of apixaban over warfarin were consistent regardless of whether or not patients were on digoxin.

Discussant Kristen K. Patton, MD, was effusive in her response to the new ARISTOTLE findings.

"This was a really, truly, beautiful observational analysis," declared Dr. Patton, an electrophysiologist at the University of Washington, Seattle.

"I think in cardiology, where our hearts have been broken before due to flawed observational studies, it's really important for people to understand that observational data, when analyzed well, with appropriate propensity matching, with new-user analysis and close attention to clinical variables that are important, can really change practice in a good way. I think that's what we see here," she said.

A beaming Dr. Lopes responded that it's likely that some of the past conflicting studies were marred by survival bias – that is, an inability to account for the fact that patients already on digoxin at the outset of a study have already declared themselves to be more tolerant of the drug. Past studies also didn't adjust for biomarker levels.

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Caution urged in extending dual-antiplatelet therapy

BY BRUCE JANCIN
Frontline Medical News

SNOWMASS, COLO. – Think very carefully before extending the duration of dual-antiplatelet therapy beyond 6 months in drug-eluting stent recipients with stable ischemic heart disease, Patrick T. O'Gara, MD, advised at the Annual Cardiovascular Conference at Snowmass.

Six months of dual-antiplatelet therapy (DAPT) in this setting received a Class I recommendation in the 2016 American College of Cardiology/American Heart Association guideline focused update on DAPT duration (J Am Coll Cardiol. 2016 Sep 6;68[10]:1082-115). That's a departure from previous guidelines, which recommended 12 months of DAPT. The shortened DAPT duration of 6 months is consistent with European Society of Cardiology recommendations.

In contrast, extending DAPT beyond the 6-month mark garnered a relatively weak Class IIb recommendation in the ACC/AHA focused update, meaning it "could be considered," noted Dr. O'Gara, director of clinical cardiology at Brigham and Women's Hospital, Boston, and professor of medicine at Harvard Medical School.

Considerable enthusiasm for extending DAPT well beyond 6 months after drug-eluting stent implantation has been generated in some quarters by the positive results of the PEGASUS TIMI 54 trial. But Dr. O'Gara and the other members of the guideline writing committee had reservations about the study, which together with other concerning evidence led to the weak Class IIb recommendation.

PEGASUS TIMI 54 included 21,162 patients with stable ischemic heart disease 1-3 years after a myocardial infarction who were randomized to low-dose aspirin plus either placebo or ticagrelor (Brilinta) at 60 mg or 90 mg b.i.d. and followed prospectively for a median of 33 months (N Engl J Med. 2015 May 7;372[19]:1791-800).

The primary efficacy endpoint, a composite of cardiovascular death, MI, or stroke, occurred in 9.0% of placebo-treated patients, compared with 7.8% of patients on either ticagrelor regimen, for a statistically significant 15% relative risk reduction in the DAPT group.

But there is more to the study than first meets the eye.

"I think what we as practitioners sometimes lose track of is that the investigators in this particular trial were very careful to enroll patients with stable ischemic heart disease who were at high risk of ischemic events over the next 3-5 years," Dr. O'Gara noted. "These were patients who were generally older, patients with diabetes, chronic kidney disease, multivessel coronary disease, or who had had a second MI."

Thus, the deck was stacked in favor of obtaining a result showing maximum efficacy. Yet, for every 10,000 patients treated with ticagrelor at 90 mg b.i.d., there were only 40 fewer cardiovascular events per year, compared with placebo. And that came at a cost of 41 more TIMI major bleeding events.

"That's a wash at 90 mg," the cardiologist said.

At 60 mg b.i.d. – the dose ultimately approved by the Food and Drug Administration – there were 42 fewer primary cardiovascular events per year per 10,000 treated patients, a benefit that came at the expense of 31 more TIMI major bleeding events.

"These are really razor thin margins, and I would encourage you to make a risk-benefit assessment of the trade-off between ischemia and bleeding in your decision making," Dr. O'Gara said.

The ACC/AHA guideline writing committee also took into account a meta-analysis of six randomized clinical trials totaling more than 33,000 high-risk patients post-MI who were assigned to more than 1 year of DAPT or aspirin alone. Extended DAPT brought a 22% reduction in the relative risk of major adverse cardiovascular events, but this was accompanied with a 73% increase in the risk of major bleeding (Eur Heart J. 2016 Jan 21;37[4]:390-9).

Turning to DAPT duration post-PCI in patients with an acute coronary syndrome, Dr. O'Gara noted that the 2016 ACC/AHA guideline focused update gave a Class I indication for 12 months of DAPT in recipients of a drug-eluting stent, but a weaker IIb recommendation for consideration of extending DAPT beyond that point – provided the patient was not at high bleeding risk and didn't have significant bleeding during the first 12 months on DAPT.

"I think there's a lot of individual and institutional variation with respect to this kind of decision making, and I don't think our guidelines are meant to be proscriptive, because our patients are quite nuanced," the cardiologist observed.

The question physicians always have to ask in considering extended DAPT is, "How many ischemic events am I going to prevent at the expense of how many bleeding events?"

The investigators in the landmark DAPT study of extended therapy have analyzed their data in a fashion that has enabled them to develop a risk scoring system, known as the DAPT prediction rule, which is readily calculated based on factors including age, presence of diabetes, heart failure, and the size of the treated vessel.

For patients with a high DAPT score, assignment to an additional 18 months of DAPT after the initial 12 months of dual therapy was associated with a net 1.67% reduction in adverse events – both ischemic and bleeding – compared with the rate in patients who stopped DAPT at 12 months. For those with a low DAPT score, extended dual-antiplatelet therapy resulted in a 1.03% net increase in adverse events (JAMA. 2016 Apr 26;315[16]:1735-49).

"I should warn you that the discriminatory power of this particular score is relatively modest," Dr. O'Gara noted. "The C-statistic is not higher than about 0.7. But I do think that the DAPT score meets the sniff test biologically and clinically. It's a real good first step. I do think this particular score needs to be validated externally in other populations going forward."

Dr. O'Gara reported having no financial conflicts of interest.

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"We could adjust for things we know today are associated with death in atrial fibrillation," he observed.

Dr. Patton added that the most surprising study finding to her involved the new users of digoxin. She suspects that the reported figure of a 78% increased risk of all-cause mortality during study follow-up actually markedly underestimates the true size of that risk during the initial months on the drug. Dr. Lopes agreed.

She also said she found worrisome and disappointing the increased mortality risk reported with initiation of digoxin in AF patients with heart failure. That hasn't been seen in other studies.

Dr. Lopes said the investigators utilized multiple means of identifying patients with heart failure and are certain they captured the full population of affected patients.

"We feel very confident that, when you have atrial fibrillation together with heart failure, it might be a different story than without atrial fibrillation," the cardiologist said.

Dr. Jagmeet P. Singh

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. Renato D. Lopes

Discussant Jagmeet P. Singh, MD, associate chief of cardiology at Massachusetts General Hospital and professor of medicine at Harvard Medical School, Boston, said the ARISTOTLE analysis carries an eye-opening take-home message: "If you have to initiate digoxin, you have to follow the serum levels more closely than we ever have before. How frequently, I don't know – maybe monthly instead of at the 6-monthly intervals that we often do. And I think maybe arrhythmia monitoring in the initial stages of putting patients on digoxin will be key to see if there are any additional proarrhythmic effects."

The original ARISTOTLE trial was sponsored by Bristol-Myers Squibb and Pfizer. However, the ARISTOTLE digoxin analysis was sponsored by the Duke Clinical Research Institute. Dr. Lopes reported serving as a consultant to and/or receiving research grants from Bristol-Myers Squibb, Pfizer, Bayer, Boehringer Ingleheim, Daiichi Sankyo, GlaxoSmithKline, Medtronic, Merck, and Portola.

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Hospitals rarely offer cessation therapy to smokers

BY BIANCA NOGRADY
Frontline Medical News

Less than one-third of smokers hospitalized for myocardial infarction receive any kind of smoking cessation therapy during their stay in hospital, according to a poster presented at the annual meeting of the American College of Cardiology.

"Inpatient smoking cessation therapy coupled with outpatient follow-up can significantly improve long-term smoking cessation rates, but little is known about how often smoking cessation therapies are used among hospitalized patients," wrote Quinn R. Pack, MD, and coauthors from the Baystate Medical Center in Springfield, and Massachusetts General Hospital.

Researchers analyzed billing data and ICD-9 codes for 36,675 current smokers hospitalized for MI at 282 hospitals in 2014, and found that overall only 29.9% of these individuals were given at least one kind of smoking cessation therapy, such as varenicline, bupropion, and nicotine replacement gums, patches, lozenges, and inhalers.

The nicotine patch was the most common therapy; 20.4% of patients received it with an average daily dose of 19.8 mg, while 2.2% of patients received bupropion, 0.4% received varenicline, 0.3% received nicotine gum, 0.2% received nicotine inhaler therapy, and just 0.04% received nicotine lozenge therapy. Nearly 1 in 10 patients received professional counseling (9.6%).

Smoking cessation was more commonly given to patients with lung disease, depression, or alcohol use or who were younger but the researchers noted significant variations in the use of smoking cessation therapies across hospitals. While the median treatment rate was 26.2%, it ranged from as low as 11.4% to a high of 51.1%.

The authors said they plan to identify the strategies and practices that the high-performing hospitals use to provide smoking cessation therapies.

"Smoking cessation is the single most effective behavior change that patients can make after a hospitalization for coronary heart disease to prevent recurrent events." There appears to be a large opportunity for improvement in the care of smokers hospitalized with CHD, because patients are usually highly motivated to quit after hospitalization, the authors noted.

Cardiac events after NSCLC radiotherapy occur early

BY MARY ANN MOON
Frontline Medical News

Cardiac events are "relatively common," affecting 23% of patients, and occur earlier than previously thought following radiotherapy for non–small cell lung cancer (NSCLC), according to a report in the Journal of Clinical Oncology (2017 Jan 23. doi: 10.1200/JCO.2016.70.0229).

Radiation-associated cardiac toxicity has long been recognized in patients treated for other thoracic cancers, but the conventional wisdom has been that it isn't a consideration in patients with stage III NSCLC because "there are few long-term survivors to experience toxicity, given the typically long latency of radiotherapy-associated heart injury and the poor prognosis" of this cancer. However, the findings "challenge the perception that minimizing heart dose is not important in the treatment of patients with stage III NSCLC," said Kyle Wang, MD, of University of North Carolina Hospitals, Chapel Hill, and his associates.

The researchers performed a retrospective post hoc analysis of data pooled from six prospective phase I and II trials. The studies assessed both dose-escalated radiotherapy and various chemotherapeutic regimens in 112 patients who were followed for a median of 8.8 years (range, 2.3-17.3 years). All the patients received induction chemotherapy, 90% received concurrent chemotherapy, and 25% received consolidation chemotherapy.

A total of 26 patients (23%) had at least one symptomatic cardiac event following radiotherapy: pericardial effusion (7 patients), MI (5 patients), unstable angina (3 patients), pericarditis (2 patients), significant arrhythmia (12 patients), and heart failure (1 patient). After the data were adjusted to account for competing risks of death, the 2-year rate of symptomatic cardiac toxicity was 10% and the 4-year rate was 18%. The first adverse cardiac event occurred at a median of 26 months.

The risk of cardiac toxicities rose with increasing radiation exposure: At 2 years, the rate of cardiac events was 4% for those exposed to less than 10 Gy, 7% for those exposed to 10-20 Gy, and 21% for those exposed to greater than 20 Gy. At 4 years, those rates were 4%, 13%, and 41%, respectively. Patients whose hearts were exposed to greater than 20 Gy had a significantly higher rate of cardiac events than did those exposed to less than 10 Gy (hazard ratio, 5.47) or to 10-20 Gy (HR, 2.76).

VIEW ON THE NEWS

Jason Lazar, MD, FCCP, comments: This retrospective analysis' findings challenge the long-held notion that radiation side effects are inconsequential given that long-term survival is considered poor. The paper contributes to the field of cardio-oncology, which focuses on treating oncology patients with pre-existing heart disease and reducing adverse cardiovascular outcomes in the treatment of oncology patients. Emerging concerns about the overlap of these conditions relate to cancer and heart disease being the two leading causes of death in the United States, the frequent co-existence of these two conditions, the toxic effects of various chemotherapeutic agents, and the recognition of radiation-induced cardiac injury. The paper alludes to the impact of cardiac symptoms to overall quality of life in oncology patients undergoing treatment and that cardiac toxicity may be diverse with variable clinical presentations. This study also suggests that synergistic effects of chemotherapy and radiation might contribute to earlier than expected cardiac side effects. Overall, it underscores the importance of a team approach for chest physicians in caring for patients with lung cancer.

CHEST names Stephen J. Welch EVP and CEO

The Board of Regents of the American College of Chest Physicians (CHEST) has finalized the appointment of Stephen J. Welch as Executive Vice President and Chief Executive Officer for CHEST. Welch had been serving as the interim EVP/CEO since May 2016. Prior to this appointment, he served in a senior staff role at CHEST for 22 years, most recently as Publisher and Senior Vice President of Publications and Digital Content, which includes managing the organization's flagship scientific journal, CHEST®.


MR. WELCH

"We appreciate the exceptional performance of Steve, his senior team, and the entire CHEST staff during this transition in executive leadership. We are excited about the opportunity to work with Steve in his new role going forward, as we begin outlining CHEST's strategic plan for the next 5 years," said CHEST President Gerard A. Silvestri, MD, MS, FCCP.

In response to the announcement, Steve remarked, "I am sincerely humbled and honored to have this opportunity and am excited for the future of CHEST, a dynamic, innovative organization that is doing great things, and we will continue our track record of excellent performance."

CHEST gets the word out with Reddit

Drs. Simpson, Hogarth, and Moores told Reddit to ask them anything—here's what happened next.

"Is there an organ or system that sepsis generally targets?"

"If I'm going to be in the back of a cramped car cross country for 16 hours straight, should I take an aspirin beforehand to cut down risk of DVT?"

"Hello Doctor. Does thermoplasty have any application for bronchiectasis patients, like myself?"

Reddit is a social news aggregation site allowing users to post a wide range of topics to create discussion. The platform is currently one of the most informative and popular social sites on the web and has a huge following of members who focus their discussions on health care/science.

Within the science AMA subsection, users have the ability to post a topic or questions about anything and respond to other users. AMA, which stands for "Ask Me Anything," describes the conversation happening between the user and the host of the topic. Users have the ability to ask questions related to the topic, or even 'upvote' particular questions that they would like answered. An 'upvote' moves a question or comment to the top of the page to become more visible to the host. AMAs can become trending topics on Reddit through 'upvotes', as well.

In an effort to help educate and inform individuals on advancements in chest medicine education, clinical research, and team-based care, CHEST has connected specialists with a deep passion for topics in pulmonary, critical care, and sleep medicine to an audience filled with questions ready to be answered. Some of the topics we've covered include:

- Sepsis with Dr. Steven Q. Simpson, FCCP, who is a pulmonologist, intensivist, CHEST board member, and a sepsis researcher and expert. Dr. Simpson discussed the recent consensus statement on sepsis diagnosis. The statement aimed to redefine the diagnostic criteria of sepsis and eliminate the concept of the systemic inflammatory response syndrome (SIRS). Dr. Simp-

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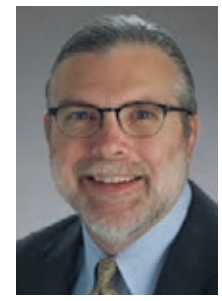
DR. SIMPSON


DR. HOGARTH


DR. MOORES

Fulfillment in giving through insurance

Robert De Marco, MD, FCCP, was one of the first Champions Circle and Founder's Society donors to make a major gift through insurance. We thank the De Marco family for their support in championing lung health, and it's our pleasure to share the highlights of a recent interview with Dr. De Marco.


DR. DE MARCO

Why did you choose to give through insurance?
I had a Universal Life Policy that I bought when I was first in practice. While it would be a nice addition to my family bequest, it would be a much better gift to the foundation.

How was the process? Did you know anything about giving through insurance beforehand?
I knew nothing about donating insurance. I heard about it during a board strategy session and realized I had a policy that could be donated. I contacted my insurance company. I was sent forms, which were easy to fill out. The forms were then forwarded to CHEST for some signatures, and it was completed. It could not have been easier.

Would you recommend this method of giving to other donors?
Absolutely. If this policy isn't vital to your family after you are gone, there could not be a better choice.

Why was this choice right for you and your family?
If you must take a significant amount of money out of your savings to make a sizable donation, you can put a serious dent in your retirement income. To be able to make that gift without any effect on my savings is a win-win for everyone.

Why do you continue to give to the CHEST Foundation?
I have spent my whole career trying to deal with diseases of the chest. What better way to sustain my efforts than to support a foundation dedicated to my life's dreams? There is nothing more fulfilling than helping fund research or a project that could forever change the future of our patients' lives. I truly believe we, as a group, are on the right path to succeeding in doing just that.

How is giving to the CHEST Foundation fulfilling to you?
How can any effort that will make the lives of our patients better not be fulfilling? Giving my time and effort without the expectation of something in return is an amazing feeling—one that I hope many donors in the future will realize. Just being a part of this great organization is a phenomenal experience.

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If you own a life insurance policy that is no longer needed for its original purpose, you may consider gifting it to the CHEST Foundation.

You can also create a new policy naming the CHEST Foundation as the owner and beneficiary. An annual gift equal to the insurance premium can be given, which would provide you with a charitable deduction. The foundation would then direct the funds to the insurance provider.

This is an excellent win-win solution for you and the CHEST Foundation.

For more information on these and other ways to support the CHEST Foundation, confidentially and with no obligation, contact Rudy Anderson at randerson@chestnet.org or 224/521-9492.

Catching up with our CHEST 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, leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's strategic initiatives. Let's check in with our first woman President, Dr. Deborah Shure.

Deborah Shure, MD, Master FCCP
President 1995-1996

When I began my year as President of the American College of Chest Physicians in 1995 in New York City, I became the first woman to serve in that role in the then 60-year history of the College. One major theme for my presidential year was inclusiveness. With the support of the Regents and the members of the College, we sought to increase the roles of our International Fellows and Affiliate Members, as well as the participation of all of our FCCPs. We also expanded the role of the College in global tobacco control.

With a focus on these goals, the presidential year was truly an exciting and fulfilling one. I was honored to meet so many members worldwide and, through the College, enable the support of regional meetings internationally. Our efforts in the Asia-Pacific area lent essential support to one of the early conferences on tobacco control in the Philippines (Asia Pacific Conference on Control of Tobacco, Subic, Philippines, 1998). My presentation in 1996 in Bangkok was the College's first International Partnering for World Health Award to H.M. King Bhumibol of Thailand for his work in the prevention and treatment of chest diseases in Thailand, was an unforgettable experience.

My presidential year ended in San Francisco. Since that time, my professional life has been varied and interesting. I was fortunate to continue my academic career encompassing both clinical and basic research. In 2005, I tried a new path and worked for the FDA Center for Devices and Radiological Health, using my background in device development (the angioscope) and clinical trials. Since 2012, I have been using my clinical, academic, and regulatory experience as an independent consultant in clinical trial design.


Deborah Shure, MD, Master FCCP

On a personal note, my partner of many years, Aymarah Robles, MD, FCCP, and I were finally able to marry in January 2015. So, we are now a happy and official two pulmonary, Cuban-American household enjoying the culture of Little Havana and the many outdoor activities of Miami!

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son shared his rebuttal New Sepsis Guidelines: A Change We Should Not Make in the journal *CHEST*. Dr. Simpson's statement expressed the concern that widespread application of this new SIRS definition could cost patient lives, and it should not be adopted. This AMA was upvoted 784 times.

- Asthma and bronchial thermoplasty with Dr. D. Kyle Hogarth, FCCP, who is a pulmonologist, member of CHEST, and the first physician in Illinois to perform bronchial thermoplasty, a nonpharmaceutical treatment for severe asthma. This AMA was upvoted 3,112 times.
- DVT with Dr. Lisa K. Moores, FCCP, who is a pulmonologist, member of CHEST, and an expert on thrombosis. Dr. Moores discussed VTE, DVT, and PE. This AMA was upvoted 903 times.

Hosting Reddit AMAs has allowed CHEST to not only reach a more public-facing audience but also health-care providers outside of chest medicine. Stepping into this platform has allowed us to position CHEST as a subject matter expert in topics like asthma, sepsis, and DVT/VTE. These AMAs have helped people to understand the role our members play within health-care by showcasing new and emerging treatments and raising public awareness of health conditions.

If you are interested in sharing your knowledge on a specific topic on Reddit, you can contact CHEST's New Media Specialist Taylor Pecko-Reid, at tpeckoreid@chestnet.org.

This month in *CHEST*: Editor's picks

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

ORIGINAL RESEARCH

Allogeneic Human Mesenchymal Stem Cells in Patients With Idiopathic Pulmonary Fibrosis via Intravenous Delivery (AETHER): A Phase I Safety Clinical Trial. By Dr. M. K. Glassberg et al.

Adult Patients With Bronchiectasis: A First Look at the US Bronchiectasis Research Registry. By Dr. T. R. Aksamit et al.

Variation of Ciliary Beat Pattern in Three Different Beating Planes in Healthy Subjects. By Dr. C. Kempeneers et al.

EVIDENCE-BASED MEDICINE

Interventional Pulmonology Fellowship Accreditation Standards: Executive Summary of the Multisociety Interventional Pulmonology Fellowship Accreditation Committee. By Dr. J. J. Mullon et al.

GIANTS IN CHEST MEDICINE

Talmadge E. King Jr., MD, FCCP. By Dr. Harold R. Collard.

NETWORKS NSCLC staging, MAPAH, cough in teen athletes

Interventional Chest/Diagnostic Procedures

Update: 8th ed IASLC lung cancer staging guidelines

The new 8th edition guidelines on the staging of non-small cell lung cancer sponsored by the International Association for the Study of Lung Cancer (IASLC), and developed jointly by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer were enacted January 1, 2017, and provide a methodologically rigorous update to staging nomenclature (Detterbeck et al. *Chest*. 2017;151[1]:193). The new guidelines were developed using a database comprising 94,708 patients in 16 countries, integrating clinical, pathologic, and survival data with multivariate analysis to establish prognostically significant staging subgroups.

In the new guidelines, tumor size has been divided into 1-cm increments for T classifications with new subcategories of T1a <1 cm, T1b 1-2 cm, and T1c 2-3 cm (Rami-Porta et al. *J Thorac Oncol*. 2015;10[7]:990). Furthermore, T2 has been broadened to include main bronchus tumors causing lobar or whole lung atelectasis extending to the hilum. Tumors with diaphragmatic involvement have been reclassified as T4. Guidance on heterogeneous nodules has also been provided, with emphasis on measurement of the solid component (based on imaging) or depth of invasion (on pathology) to determine T classification.

The N classification remains unchanged from the 7th edition. Exploratory analysis suggested prognostic significance to the number of involved N1/N2 lymph nodes; however, this requires detailed pathologic assessment and was not adopted as a staging criterion (Asamura et al. *J Thorac Oncol*. 2015;10[12]:1675).

Classification of metastatic disease has been modified from M1a/M1b to M1a for thoracic metastasis, M1b for single/oligometastatic extrathoracic metastasis, and the new category M1c for multiple/disseminated metastases. M1c involvement now denotes stage IVb disease, with lower survival compared to IVa disease (0% vs 10% 5-year survival (Goldstraw et al. *J Thorac Oncol*. 2015;11[1]:39). Application in broader cohorts, including patients undergoing bronchoscopic staging, will be needed to further validate the new guidelines.

Vivek Murthy, MD
Fellow-in-Training Member
Steering Committee

Pulmonary Physiology, Function, and Rehabilitation

6-minute walk test

The 6-minute walk test (6MWT) is a widely used measure of functional status and exercise capacity. Though it does not diagnose specific etiologies of impairment, the 6MWT provides an assessment of the overall integrated physiologic responses to exercise (*Am J Respir Crit Care Med*. 2002;166[1]:111). The test is a self-paced, submaximal study. Patients are instructed to "walk as far as possible for 6 minutes" with this distance (6MWD) measured as the primary outcome. 6MWD is associated with clinical outcomes in many cardiopulmonary disorders and is reliable, valid, and responsive to treatment. Normative equations provide predicted and lower limit of normal values (Singh et al. *Eur Respir J*. 2014;44[6]:1447). In addition to patient comorbidities, several important factors impact 6MWD interpretation. Standardization of the testing course, patient instructions, encouragement, technician assistance, walking aids, and supplemental oxygen use are important in reducing testing variability (Holland et al. *Eur Respir J*. 2014;44[6]:1428). A significant learning effect exists during the first several walks. An improvement of about 26 m (range 24-29 m) has been reported in patients with COPD, with the majority improving during the second test despite a short time interval lapse. Assessing for longitudinal change in serial testing is based on the minimal clinically important difference (MCID). This represents the difference in 6MWD that is perceived as important to the patient or leads to change in management. Techniques to develop these estimates are based upon statistical analysis of study sample data (distribution-based) or changes in a different, but related, clinical variable that is used as a reference (anchor-based). While minor differences in MCID are reported based on specific disease processes, a European Respiratory Society/American Thoracic Society review based on data from patients with COPD, ILD, and PAH found a MCID value of about 30 m (range 25-33 m) for adults with chronic respiratory disease, independent of specific disease, which is only slightly larger than the short term variability (Puente-Maestu et al. *Eur Respir J*. 2016;47[2]:429). Knowledge of these factors can assist in proper interpretation of the 6MWT.

Lana Alghothani, MD
NetWork Member
Nitin Bhatt, MD
Steering Committee Member

Pulmonary Vascular Disease

Methamphetamine-associated pulmonary hypertension (MAPAH): "tip of the iceberg"

Pulmonary hypertension (PH) is a devastating condition with serious morbidity and mortality. The Evian Classification and more recent revisions (*J Am Coll Cardiol*. 2013;62(25 Suppl):D34) reclassified PH into five subgroups based upon etio-pathogenesis. Group I PH (pulmonary arterial hypertension, PAH) represents a growing list of entities, with Drugs & Toxins (Group 1.3) as a separate subgroup. This subgroup was first recognized following the discovery of an association between PH and the ingestion of the anorexigen aminorex (Gurtner HP. *Schweiz Med Wochenschr*. 1985;115[24]:818).

Methamphetamine (ME) as a potential etiology for PAH was first reported in 1993 (Schaiberger et al. *Chest*. 1993;104[2]:614). More recently, Chin et al suggested an association between stimulant use and PAH in 28.9% of their patients diagnosed with idiopathic PAH (*Chest*. 2006;130[6]:1657). The growing body of evidence linking ME to PAH resulted in upgrading of ME from "Possible" to "Likely" in the latest revision of the PH classification.

Recent gene sequencing data showed carboxylesterase-1, an enzyme that protects against ME-mediated pulmonary vascular injury, may be downregulated in patients with methamphetamine-associated PAH (MAPAH) (Perez et al. *Am J Respir Crit Care Med*. 193;2016:A2912). Furthermore, amphetamines promote mitochondrial dysfunction and DNA damage in pulmonary hypertension (Chen PI. *JCI Insight*. 2017;2[2]:e90427). Importantly, Barnett et al demonstrated a poorer prognosis in MAPAH compared with individuals with idiopathic PAH, but they are less likely to be treated with infused prostanoid therapies (*Circulation*. 2012;126:A13817).

Amphetamine-type stimulants have become the second most widely used class of illicit drugs worldwide (United Nations Office on Drugs & Crime. *World Drug Report* 2012). An estimated 4.7 million Americans (2.1% of the US population) have tried MA at some time in their lives (*J Psychoactive Drugs*. 2000;32[2]:137). The true incidence and prevalence of MAPAH remains unknown. One can surmise that with the widespread use of ME, we are only witnessing the "tip of the iceberg."

Vijay Balasubramanian, MD, FCCP
Steering Committee Member
Franck Rahaghi, MD, FCCP
NetWork Member

Thoracic Oncology

Immunotherapy for lung cancer

The management of non-small cell lung cancer has traditionally focused on surgical resection of early and limited stage tumors and radiation and cytotoxic chemotherapy for patients with advanced disease. Recent progress in the management of patients with metastatic lung cancer treatment has concentrated on the precise histologic diagnosis and the characterization of molecular drivers of malignant progression. Distinguishing small cell from non-small cell carcinomas, as well as differentiating adenocarcinoma from squamous cell carcinomas, enables clinicians to more effectively tailor appropriate chemotherapy. The identification of molecular mutations in EGFR (epidermal growth factor receptor) or fusions in ELM4-ALK translocations as drivers of the malignant process has facilitated tumor regression by targeting the molecular pathways with small molecular inhibitors (tyrosine-kinase inhibitors) or synthetic antibodies. Unfortunately, not all lung cancers carry activating mutations, and those that do may develop resistance to this molecular-targeted approach and show tumor progression.

Immunotherapy, an anticancer therapeutic approach that activates the host immune system to target the tumor, has historically been either a broad spectrum management utilizing immune cytokine modifiers to augment host immune activity or a directed adaptive recruitment and stimulation of host lymphocytes to attack targeted tumor cells. More recently, immunotherapy has taken a targeted molecular approach to modify immune checkpoint inhibitory pathways, the "brakes" of the immune system that tumor cells have manipulated to evade immune surveillance. Cancer cells may be attacked by activated T cells through the MHC complex and T cell receptor pathways. However, cancer cells that express a checkpoint ligand can deactivate T cells through its checkpoint pathway. Cancer cells may evade immune recognition by signaling inhibitory checkpoint receptor pathways, such as PD-1/PDL-1, or CTLA-4 receptors. Blocking the checkpoint inhibition may reactivate the immune response and en-

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hance host immune recognition and killing of tumor cells. Infusions containing FDA-approved nivolumab (Opdivo) and pembrolizumab (Keytruda) block the PD-1 receptor checkpoint, whereas atezolizumab (Tecentriq) blocks PD-L1, the ligand that binds PD-1. These immune therapeutic approaches have been successfully utilized in a variety of solid tumors, including lung cancer and malignant melanomas. Impressive clinical results of prolonged tumor regression have been demonstrated in second-line immunotherapy with improvements over chemotherapy; newer immunotherapy trials have demonstrated efficacy in the first-line setting for metastatic disease. Tumors with high PDL-1 expression and high mutational load predict improved immunotherapy outcomes. As expected, blocking checkpoint immune inhibition may lead to autoimmune-like conditions of pneumonitis, hepatitis, colitis, and dermatitis. Tumor tissue markers predictive of a therapeutic immune response are in the research phase. Immunotherapy against lung cancer adds to the therapeutic armamentarium of cancer management and provides an exciting new research arena into the biology and immunology of lung cancer.

Arnold M. Schwartz, MD, PhD, FCCP
Steering Committee Member

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Pediatric Chest Medicine

Recommendations for teen athletes included in new guidelines

Approximately 8 million American teens participate in organized sports. Exercise-induced bronchospasm (EIB) and asthma are common in this age group and can be seen even in those performing at an elite level. Cough is a prominent symptom in these disorders and can be related to the type of sport and environment in which the sport is played, as well as the level of intensity and endurance involved. Physicians need to be able to distinguish EIB and asthma from other causes of acute or recurrent cough.

The American College of Chest Physicians is a leading resource in evidence- and consensus- based guidelines on important topics affecting both children and adults. The most recent guideline published in the February issue of *CHEST* is titled "Cough in the Athlete" (*Chest*. 2017;151(2):441-454). This guideline is based on an analysis of 60 relevant papers utilizing the CHEST methodologic guidelines and Grading of Recommendations Assessment, Development, and Evaluation framework and provides recommendations for adult and adolescent athletes ages 12 years and above.

The Expert Panel Report highlights differences in cough etiology between athletes and the general population and addresses the links between the type of sport and the environment in which it is played.

Key messages include:

- Initial evaluation of cough in athletes should focus on the most common etiologies.
- Systematic investigation should be based on the initial assessment and consideration into the specific sport, playing environment, and context.
- Suggested investigations include pulmonary function testing, particularly bronchoprovocation challenges, and evaluation of allergen and environmental exposures.
- Treatment trial directed at the suspected etiology is suggested with consideration of the specific sport and training environment.
- When evaluating and treating athletes participating in organized sports, consideration of training context and anti-doping regulations need to be considered.

The Panel recognizes the lack of randomized controlled trials to help determine the optimal evaluation and treatment of cough in athletes. Until specific evidence-based data are available, current-based guidelines should be applied to athletes.

John B. Bishara, DO
Fellow-in-Training Member
Steering Committee

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Explore the arts of Toronto

Explore the talent of Canadian artists and the culture of Toronto during CHEST Annual Meeting 2017.

Over the last decade, Toronto's art scene has moved to the former industrial district, creating a new home for galleries, especially those of contemporary art. While Toronto's galleries may not be very busy outside of opening nights, they allow you to visit at any time and admire the artwork at your own pace. Along with art galleries, there are many options available to experience music and performance art, as well as family-friendly activities. Here are a few places you'll want to visit:

CHEST® Annual Meeting 2017

Art Galleries

- **The Power Plant** (4-minute drive), one of Toronto's most established contemporary art galleries, is located within Harbourfront in an actual power plant - one that was in operation for most of the 1900s. If you're with young family members, a free, hands-on art workshop led by artists with activities designed around the current exhibitions is available called Power Plant: Power Kids.
- **Art Metropole** (15-minute drive) is a non-profit organization with an eclectic collection of merchandise, including a huge selection of artist-created books, periodicals, posters, clothing, audio, video, and more. The name is taken from the building's original tenant, Art Metropole, which operated as one of Toronto's earliest galleries from 1911 to the 1940s. Art Metropole has always been the leader of Toronto's artistic community. In 1997, over 13,000 items were transferred to the National Gallery of Canada as the "Art Metropole Collection." The works of world-renowned artists, such as Yoko Ono, Sol Lewitt, Joseph Beuys, and Marcel Duchamp, are included in the collection.
- **Daniel Faria Gallery** (18-minute drive) is a bright contemporary art space found in a warehouse that used to be an auto body shop. A number of reputable, mostly Canadian, artists' works are displayed by owner Daniel Faria, including works by Shannon Bool, Chris Curreri, Kristine Moran, and Coupland. Check out other neighboring galleries within walking distance, including Tomorrow Gallery and the artist-run Mercer Union.

Music and Theatre

- **The Rex Jazz & Blues Bar** (6-minute drive) has two to three (mostly free) shows every day, about 19 shows a week, jazz jams on Tuesdays, local and international talent, and a fantastic location. This place is truly hard to beat.
- Spend an evening at the **Canadian Opera Company** (6-minute drive). During the week of CHEST 2017, the COC will be showing The Elixir of Love, a Cinderella story presented with a twist, as a poor and uneducated young man dreams ofwinning the heart of a rich, clever, and beautiful woman.
- For a wide variety of events and visual art, visit the **Harbourfront Centre** (4-minute drive). During your time at CHEST 2017, you'll find options for literary arts, like the International Festival of Authors, theatre, music, shopping, and more. You may even get a chance for family skating on the Natrel Rink, which opens in November!

Note: all estimated times assume you are starting at the Metro Toronto Convention Centre.

The arts and culture of Toronto are sure to inspire you, as will CHEST 2017. When you visit Toronto, October 28 to November 1, you'll have access to cutting-edge education on pulmonary, critical care, and sleep medicine topics.

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Shopping at Harbourfront Centre

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The Concert Stage at the Habourfront Centre

Jennifer Hart

Ice-skating at the Natrel Rink

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The Power Plant

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Canadian Opera Company

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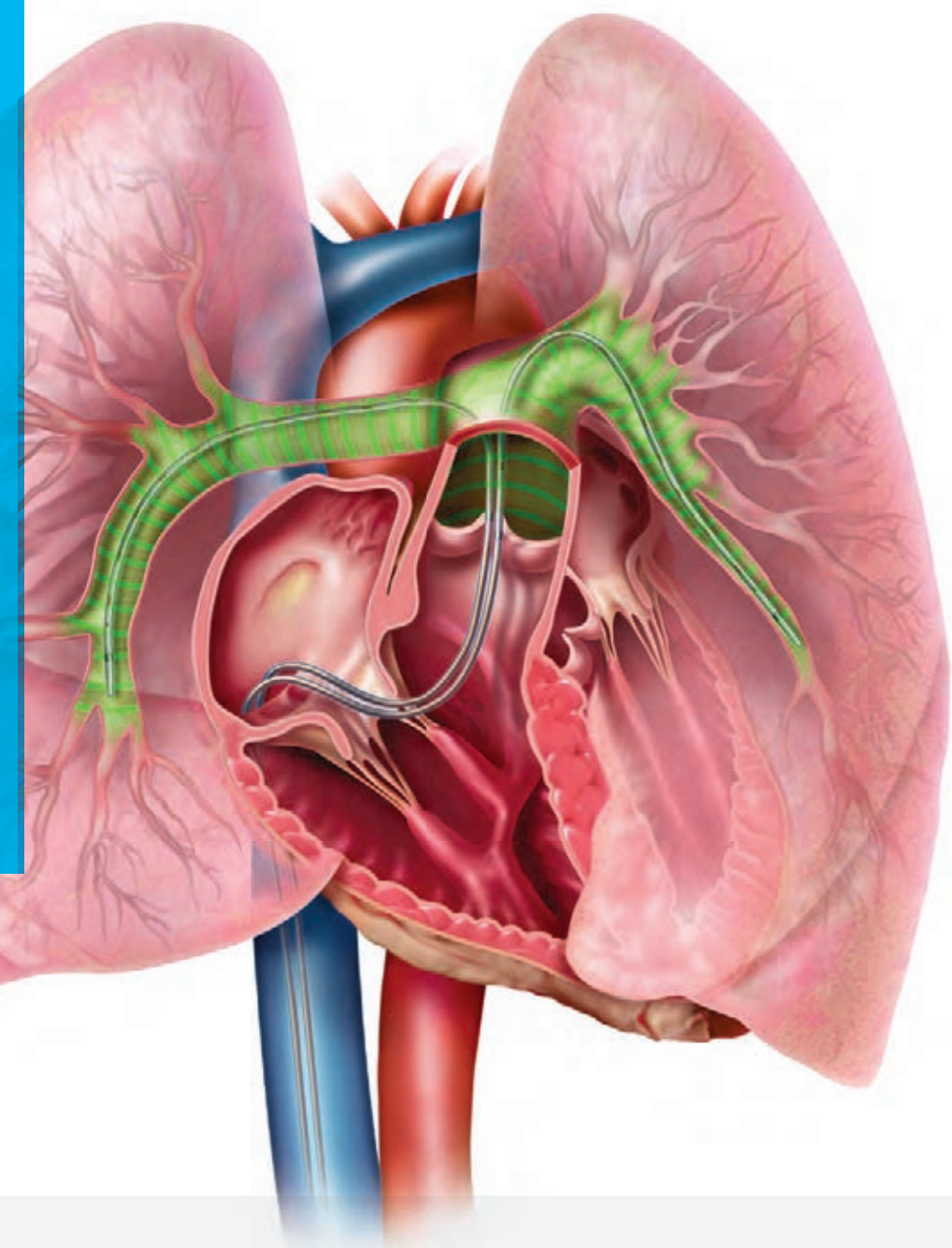

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2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

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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