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," the researchers said.

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

**DNRs affect residents’ patient care decisions**

**BY ELI ZIMMERMANN**

**Frontline Medical News**

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 reduction in apnea-hypopnea index events per hour is seen.”

Postoperative oxygen reduced number of AHI events

**Carbon dioxide retention a concern.**

**BY JIM KLING**

**Frontline Medical News**

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

**BY HEIDI SPLETE**

**Frontline Medical News**

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

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 departments.

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

**COMING SOON**

**A new look for CHEST Physician**

The Newspaper of the American College of Chest Physicians
**HELP PRESERVE MORE LUNG FUNCTION**

Reduce lung function decline with Esbriet®

**BROAD PATIENT POPULATION**

Clinical trials included patients with IPF with a range of clinical characteristics, demographics, and select comorbidities.*

**DEMONSTRATED EFFICACY**

In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF.†‡

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**Indication**

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

**Select Important Safety Information**

**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 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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*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 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). 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 (%DLCO) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks. In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DLCO ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DLCO ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks. Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND. 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). 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 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).

3 Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

4 The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.
Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

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

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


Learn more about Esbriet and how to access medication at EsbrietHCP.com.
ICU transfers tied to code status

DNRs from page 1

A internet 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]:336-42). 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, esophago-gastro-duodenoscopy, 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 were not always possible to reliably estimate their frequency. In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

| Table 2. Adverse Reactions Occurring in >10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3 |
|-------------------|-----------------|-----------------|-----------------|
| Adverse Reaction   | ESBRIET 2403 mg/day (N = 623) | Placebo (N = 624) |
| Nausea            | 18%             | 16%             |
| Rash              | 10%             | 10%             |
| Abdominal Pain    | 24%             | 15%             |
| Upper Respiratory Tract Infection | 27% | 25% |
| Diarrhea          | 26%             | 20%             |
| Fatigue           | 26%             | 19%             |
| Headache          | 22%             | 19%             |
| Dysgeusia         | 19%             | 7%              |
| Dizziness         | 18%             | 11%             |
| Vomiting          | 13%             | 6%              |
| Anorexia          | 13%             | 5%              |
| Gastro-esophageal Reflux Disease | 11% | 7% |
| Sinusitis         | 11%             | 10%             |
| Insomnia          | 10%             | 7%              |
| Weight Decreased  | 10%             | 5%              |
| Arthralgia        | 10%             | 7%              |

(Dosages and Administration section 2.3 in full Prescribing Information)

5.1 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 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. 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 the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations (see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information).

5.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a lower incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash (see Dosage and Administration section 2.3 in full Prescribing Information).

5.3 Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-oesophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. 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. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions (see Dosage and Administration section 2.3 in full Prescribing Information).

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

• Liver Enzyme Elevations (see Warnings and Precautions 5.1)
• Photosensitivity Reaction or Rash (see Warnings and Precautions 5.2)
• Gastrointestinal Disorders (see Warnings and Precautions 5.3)

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials. ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials. At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction. The most common adverse reactions with an incidence of >10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from CYP 2C9 isoenzymes including CYP2C9, 2C19, 2D6 and 2E1. Strong CYP1A2 inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET (see Clinical Pharmacology section 12.3 in full Prescribing Information) Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during
ESBRIET® (pirfenidone)

ESBRIET treatment. In the event that fluvoxamine or other strong CYP3A4 inhibitors are the only drugs of choice, dosage reductions are recommended. Monitor for adverse reactions and consider dosage adjustment of ESBRIET as needed. [see Dosage and Administration section 2.4 in full Prescribing Information]

Moderate CYP3A4 Inhibitors

Concomitant administration of ESBRIET and cilostazol (a moderate inhibitor of CYP3A4) moderately increases exposure to ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information] if cilostazol is at the dose of 500 mg twice daily cannot be avoided, dosage reductions are recommended. [see Dosage and Administration section 2.4 in full Prescribing Information].

Monitor patients closely when cilostazol is used at a dose of 250 mg or 500 mg once daily.

Concomitant CYP3A4 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP3A4 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, CYP19, 2C9, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

7.2 CYP3A4 Inducers

The concomitant use of ESBRIET and a CYP3A4 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP3A4 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP3A4 inducer [see Clinical Pharmacology section 12.3 in full Prescribing Information].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risks for major birth defects and miscarriage. In animal reproduction studies, pirfenidone was not teratogenic in rats and rabbits at oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults. [see Data]

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

Animal Data

Animal reproduction studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, and 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. In these studies, pirfenidone at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (mg/m² basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclovir/regular cycles (e.g., prolonged estrus cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (mg/m² basis at maternal doses of 450 mg/kg/day in rats and 300 mg/kg/day in rabbits). In a pre- and post-natal development study, female rats received pirfenidone at oral doses of 0, 30, 100, and 1000 mg/kg/day from GD 7 to lactation day 20. Prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at oral doses approximately 2 times the MRDD in adults (mg/m² basis at a maternal oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ESBRIET and the potential adverse effects on the breastfed child from ESBRIET or from the underlying maternal condition.

Data

Animal Data

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk. The effects of pirfenidone on the breastfed child, or its effects on milk production, are unknown.

C. 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 = 0.0008).

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 clinical 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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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 based on the preferences of the doctors, which is very concerning. Encouraging 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. Msha 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

A round 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 in the European Respiratory Journal (2018;42:630-638) that there are still insufficient data to support the use 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, with severe or refractory sarcoidosis involving two-thirds of patients.

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.
Some experienced substantial CO₂ retention

Postop O₂ 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 CO₂ retention. Specifically, for at least 10% of the nights, these patients had a partial pressure of CO₂ of at least 55 mm Hg, according to measurements taken with a transcutaneous CO₂ 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.
Continued from previous page

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 antibacterial 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.

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**INDICATION**

Tyvaso is a prostanoyl vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor).

The controlled clinical experience was limited to 12 weeks in duration.

References:

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**增加Tyvaso（treprostinil）的功效时添加至口服单药治疗**

- 添加Tyvaso后6分钟步行距离（6MWD）增加20 m（P<0.001）
- Tyvaso在TRIUMPH I中，12周、双盲、安慰剂对照、多中心研究中，患者（N=235）在PAH患者中，接受了稳定的bosentan或sildenafil治疗≥3个月后
- 患者接受每天4次治疗，每次54 mcg
- Tyvaso在TRIUMPH I研究中的使用，增加了6MWD（P<0.001）
- Tyvaso可以融入日常生活**

- 每次治疗要从3次呼吸开始，每1-2周增加3次呼吸
- 每天治疗 session
- 治疗 session的间期应为2-4小时
- 每天应服用3次呼吸，1-2周内
- 最常见的副作用包括咳嗽、头痛、喉咙不适/喉咽痛、恶心

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**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.
IMPORTANT SAFETY INFORMATION FOR TYVASO

WARNINGS AND PRECAUTIONS

• The efficacy of Tyvaso has not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
• Tyvaso is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension.
• Titrate slowly in patients with hepatic or renal insufficiency, as exposure to treprostinil may be increased in these patients.
• Tyvaso inhibits platelet aggregation and increases the risk of bleeding, particularly in patients receiving anticoagulants.
• Co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil may increase exposure to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to oral treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8.
• There are no adequate and well-controlled studies with Tyvaso in pregnant women. It is not known whether treprostinil is excreted in human milk.

ADVERSE REACTIONS

• The most common adverse events seen with Tyvaso in 24% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%).

Please see Brief Summary of Full Prescribing Information.

For additional information about Tyvaso, visit www.tyvaso.com or call 1-877-UNITHER (1-877-864-8437).

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TYVASO
(treprostinil)
INHALATION SOLUTION
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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 email 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 beta2-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 .007).

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 those in pediatric critical care to use continuous nebulized beta2-agonists for initial management or to add parenteral selective beta, 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.
Study mixed 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 19.3% 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.

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 set 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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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: INF00000000000001550).

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What do doctors want from health reform?

By Alicia Gallegos

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.

“With 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.

Improving reimbursement for Medicaid services is a necessary health reform change, said Diane J. Horvath-Cosper, MD, an obste-trician-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.”

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. “The doctors can sign away their rights to a proper insurance payment,” she 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 patient 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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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-inefficient 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.

For uncontrolled asthma in patients aged ≥6 years on ICS or ICS + LABA
SPIRIVA RESPIMAT – A different approach adds new expectations for asthma

SPIRIVA RESPIMAT, 1.25 mcg, is a bronchodilator indicated for the long-term, once-daily, maintenance treatment of asthma in patients 6 years of age and older. SPIRIVA RESPIMAT is not indicated for relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION

SPIRIVA RESPIMAT is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any component of this product. Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for asthma and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. In the event of an attack, a rapid-acting beta₂-agonist should be used.

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, discontinue SPIRIVA RESPIMAT at once and consider alternative treatments. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT.

Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated with an inhaled short-acting beta₂-agonist, such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered.

SPIRIVA RESPIMAT 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.
IMPORTANT SAFETY INFORMATION (continued)

Since dizziness and blurred vision may occur with the use of SPIRIVA RESPIMAT, caution patients about engaging in activities such as driving a vehicle, or operating appliances or machinery. SPIRIVA RESPIMAT 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.

Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects.

The most common adverse reactions >2% incidence and higher than placebo with SPIRIVA RESPIMAT (placebo) in asthma trials in adults were pharyngitis 15.9% (12.4%), headache 3.8% (2.7%), bronchitis 3.3% (1.4%), and sinusitis 2.7% (1.4%). The adverse reaction profile for adolescent and pediatric patients was comparable to that observed in adult patients with asthma.

SPIRIVA RESPIMAT may interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs.

Inform patients not to spray SPIRIVA RESPIMAT into the eyes as this may cause blurring of vision and pupil dilation.

Please see Brief Summary of full Prescribing Information on the following pages.
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 is a game-changer for them," she said in an interview.

Mary Ann Namani, vice president at Avalere Health.

"Continued from previous page..."

"Preventives and..."
if President Trump makes good on his threat to withhold cost-sharing subsidies to insurers. The subsidies already are subject of a lawsuit brought by the House of Representatives against the Obama administration; they continue to be paid while the lawsuit 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.”

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, co-signed 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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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.
The power of flexibility is yours with REVATIO Oral Suspension

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

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Indication

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

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

Important Safety Information

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

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

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

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

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

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

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

Co-administration of REVATIO with potent CYP3A4 inhibitors (e.g., 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.
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 predominantly patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic pulmonary hypertension (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.

DOSE 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. Add 60 mL of water to the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Measure out 20 mL of the suspension by inserting a dropper into the neck of the bottle. The dropper 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 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 nitrates, a guanylate cyclase stimulator, PDE-5 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 use of the 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 about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic, 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 concomitantly 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. The effect was 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 (8% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with uncontrolled bleeding disorders.

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 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 increased risk 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 an event is associated with 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 who 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 vascular 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 VAGRA®. The safety and efficacy combinations of REVATIO with VAGRA® or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VAGRA® or other PDE-5 inhibitors.

Priapism
Use REVATIO with caution in patients with anatomic deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which 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 trial (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 than 5% in REVATIO-Treated Patients and Less than 3% in Placebo-Treated Patients)

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

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diaphoresis, 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 1.3% 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 hemorrhage have been reported in less than 2% of patients. 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 sexual activity in patients who had not used 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 CYP3A4 Inhibitors
Concomitant use of ritonavir and other potent CYP3A4 inhibitors is not recommended.
There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope. Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Category B** There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD). Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

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

**Pediatric Use** In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (22%), II (57%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

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

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 1.39, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

**Geriatric Use** Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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

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

**PATIENT COUNSELING INFORMATION**

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

Rx only  Rev. June 2015

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Pfizer

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 at 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 have no surgical option. The data show that untreated comorbidities really impact prognosis,” said Dr. Sorajja 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 (65%) of the patients.

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 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 beta₂-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 AEROSPHERE 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 beta₂-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 sympathomimetic 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 beta₂-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

MAXIMIZE BRONCHODILATION†

Improved lung function1 vs placebo including:

• 150-mL improvement in predose FEV₁, at 24 weeks
• Nearly a 300-mL improvement in peak FEV₁, at 24 weeks
• Nearly a 200-mL improvement in FEV₁, at 5 minutes on Day 1

In a separate study vs placebo:

• Achieved a 381-mL improvement in peak inspiratory capacity on Day 29

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

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.

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.


*BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting β₂-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

†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 FEV₁ of ≤80% of predicted normal values, and FEV₁/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV₁, at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mg fumarate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; P<0.001 for all treatment comparisons. Statistical significance results were also seen in Trial 2.12

‡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.21

§Primary endpoint, FEV₁ AUC₂₄: Study A – BEVESPI AEROSPHERE (n=35) vs placebo (n=31) = 249 mL (baseline FEV₁ 1.382 L and 1.345 L, respectively); Study B – BEVESPI AEROSPHERE (n=65) vs placebo (n=63) = 265 mL (baseline FEV₁ 1.328 L and 1.333 L, respectively); both P<0.0001.12

¶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<0.0001.12

Learn more at DUALBRONCHODILATION.COM
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 beta₂-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 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 (5.5) 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 risk 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; 0.07% vs. 0.02%). The risk of asthma-related death was not increased when LABAs were compared with placebo in other studies of patients with COPD.

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 (5.3) in the full Prescribing Information)
• Cardiovascular effects (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 following adverse reactions are described in greater detail elsewhere in the labeling:

• Paradoxical bronchospasm
• Hypersensitivity reactions
• Cardiovascular effects
• Worsening of urinary retention

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=2,103 and n=1,816, 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 (FEV₁) 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: % Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BEVESPI AEROSPHERE (n=1036)</th>
<th>Glycopyrrolate 18 mcg BID (n=896)</th>
<th>Placebo (n=443)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Cough</td>
<td>4.0</td>
<td>3.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Infections and infestation</td>
<td>2.0</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Urinary tract incontinence</td>
<td>2.6</td>
<td>1.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

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, prophyllergic pain, vomiting, pain in extremity, dizziness, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.
Long-Term Safety Extension Trial
In a 28-week long-term safety extension trial, 683 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 sympathomimetic 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, adrenergic-agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparring Diuretics
The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparring 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. Approximately 17% of subjects were taking non-potassium sparring diuretics during the two 24-week placebo-controlled trials in subjects with COPD.

The incidence of adverse events in subjects taking non-potassium-sparring 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 sparring diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparring diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs
BEVESPI AEROSPHERE, as with other beta-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-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/m² basis) at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 3.5 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, embryotoxic, 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 81,000 (rabbits) times the MRHDID (on a mg/m² 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/m² basis at maternal oral doses of 3 mg/kg and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7,600 times the MRHDID (on a mg/m² 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/m² basis at maternal intramuscular injection 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/m² basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3,800 times the MRHDID (on a mg/m² 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 beta₂-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 m²) 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 overdose for the individual components described below apply to BEVESPI AEROSPHERE.

Treatment of overdose 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 bronchospasms. Cardiac monitoring is recommended in case of overdose.

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 intracranial pressure (causing pain, vision disturbances or reddening of the eye), obtipation 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 beta₂-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular arrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, restlessness, 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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By: Aventis Pharma LTD, Holmes Chapel CW488, United Kingdom
04/16 3309803 11/16
Preoperative variables can predict prolonged air leak

By Richard Mark Kirkner

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.

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

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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.

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 peritoneum 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.

PAP sensor may cut real-world heart failure hospitalization

By Mary Ann Moon

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

Continued on following page
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.

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**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.”

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.

“We also think that pathways can have a major impact on things like symptom management and survi-
Consistent Treatment Effect on Time to First Disease Progression Event, Irrespective of PAH Background Therapy

**PRIMARY ENDPOINT: TIME TO FIRST DISEASE PROGRESSION EVENT IN GRIPHON**

A primary endpoint event was experienced by 27.0% (155/574) of UPTRAVI-treated patients vs 41.6% (242/582) of placebo-treated patients. Disease progression primary endpoint comprised the following components as first events (up to end of treatment; UPTRAVI vs placebo):

- Hospitalization for PAH (13.6% vs 18.7%)
- Other disease progression events (6.6% vs 17.2%)
- Death (4.9% vs 3.1%)
- Initiation of parenteral prostanoid or chronic oxygen therapy (1.7% vs 2.2%)
- PAH worsening resulting in need for lung transplantation or balloon atrial septostomy (0.2% vs 0.3%)

Reductions in PAH-related hospitalization and other disease progression events drove an overall 40% risk reduction.

Add UPTRAVI to an ERA + PDE-5i for All-oral TRIPLE-combination Therapy

### IMPORTANT SAFETY INFORMATION (cont’d)

### DOSAGE AND ADMINISTRATION

**Recommended Dosage**

Recommended starting dose is 200 mcg twice daily. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

**Patients with Hepatic Impairment**

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

**Dosage Strengths**

UPTRAVI tablet strengths:

- 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg

Please see Brief Summary of Prescribing Information on the following page.

*An ERA, PDE-5i, or both.

Other disease progression defined as a 15% decrease from baseline in 6MWD plus worsening of Functional Class or need for additional PAH-specific therapy.

6MWD=6-minute walk distance; ERA=endothelin receptor antagonist; ERS=European Respiratory Society; ESC=European Society of Cardiology; PDE=Phosphodiesterase type-5 inhibitor; WHO=World Health Organization.


Visit www.UPTRAVI.com/hcp to learn more

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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.”

More information, 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 it 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 chemotherapy, oral chemotherapy, 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 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.”

Continued on following page

More evidence of benefit

Continued from previous page

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

30 LUNG CANCER MAY 2017 • CHEST PHYSICIAN

Brief Summary

Discontinue nursing or discontinue Uptravi.

It is not known if uptravi is present in human milk. Selexipag or its metabolites may be excreted in human milk. Selexipag is an inhibitor of important breast cancer resistance protein (BCRP).

Uptake by the Breast Cancer Resistance Protein (BCRP).

Selexipag is a substrate of human hepatic cytochrome p450 enzyme CYP3A4 and the glucuronidation of the active metabolite is catalyzed by UGT1A3. Selexipag is a substrate of OATP1B3 and P-gp. The cytochrome p450 is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. The active metabolite is a substrate of the transporter of breast cancer resistance protein (BCRP).

selexipag do not inhibit or induce hepatic cytochrome P450 enzymes at clinically relevant concentrations. Selexipag and its active metabolite do not inhibit BCRP and other transport proteins.

The effect of strong inhibitors of CYP3A4 (such as gemfibrozil) on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration with strong inhibitors of CYP3A4 may result in a significant increase in exposure to selexipag and its active metabolite [see Drug Interactions].

The results on in vivo drug interaction studies are presented in Figure 1.

Figure 1 Effect of Other Drugs on Uptravi and its Active Metabolite (A) and Effect of Uptravi on Warfarin (B)
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

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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.

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.

“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.
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.

“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 29,049 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/m² (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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Continued from previous page

guidelines around biomarker testing in advanced NSCLC, and we saw significant variation in testing in the squamous population and the non-squamous 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 non-squamous 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.

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 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.
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,-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.

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.
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).!

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 beta₂-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 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.

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.

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† 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.

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 beta₂-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.

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.
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 wlm FEV₁ (0-24 hours) vs placebo (n=51) at end of the 28-day treatment period (P<0.001).³,⁴

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 FEV₁ of 50% and a mean postbronchodilator FEV₁/FVC ratio of 53%.

Primary endpoint: wlm FEV₁ (0-24 hours) at end of 28-day treatment period.

Secondary endpoint: serial FEV₁ (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 wlm FEV₁ (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 FEV₁, 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 FEV₁ of 48% and a mean postbronchodilator FEV₁/FVC ratio of 48%.

¶The trough FEV₁ comparison of BREO with VI, the LABA component, evaluated the contribution of FF to BREO. VI is not approved as monotherapy.


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.

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).


Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.
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, darithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, 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.
- Vilterol 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 intracocular 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 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, darithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, 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 vilterol, 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 vilterol, 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.
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; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta-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 (13/13,176) vs. placebo (6/13,179) in subjects treated with placebo; relative risk: 4.37 (95% CI: 1.25, 15.34). The increase in asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. 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 bronchostenosis; the patient’s inhaled, short-acting, beta-, agonist should be considered less effective; or if beta-, 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,-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special attention 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 this purpose. In clinical trials, the development of localized infections of the mouth and pharynx with furoate/vilanterol has occurred in subjects treated with BREO. In clinical trials, the use of systemic corticosteroids should be instructed to resume oral corticosteroids in patients with asthma during and after treatment with BREO. 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 including symptoms of adrenal insufficiency, which may be suggestive of systemic corticosteroid withdrawal. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, urticaria, eczema, atopic dermatitis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systematically 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 systematically 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 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 have experienced side 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-acting ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, etc.).
chondromycosis, 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 angioedema, anaphylaxis, rash, and urticaria may occur after administration of corticosteroids. 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: Vilastron, like other beta,-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 4/10 (the recommended dose of vilanterol, representing a 12- to 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 been of potential for producing cardiac 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. Vilastron has been shown to cause decreases in 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 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,-adrenergic agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketosis or hyperglycemia.

5.16 Hypokalemia and Hyperglycemia: Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shifting, which has the potential to produce adrenergic cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines 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: Daily 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 AVERSE REACTIONS

LABA, such as vilastron, 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 in adult patients in asthma-related deaths in subjects receiving salmeterol. [See Warnings and Precautions (5.1)] Systemic and local corticosteroid use may result in the following: Cauda albuginea injection [see Warnings and Precautions (4.1)] increased intraocular pressure in COPD and asthma and Warnings and Precautions (5.3); Immunosuppression [see Warnings and Precautions (5.6)]. Hyperglycemia and adrenal suppression [see Warnings and Precautions (4.7)]. It is not clear whether corticosteroid use is a risk factor for severe asthma and exacerbation of asthma. [See Warnings and Precautions (5.1), 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. Other causes of variations in rates of clinical trials of a drug may be due to differences in the types and severity of the populations evaluated, as well as other inherent differences in the trials. 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 considered.

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 months of short-course trials. Of 2,034 subjects with COPD received at least 1 dose of BREO 100/25, and 1,987 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.

6.2 Long-Term Trials: The incidence of adverse reactions associated with BREO 100/25 is based on 2 placebo-controlled, 6-month clinical trials (10,020 subjects): 1,224 subjects treated with BREO 100/25, 1,236 subjects treated with placebo, and 1,254 subjects treated at the 2,524 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 FEV1 was 48% (range: 14% to 87%), and the mean postbronchodilator FEV1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: 0% to 152%). Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/cc, fluticasone furoate 100 mcg fluticasone 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 [n=410]; or placebo [n=412]) were: nasopharyngitis 9% (10%, 8%, 6%); upper respiratory tract infection 7% (5%, 4%, 3%); headache 7% (7%, 5%, 5%); and oropharyngeal candidiasis 5% (2%, 3%, 2%). Oropharyngeal candidiasis includes oral candidiasis, candidiasis, and fungous oropharyngitis.

6.2.1 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 voluntarily reported from a population of uncertain size, it is not always possible to reliably estimate the estimates or establish the causal relationship to drug exposure. These events have been chosen for inclusion due to their seriousness, frequency of reporting, or cause of death to BREO or a combination of these factors.


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, claramben, nelﬁnavir, saquinavir, telithromycin, voriconazole) [see Warnings and Precautions (5.3)].

7.2 Monooamine Oxidase Inhibitors and Tricyclic Antidepressants: Vilastron, like other beta,-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors. The duration of effect of these agents may extend beyond 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 drugs. Concomitant use of these agents with other drugs 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 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.
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 (5.4) 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 2,518 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, overdose of fluticasone furoate is unlikely to require any other treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur [see Warnings and Precautions (5.4)]. 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 associated with excessive beta-adrenergic stimulation (e.g., tachycardia, tremor, nervousness, palpitations, tremor, muscle cramps, dry mouth, hypokalemia, 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
Advises 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 patients 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-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-agonists; need for more inhalations than usual of inhaled, short-acting beta-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-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, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression:
Advises 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:
Advises 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-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Hypersensitivity Reactions, Including Anaphylaxis:
Advises 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; patients with severe milk protein allergy should not use BREO.

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BREO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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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 underrated 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, otolaryngology/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/m² (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.

"Work 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.

Ezimmerman@frontlinemedcom.com
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).

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.
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:g5396). 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

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**OFEV has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials**

**INPULSIS®-1 (Study 2)**

<table>
<thead>
<tr>
<th>Group</th>
<th>FVC Decline (mL/year)</th>
<th>Relative Reduction</th>
<th>P Value</th>
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<tr>
<td>Placebo (n=204)</td>
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<td>OFEV (n=309)</td>
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**INPULSIS®-2 (Study 3)**

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<td>OFEV (n=329)</td>
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**TOMORROW (Study 1)**

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<th>Relative Reduction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
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<td>Placebo (n=83)</td>
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<tr>
<td>OFEV (n=84)</td>
<td>-191</td>
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</table>

*The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.*

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**IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)**

**Elevated Liver Enzymes**

- OFEV (nintedanib) was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN.
- Conduct liver function tests prior to treatment, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Monitor for adverse reactions and consider dosage modifications, interruption, or discontinuation as necessary for liver enzyme elevations.

**Gastrointestinal Disorders**

**Diarrhea**

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and 1% in placebo patients, respectively.
- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and anti-diarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

**Nausea and Vomiting**

- Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

**Embryofetal Toxicity**: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to starting OFEV.
Arterial Thromboembolic Events: Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

In INPULSIS®-2 trials, similar results were observed. Lung function improvement is defined as a ≥0% decline in predicted FVC at 52 weeks, meaning patients’ predicted FVC increased from baseline. More patients had improved lung function with OFEV than with placebo in the INPULSIS® trials.

Less than one-third of patients on OFEV had a meaningful decline in lung function in the INPULSIS® trials. A meaningful decline is defined as patients with an absolute decline of ≥10 percentage points in predicted FVC at 52 weeks.

In INPULSIS® trials, there was not a statistically significant difference in all-cause mortality for OFEV compared with placebo.

According to American Thoracic Society (ATS) guidelines, ≥10% FVC decline is an established measure of IPF disease progression and a surrogate marker in mortality.

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT’D)

Arterial Thromboembolic Events: Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Please see additional Important Safety Information and brief summary for OFEV on the following pages.
Continued from previous page

tuple 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-

OFEV is only available through participating specialty pharmacies

TO GET YOUR APPROPRIATE PATIENTS WITH IPF STARTED ON OFEV:

CONDUCT liver function tests (ALT, AST, and bilirubin) prior to initiating treatment with OFEV (nintedanib)

COMPLETE the OFEV Prescription Form—available at www.OFEVhcp.com—and fax it to one of the participating specialty pharmacies

OFFER enrollment in OPEN DOORS™, a patient support program for patients receiving OFEV

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT’D)

Risk of Bleeding: OFEV may increase the risk of bleeding. Bleeding events were reported in 10% of OFEV versus 7% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation: OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus in 0% placebo patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

• Adverse reactions reported in ≥5% of OFEV patients included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.

• The most frequent serious adverse reactions reported in OFEV patients were bronchitis and myocardial infarction. The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

• Adverse reactions reported in ≥1% of OFEV patients included abnormal liver function tests and increases in ALT, AST, and bilirubin.

• The most frequent adverse reactions reported in ≥1% of placebo patients included infection (11.0% vs. 10.3%), decreased appetite (10.2% vs. 9.3%), and diarrhea (6.5% vs. 5.3%).

• There were some serious adverse reactions reported in ≥1% of OFEV versus placebo patients, including liver failure, pancreatitis, gastrointestinal perforation, and renal failure.

• Adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.

COMMENTS

Please see accompanying brief summary of Prescribing Information, including Patient Information.

A recent report of hypoglossal nerve endoscopy may also be considered. Interventions based on assessment of oral therapy to encourage avoidance 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. Shabt 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

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.”

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.
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 postsepsis 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.

“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,” Dr. Reznik said.

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 3% 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.

jevans@frontlinemedcom.com
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 significantly 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 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 13% (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 13.3 days. Progression to proven lower respiratory tract infection affected 3% of the HCT recipients.

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

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 disinfection is an overlooked method for reducing transmission of pathogens.

“Floors in hospital patients’ rooms are frequently contaminated with pathogens such as Clostridium difficile, methicillin-resistant Staphylococcus aureus, and vancomycin-resistant enterococci,” the authors wrote. “Disinfection of the floor of the patient’s room may be an easy method to reduce transmission.”

In a retrospective study at a hospital, researchers found that 75% of patients with a positive nasal swab were colonized on the floor of their rooms. Pathogens were detected from 24% of the floors, and 10% of the floors were contaminated by two or more pathogens.

The researchers concluded that floors are an overlooked route of transmission and that floor disinfection should be considered as an additional method of reducing hospital-acquired infections.

Continued on following page
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 an HR of 3.66 for progression to lower respiratory tract infection.

Floors Continued from previous page

Infection 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 hands, 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.

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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SYMBICORT 160/4.5 for the maintenance treatment of COPD

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

** IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING **

2. WARNING: Long-acting beta-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA

3. SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

4. SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD

5. Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason

6. Localized infections of the mouth and pharynx with Candida albicans has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT

7. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids

8. Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients

9. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids

10. Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors

11. As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT

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

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNING, on following pages.
Improvement at 5 minutes Improvement at 1 hour SYMBICORT 160/4.5 mcg ‡

serial spirometry subset (n=121)

Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Long-term use of orally inhaled corticosteroids may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter.

Glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts.

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients.

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions.

FDA clears procalcitonin test to hone antibiotic use

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.

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BY DEEPAK CHITNIS

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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 BRUCIE JANCIN

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 empirically 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.”

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION
For full Prescribing Information, see package insert.

WARNING: ASTHMA-RELATED DEATH
Long-acting beta-2-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of anotherLABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA. Although available data are inadequate to determine whether the concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with an inhaled corticosteroid and LABA. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. (see Warnings and Precautions [5.1]).

INDICATIONS AND USAGE
Treatment of Asthma
SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older. LABA, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. 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]) and the full Prescribing Information). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. (see Warnings and Precautions [5.1]).

Important Limitations of Use:
• SYMBICORT is not indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease
SYMBICORT 160/4.5 is indicated for the twice daily maintenanced treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only strength indicated for the treatment of airflow obstruction in patients with COPD. (see Warnings and Precautions [5.1]).

Important Limitations of Use:
• SYMBICORT is not indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS
The use of SYMBICORT is contraindicated in the following conditions:
• Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where ventilation is compromised.

Inhaled corticosteroids are indicated in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only strength indicated for the treatment of airflow obstruction in patients with COPD. (see Warnings and Precautions [5.1]).

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• SYMBICORT is not indicated for the relief of acute bronchospasm.

WARRIORS AND PRECAUTIONS
Asthma-Related Death
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Important Limitations of Use:
• SYMBICORT is not indicated for the relief of acute bronchospasm.

Immunosuppression
Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox 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 three diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, rate, and duration of corticosteroid administration affects 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 unknown. Influenza, pneumonia, and varicella zoster immune globulin (VZIG) or intravenous immunoglobulin (IVIG) may be indicated. (see the respective package insert for complete VZIG and IVIG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma aged 2 to 18 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=131) or noncorticosteroid asthma therapy (n=42) (i.e., long-acting beta-2 agonists, inhaled long-acting muscarinic antagonists). The percentage of patients developing a serum neutralizing antibody titer of ≥ 5 (geometric mean value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%) compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhalated corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or sarcoidosis.

Transferring Patients From Systemic Corticosteroid Therapy
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. 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 per day 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 gastrointestinal) or other conditions associated with severe stress. Although SYMBICORT may provide control of asthmatic 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 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 supplemental systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the targeting blood levels below 1.2 ng/
fibrillation guidelines recommend digoxin for rate control in patients with AF, and neither set of guidelines contains any specific recommendation about serum digoxin levels.

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 13;365(11):981-92), demonstrated that apixaban was the superior oral anticoagulant in prevention of stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. ARISTOTLE had some unique features that rendered the study data valuable for use in a large observational study of digoxin’s safety in patients with AF. It included a detailed serial assessment of concomitant treatments.

Continued on following page
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 independent of baseline related to 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 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 for 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.

Fourty-three percent of ARISTOTLE participants had heart failure at enrollment. Interestingly, the increased risk of death associated with on-treatment 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 really a truly, 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,” said Dr. Lopes.

A beaming Dr. Lopes responded that it’s likely that some of the past conflicting studies were marred by survival bias—the 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.

Continued on following page
Caution urged in extending dual-antiplatelet therapy

BY BRUCE JANCI
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 institution-al variation with respect to this kind of decision making, and I don’t think our guidelines are meant to be prescriptive, 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 willing 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.

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 proarhythmic 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 Ingeheim, Daiichi Sankyo, GlaxoSmithKline, Medtronic, Merck, and Portola.

Dr. Renato D. Lopes, 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 proarhythmic effects.”

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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 recurring 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 those exposed to less than 10 Gy (hazard ratio, 5.47) or to 10-20 Gy (HR, 2.76).

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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 coexistence 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®.

“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. Simpson continued on page 59

> Learn More livelearning.chestnet.org

Live Learning Courses Courses held at the CHEST Innovation, Simulation, and Training Center in Glenview, Illinois.

Advanced Critical Care Echocardiography
June 2-4

Mechanical Ventilation: Advanced Critical Care Management
July 28-30

Ultrasoundography: Essentials in Critical Care
September 15-17

Comprehensive Bronchoscopy With Endobronchial Ultrasound
September 29 - October 1

Difficult Airway Management
July 14-16

Comprehensive Pleural Procedures
August 4-5

Cardiopulmonary Exercise Testing
September 22-24

Critical Care Ultrasound: Integration into Clinical Practice
November 10-12

Bronchoscopy and Pleural Procedures for Pulmonary and Critical Care Medicine Fellows
July 21

Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers
August 11-13

Calendar subject to change. For most current course list and more information, visit livelearning.chestnet.org
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.

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.

Easy Solutions for a Greater Impact

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, I sought feedback from our members, 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.

Continued from page 57

This month in CHEST: Editor’s picks

Original Research

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 Healthy Subjects. By Dr. C. Kempecevs.

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.

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.

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!
6MWD is associated with clinical outcomes in many distance (6MWD) measured as the primary outcome. To "walk as far as possible for 6 minutes" with this overall integrated physiologic responses to exercise impairment, the 6MWT provides an assessment of the though it does not diagnose specific etiologies of im-

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 (Am J Cardiol. 2013;62[5 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 et al. J Thorac Oncol. 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 carbonylase-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 prostanooid 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
Pulmonologist and Critical Care Physician

Monongalia General Hospital in Morgantown, WV is seeking a full time Board Certified or Board Eligible pulmonologist and critical care physician. This is a great opportunity for someone who wants to join a very busy practice.

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The 189-bed not-for-profit community hospital recently completed a $92M renovation and expansion. Mon General Hospital is one of only 2% of hospitals nationally awarded both a Patient Safety Award and a Patient Experience Award by Healthgrades, a leading online resource for comprehensive information about physicians and hospitals. We are a Level IV Trauma Center and a certified Chest Pain Center with a university hospital operating a Level I trauma center is less than 1 mile away.

Morgantown is a lovely place to practice medicine. Home to West Virginia University, the area has amenities that only a “college town” offers – great sports, theatre, shopping, nightlife and restaurants. Morgantown is a short drive to Pittsburgh, 3-4 hours to the Baltimore/Washington Metro area. Within an hour’s drive you’ll find class 4-5 white water rafting, snow/water skiing, mountain biking, hunting, fishing, golfing and a quality of life that is increasingly difficult to find. It also boasts an excellent public and private school system.

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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 methodological 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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PROFESSIONAL OPPORTUNITIES
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:

**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 of winning 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. Learn more, and register today at chestmeeting.chestnet.org.
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EKOS® does much more than the current standard of PE care. It speeds time to dissolution by unwinding the clot’s fibrin structure, allowing greater lytic dispersion and accelerated absorption. It also minimizes bleeding risk, requiring up to 4x less drug dosage than systemic delivery.

Visit www.ekoscorp.com to learn more about the only endovascular device cleared by the FDA for the treatment of pulmonary embolism.

1. In the Seattle II study of 150 patients with massive or submassive PE using an EKOS® and lytic combination, the mean RV/LV ratio decreased from 1.55 pre-procedure to 1.13 at 48 hours post-procedure (P<0.0001) while PA systolic pressure decreased from 51.4mmHg to 36.9mmHg (P<0.0001).


FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS: Peripheral Vasculature: The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. Pulmonary Embolism: The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with a 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure >25mmHg) or echocardiographic evaluation.