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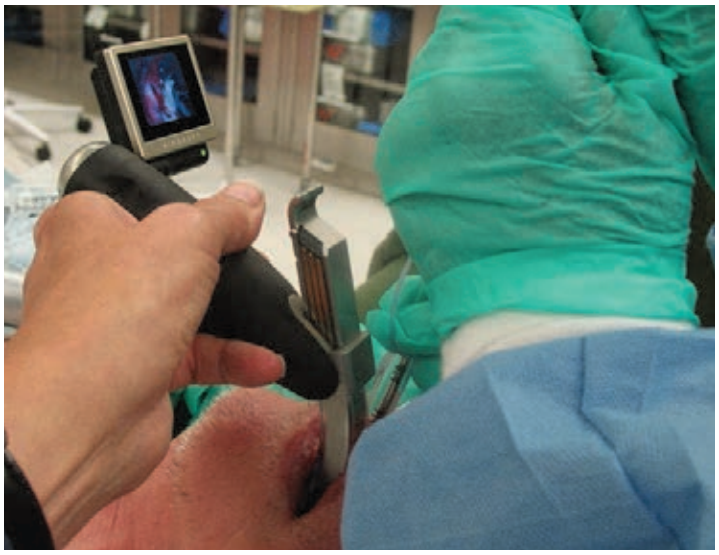

Improved glottis visualization with video laryngoscopy did not lead to a higher success rate for first-pass intubation.

Worse outcomes with video laryngoscopy

BY AMY KARON
Frontline Medical News

When used in intensive care units, video laryngoscopy did not improve the chances of successful intubation on the first try, compared with direct laryngoscopy, and was associated with a significantly higher risk of severe life-threatening complications, researchers reported.

In a multicenter, randomized trial of 371 patients, first-pass intubation rates did not differ significantly whether video or direct laryngoscopy was used, at 67.7% and 70.3%, respectively, Jean Baptiste Lascarrou, MD, of District Hospital Centre, La Roche-sur-Yon, France, and his associates wrote. Meanwhile, the combined rate of death, cardiac arrest, severe cardiovascular collapse, and hypoxemia was 9.5% with video laryngoscopy and just 2.8% with direct laryngoscopy, a significant difference (JAMA. 2017 Jan 24;317[5]:483-93).

"Improved glottis visualization with video laryngoscopy did not translate into a higher success rate for first-pass intubation, because tracheal catheterization under indirect vision was more difficult, in keeping with earlier data," the researchers concluded. "Further studies are needed to assess the comparative effectiveness of these two strategies in different clinical

See **Intubation** • *page 7*

CF guidelines include lower sweat chloride threshold

BY WHITNEY MCKNIGHT
Frontline Medical News

Updated guidelines for the diagnosis and treatment of cystic fibrosis (CF) include two major changes.

The first important update is that clinicians use the latest classifications of the specific CF transmembrane conductance regulator (CFTR) gene mutations, from the Clinical and Functional TRanslation of CFTR (CFTR2) database, to aid with making a CF diagnosis in any patient, newborn to adult. The other of these changes relates to the chloride concentration level used to confirm CF diagnosis through a sweat test. Under the new guidelines, the sweat chloride threshold for "possible" CF or a CF-related disease was reduced to 30 mmol/L of chloride concentration from 40 mmol/L across all ages. The guidelines, written by an international team of collaborators and published by the Cystic Fibrosis Foundation, are available online in the Journal of Pediatrics (2017 Feb;181[suppl]:S4-15. doi: 10.1016/j.jpeds.2016.09.064).

Since its inception in

See **CF guidelines** • *page 4*

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Watch and wait often better than resecting in ground-glass opacities

BY WHITNEY MCKNIGHT
Frontline Medical News

FROM CHEST

Three years of follow-up is adequate for partially solid ground-glass opacity lesions that do not progress, while pure ground-glass opacity lesions that show no progression may require further follow-up care, a study suggests.

The results of the study strengthen the argument for taking a "watch and wait" approach, and raise the question of whether patient outcomes can be improved without more precise diagnostic criteria, said study author Shigei Sawada, MD, PhD, a researcher at the Shikoku Cancer Center in Matsuyama, Japan, and his colleagues. They drew these conclusions from performing a long-term outcome investigation of 226 patients with pure or mixed ground-

See **Ground-glass opacities** *page 7*

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

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  - —eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Esbriet® (pirfenidone) capsules 267 mg

Genotyping is recommended

CF guidelines *from page 1*

2008, the CFTR2 project has described over 300 specific variants in the CF gene and their various functional and clinical impacts. The project involves amassing phenotypic and genotypic information from patient registries to collect, quantify, and describe mutations reported in individuals with CF. Such mutations are categorized as CF causing, carrying a variety of potential clinical consequences; non–cystic fibrosis causing; or unknown. The previous guidelines, written in 2008, relied on a 23-mutation panel from the American College of Medical Genetics and Genomics and the American Congress of Obstetricians and Gynecologists.

"We've more precisely defined what cystic fibrosis is," Patrick R. Sosnay, MD, assistant professor of medicine at Johns Hopkins University, Baltimore, and coauthor of the guidelines, said in a statement. "The stakes in categorizing a mutation are particularly high. For example, claiming that a mutation 100% caus-

The stakes in categorizing a mutation are particularly high. A person's reproductive decisions, for example, might be affected by learning he could have a child with a mutation that is 100% causing cystic fibrosis, according to a statement from Dr. Sosnay.

es cystic fibrosis may affect people's reproductive decisions if they believe their child will have the mutation."

In the CFTR2 project, the "disease-liability" of each mutation is evaluated through a combination of sweat chloride and functional activity identified in cell-based systems, according to a supplement published simultaneously with the updated guidelines (J Pediatr. 2017 Feb;181[suppl]:S52-7. doi: 10.1016/j.jpeds.2016.09.068). Data from this project led to the discovery of a cohort of 746 persons diagnosed with

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: A comprehensive supplement in the Journal of Pediatrics entitled, "Introduction to 'Cystic Fibrosis Foundation Consensus Guidelines for Diagnosis of Cystic Fibrosis,'" reflects information introduced at the North American Cystic Fibrosis Conference in the fall 2016 (J Pediatr. 2017 Feb;181[suppl]:S1-3. doi:10.1016/jpeds.2016.09.062). It represents the work of an international committee of cystic fibrosis experts whose goal was to provide consensus on the diagnosis of cystic fibrosis, especially for newborns and for complex cases in older patients. The committee strove to combine the efforts of both the United States and European guidelines so that terminology would be more consistent also. Two highlights are lowering the normal sweat chloride result for all ages to less than 30 mmol/L and using the data from the Clinical & Functional Translation of CFTR team to understand how a specific mutation may or may not cause disease. This set of guidelines will lead to quality improvement in the diagnosis of CF in patients who may have CFTR-related disorders but not meet the criteria for a full CF diagnosis.

CF despite sweat chloride levels less than 60 mmol/L. These findings were the basis for the guideline authors' decision to lower the threshold of chloride concentration in sweat in order for an individual to be considered having a possible CF diagnosis, according to the supplement.

The guidelines include 27 approved consensus statements spanning four overlapping categories, and applying to screened and nonscreened populations; newborn screened populations and fetuses undergoing prenatal testing; infants with an uncertain diagnosis and designated as having either CFTR gene-related metabolic syndrome or being CF-screen positive, inconclusive diagnosis; and nonscreened patients who present with symptoms, including children before newborn

Continued on following page

Continued from previous page

screening implementation, those with false-negative tests, and older, nonscreened patients.

Although not specified in the consensus statements, the authors of a second supplement published simultaneously with the updated guidelines (J Pediatr. 2017;181[suppl]:S27-32. doi: 10.1016/j.jpeds.2016.09.063), wrote that they supported genotyping all individuals diagnosed with CF, even if physiologic tests establish the diagnosis, to better understand the disease's genetic epidemiology and to refine future therapies. "If the identified mutations are known to be associated with variable outcomes, or have unknown consequence, that genotype may not result in a CF phenotype. In these cases, other tests of CFTR function may help," this supplement's authors concluded.

The updated guideline authors recommend avoiding the use of terms such as "atypical" or "nonclassical" CF, as there is no consensus on the specific taxonomy of CF, since the genetic data are still emerging.

When a newborn test is administered, the guidelines warn that the heterogenous nature of newborn screening often leads to false-positive results, thus the need for the sweat test.

Although obtaining an adequate sweat specimen for chloride measurements can be difficult, the authors say it is possible, especially in full-term infants aged 1 month. Repeat sweat testing is recommended, as is nasal potential difference and intestinal current measurement in some cases.

"Understanding a disease's genetic epidemiology helps identify patients who may be subject to the clinical manifestations of that disease. As we learn more about the variants in cystic fibrosis genetics and the functional and clinical impacts, there is a greater opportunity to better characterize a CF mutation," Dr. De Palo said.

Another change to the guidelines is that newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional and genetic testing may now be designated as having CFTR-related metabolic syndrome/CF-screen positive inconclusive diagnosis (CRMS/CFSPID), instead of CFTR-related metabolic syndrome or CF-screen positive, inconclusive diagnosis. Regarding changes to screening for CRMS/CFSPID, the older guidelines called for such an assessment by age 2 months, repeated every 6-12 months, while the new guidelines say their recommendation on the duration and frequency of follow-up "remains to be determined."

The authors of the first supplement decry the lack of standardized CF diagnostic criteria for those diagnosed with CF outside of the neonatal period, and urge clinicians to rely on clinical evidence including organ pathologies typical in CF, such as bronchiectasis or pancreatic insufficiency, along with testing for the presence of CFTR dysfunction with sweat chloride testing, CFTR molecular genetic analysis, or CFTR physiologic tests.

In contrast, the second supplement states that "clinical suspicion should always take precedence" in making a CF diagnoses for individuals in this age group.

"Understanding a disease's genetic epidemiology helps identify patients who may be subject to the clinical manifestations of that disease. As we learn more about the variants in cystic fibrosis genetics and the functional and clinical impacts, there is a greater opportunity to better characterize a CF mutation," noted Vera A. De Palo, MD, MBA, FCCP, of Signature Healthcare in Brockton, Mass. "These guidelines will bring that enhanced knowledge to providers identifying and caring for cystic fibrosis patients."

Dr. Sosnay and Philip M. Farrell, MD, PhD, a coauthor of the guidelines, received funds from the Cystic Fibrosis Foundation, where guideline coauthor Terry B. White, PhD, is an employee. Kris De Boeck, MD, a coauthor of the first supplement, receives funding from Vertex Pharmaceuticals, Ablynx, Aptalis, Galapagos, Gilead, Pharmaxis, and PTC Therapeutics. The guideline and supplements' other authors have no disclosures.

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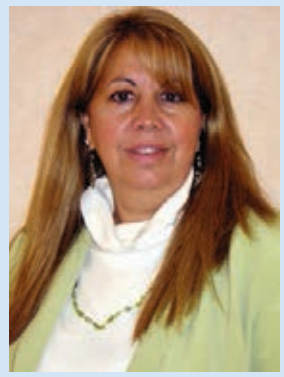

Vera A. De Palo, MD, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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AEs higher after video procedure

Intubation *from page 1*

settings and among operators with diverse skill levels."

Intubation in the ICU carries an inherently high risk because patients are often acutely unstable, and the intubating clinician is usually a nonexpert, the investigators noted. At the same time, the procedure must be done quickly to prevent aspiration because patients usually have not fasted. Care bundles and training on simulators have improved safety, but ICU intubations remain riskier than those done in the operating room.

Observational studies and smaller trials in ICUs seemed to support video laryngoscopy over the Macintosh laryngoscope, but raised questions about intubation time and mortality, the investigators noted. To help resolve these issues, they randomly assigned adults needing orotracheal intubation at seven ICUs in France to either video or direct Macintosh laryngoscopy, and followed them for 28 days. Patients averaged 63 years of age, and 37% were women.

For both arms, residents performed the initial intubation attempt in about 80% of cases, and successful intubation usually took 3 minutes. Video laryngoscopy did not significantly increase the combined risk of esophageal intubation, aspiration, arrhythmia, or dental injury (5.4% versus 7.7% for direct laryngoscopy). But the only death in the study occurred after video laryngoscopy, and there were four cardiac arrests after video laryngoscopy and none after direct laryngoscopy, the researchers said. Furthermore, the rate of severe hypoxemia was nearly six times higher after video laryngoscopy than with direct laryngoscopy, and the rate of hypotension was twice as high.

The researchers did not identify predictors of life-threatening complications with video laryngoscopy, but hypothesized that being able to clearly visualize the glottis might create "a false impression of safety," especially among nonexperts. "In addition, poorer alignment of the pharyngeal axis, laryngeal axis, and mouth opening despite good glottis visualization by video laryngoscopy can lead to mechanical upper airway obstruction and faster progression to hypoxemia," they wrote.

"As healthcare providers, we strive to continuously improve outcomes for our patients. As techniques and technologies continue to improve, clinical study permits us to evaluate new strategies," noted Vera A. De Palo, MD, MBA, FCCP, of Signature Healthcare in Brockton, Mass.

"While this study demonstrated no difference in first-pass orotracheal intubation rates between video laryngoscopy and direct laryngoscopy, the reported association of higher rates of severe life-threatening complications with video laryngoscopy bears further study."

Centre Hospitalier Département de la Vendée sponsored the study Dr. Lascarrou reported having no relevant conflicts of interest. Four coinvestigators disclosed ties to Fisher & Paykel, LFB, Merck Sharp & Dohme, Astellas, Basilea Pharmaceutica, Gilead, Alexion, and Cubist. The remaining coinvestigators had no disclosures.

VIEW ON THE NEWS

Video laryngoscopy creates blind spots

The results of this trial illustrate the fundamental problem with video laryngoscopy: It generates excellent views of the larynx but may not facilitate tracheal intubation.

The use of video laryngoscopy can lead to the creation of blind spots, both visual and cognitive. Because the lens of the laryngoscope is located at the tip of the device, the pharynx and hypopharynx are not visualized during video laryngoscopy. Manipulating the endotracheal tube into view therefore occurs within this blind spot, and this can be difficult depending on the patient's pharyngeal anatomy. This phenomenon has been linked to higher rates of pharyngeal soft tissue injury and longer intubation times in patients undergoing video laryngoscopy as compared with direct laryngoscopy.

The view during video laryngoscopy can also create a cognitive blind spot: Laryngoscopists may fail to abort a laryngoscopy attempt in a timely manner because they have such a clear view of the larynx.

Brian O'Gara, MD, and Daniel Talmor, MD, of Harvard Medical School, Boston, and Samuel Brown, MD, MS, of the University of Utah School, Murray, Utah, made these comments in an accompanying editorial (JAMA. 2017 Feb 7; doi: 10.1001/jama.2016.21036). None of the authors had relevant financial disclosures.

CT exam frequency

Ground-glass opacities *from page 1*

glass opacity lesions shown by CT imaging to be 3 cm or less in diameter.

Once established that the disease has stabilized in a pure or mixed ground-glass opacity lesion, "the frequency of CT examinations could probably be reduced or ... discontinued," the investigators wrote. The study is published online in Chest (2017;151[2]:308-15).

Because ground-glass opacities often can remain unchanged for years, reflexively choosing resection can result in a patient's being overtreated. Meanwhile, the use of increasingly accurate imaging technology likely means detection rates of such lesions will continue to increase, leaving clinicians to wonder about optimal management protocols, particularly since several guidance documents include differing recommendations on the timing of surveillance CTs for patients with stable disease.

The study includes 10-15 years of follow-up data on the 226 patients, registered between 2000 and 2005. Across the study, there were nearly twice as many women as men, all with an average age of 61 years. About a quarter had multiple ground-glass opacities; about a quarter also had partially consolidated lesions. Of the 124 patients who'd had resections, all but one was stage IA. The most prominent histologic subtype was adenocarcinoma in situ in 63 patients, followed by 39 patients with minimally invasive adenocarcinomas, and 19 with lepidic predominant adenocarcinomas. Five patients had papillary-predominant adenocarcinomas.

Roughly one-quarter of the cohort did not receive follow-up examinations after 68 months, as their lesions either remained stable or were shown to have reduced in size. Another 45 continued to undergo follow-up examinations.

After initial detection of a pure ground-glass opacity, the CT examination schedule was every 3, 6, and 12 months, and then annually. After detection of a mixed ground-glass opacity, a CT examination was given every 3 months for the first year, then reduced to every 6 months thereafter. In patients with stable disease, the individual clinicians determined whether to obtain additional CT follow-up imaging.

A ground-glass lesion was determined to have progressed if the diameter increased, as it did in about a third of patients; or, if there was new or increased consolidation, as there was in about two-thirds of patients. The table of consolidation/tumor ratios (CTR) used included CTR zero, also referred to as a pure ground-glass lesion; CTR 1-25; CTR 26-50; and CTR equal to or greater than 51. When there were multiple lesions, the largest one detected was the target.

All cases of patients with a CTR of more than zero were identified within 3 years, while 13.6% of patients with a CTR of zero required more than 3 years to identify tumor growth. Aggressive cancer was detected in 4% of patients with a CTR of zero and in 70% of those with a CTR greater than 25% (*P* less than .001). Aggressive cancer was seen in 46% of those with consolidation/tumor ratios that increased during follow-up and in 8% of those whose tumors increased in diameter (*P* less than

Continued on page 12

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: This study provides further support that the biology of ground-glass and part-solid nodules is different than fully solid nodules – and we should not be in a rush to resect these lesions. While the recommendations are likely to evolve over time as more information becomes available, this conservative approach toward nonsolid nodules is currently adopted in the Lung-RADS guidelines. Invasive action on these nodules is based on solid component size and growth, and usually the interval for following them once they have demonstrated early stability is annually. The optimal duration of follow-up is still in question, but ceasing follow-up for all part-solid nodules at 3 years likely is premature given the variable slow progression these nodules exhibit.

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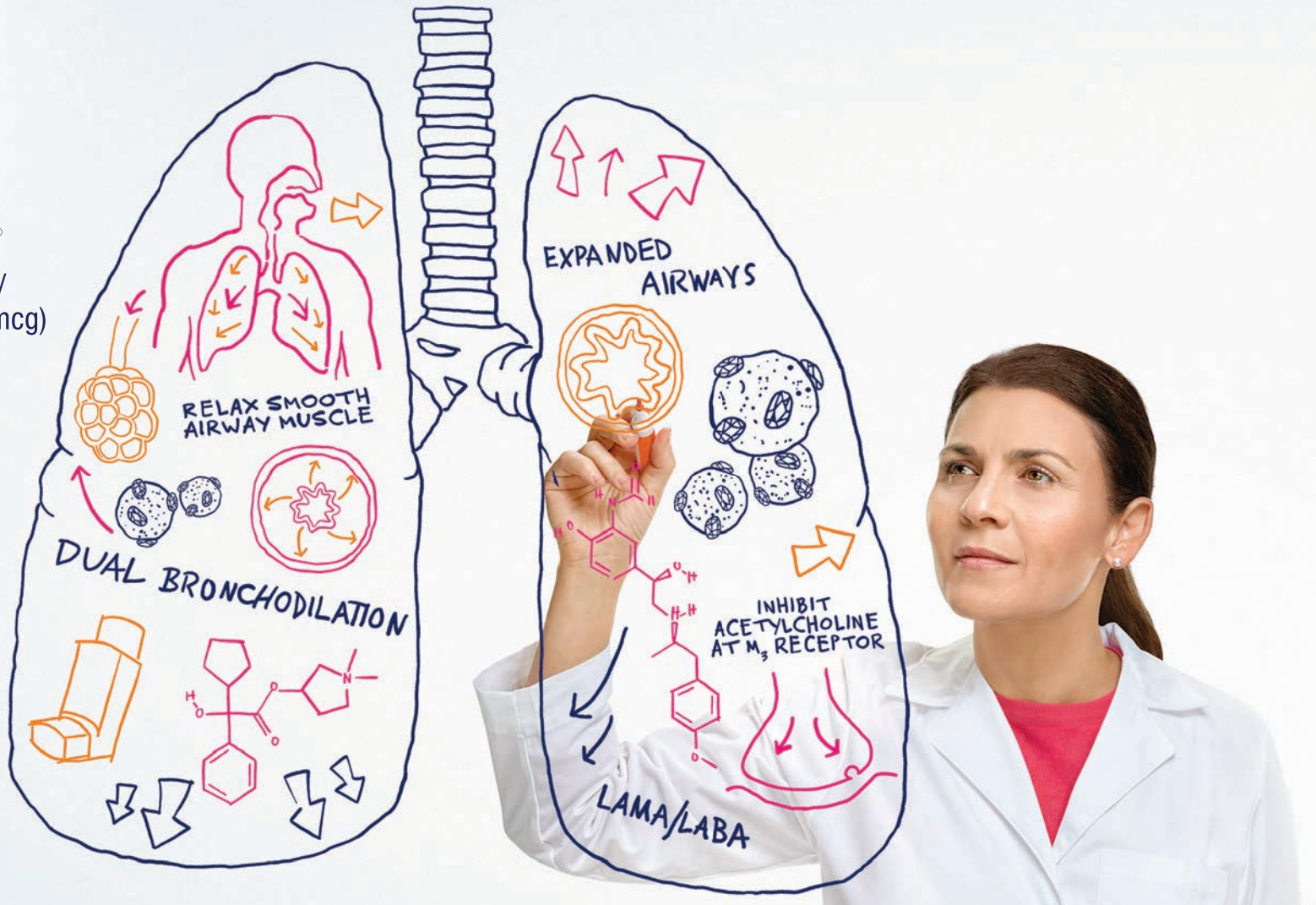
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



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

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting $beta_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

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

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

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions, including angioedema, urticaria, or skin rash, occur, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI (≥2% and more common than

FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

INTELLIGENT FORMULATION*

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

MAXIMIZE BRONCHODILATION†

Improved lung function‡ vs placebo including[1]

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

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

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

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

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

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placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

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

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

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

‡Demonstrated in two 24-week efficacy and safety studies in patients with moderate to very severe COPD (n=3699). The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; $P<0.0001$ for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[1,3]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2016. **2.** Data on File, 3236300, AZPLP. **3.** Data on File, 3236400, AZPLP.

AstraZeneca

BEVESPI AEROSPHERE™

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs.

A 28-week, placebo-controlled US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

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

Deterioration of Disease and Acute Episodes

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

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

When beginning BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

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

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

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

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

Cardiovascular Effects

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. If such effects occur, BEVESPI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

Worsening of Narrow-Angle Glaucoma

BEVESPI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention

BEVESPI AEROSPHERE should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ADVERSE REACTIONS

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

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

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

Clinical Trials Experience

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

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

24-Week Trials

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

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

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

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

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

Long-Term Safety Extension Trial

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

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

DRUG INTERACTIONS

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

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

Non-Potassium Sparing Diuretics

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

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

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

Beta-Blockers

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

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

Pregnancy Category C. There are no adequate and well-controlled trials of BEVESPI AEROSPHERE or its individual components, glycopyrrolate and formoterol fumarate, in pregnant women. Because animal reproduction studies are not always predictive of human response, BEVESPI AEROSPHERE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BEVESPI AEROSPHERE.

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Glycopyrrolate

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

Formoterol Fumarate

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

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom

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Continued from page 7

.007). After about 10 years of follow-up after resection, 1.6% of cancers recurred.

There were two deaths from lung cancer among the study's patients. The first, a 54-year-old man, had an acinar-predominant adenocarcinoma, 5 mm in diameter with a consolidation/tumor ratio of 0.75 that increased during follow-up. The recurrence developed in the mediastinal lymph nodes 51 months after resection surgery. The second patient had a papillary-predominant adenocarcinoma appearing as a pure ground-glass opacity 27 mm in diameter. The consolidation/tumor ratio also increased during follow-up, with recurrences in the bone and mediastinal lymph nodes at 30 months post resectioning.

Neither patient was re-biopsied, and both were diagnosed according to CT imaging alone. There were 13 other patient deaths from non–lung cancer related causes.

Given the 3-year timespan necessary to detect tumor growth in all but the CTR zero group, and the study's size and long-term nature, the investigators concluded that a follow-up period of 3 years for patients with part-solid lesions "should be adequate."

By contrast, CHEST recommends CT scans be done for at least 3 years in patients with pure ground-glass lesions and between 3 and 5 years in the other CTR groups with nodules measuring 8 mm or less. The National Comprehensive Cancer Network guideline advises low-dose CT scanning until a patient is no longer eligible for definitive treatment.

Dr. Sawada and his colleagues did not use an exact criterion for tumor growth in their study, such as a precise ratio of increase in size or consolidation, in part because at the time of the study the most common form of CT evaluation was visual inspection; they reported that tumors exhibiting growth most commonly increased between 2 and 3 mm in either size or consolidation. "Evaluations based on visual inspections can be imprecise, and different physicians may arrive at different judgments," the investigators wrote. "However, [the use of] computer-aided diagnosis systems are not yet commonly applied in clinical practice."

Although imaging should have guided the decision to resect, according to Dr. Sawada and his coauthors, two-thirds of patients in the study were given the procedure even though their lesions were not shown by CT scans to have progressed. This was done either at the patient's request, or per the clinical judgment of a physician.

Although the study "represents a major advance," according to Frank C. Detterbeck, MD, FCCP, surgical director of thoracic oncology at Yale University, New Haven, Conn., who wrote an editorial accompanying the study, the results should spur the field to get more specific, and question whether a 3-year window was enough. "This seems counterintuitive given the chance of it becoming an invasive cancer," Dr. Detterbeck wrote, indicating that not rushing to resection should mean more use of CT. "We should just look at what is already in front of our eyes: the radiographic features of [ground-glass nodules] are highly predictive of biological behavior. It will be hard to do better than this."

Also becoming more specific about changing CTRs would be helpful in developing management protocols, according to Dr. Detterbeck. "In my opinion, we need to start factoring in the rate of change. A gradual 2 mm increase in size over a period of 5 years may not be an appropriate trigger for resection."

Neither the investigators nor the editorial writer had any relevant disclosures.

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Sarcoidosis doubled risk of hospitalization for infection

BY WHITNEY MCKNIGHT
Frontline Medical News

Persons with sarcoidosis were found to have double the risk of hospitalization, compared with age-matched controls in a population-based cohort study that also linked glucocorticoid use with an increased risk of hospitalization in this group.

Using data from the Rochester Epidemiology Project record-linkage system, Patompong Ungprasert, MD, an assistant professor of medicine at the Mayo Clinic in Rochester, Minn., and his colleagues identified 345 incident cases of sarcoidosis recorded between 1976 and 2013, confirmed by individual medical records (Ann Am Thorac Soc. 2017 Feb 8. doi: 10.1513/AnnalsATS.201610-750OC). With use of random selection, each patient was age and sex matched with sarcoidosis-free controls taken from the same database. Medical records across the study were examined for community-acquired infections requiring hospitalization that occurred after the index date or the date of diagnosis.

The nearly all white population across the study had an average age of 45 years and was evenly divided according to sex. The mean length of follow-up was 15 years for the study arm, and 16.8 years for controls.

Risk factors for infection, such as smoking status, obesity, diabetes, and others were also matched, although there were nearly twice as many controls who smoked, compared with study subjects – 36% vs. 19% (*P* less than .001) – whereas the obesity rate was twice as high in the study arm: 41% vs. 21% (*P* less than .001). Results were adjusted for sarcoidosis patients who either had or had not been exposed to immunosuppressive therapies.

These patients should quickly seek medical attention when they develop symptoms of infection.

DR. UNGPRASERT

Dr. Ungprasert and his coinvestigators found that those with sarcoidosis had double the risk of all forms of specific hospitalized infection when compared with controls – a 2.00 hazard ratio (95% confidence interval, 1.41-2.84). The results were similar when adjusted for infection risk factors: 2.13 HR (95% CI, 1.35-3.34).

The risk of hospitalized infection in the sarcoidosis arm was higher than in controls regardless of disease stage: an HR of 1.70 (95% CI, 1.12-2.58, $P = .013$) in those with stage I; an HR of 2.00 (95% CI, 1.22-3.29, $P = .006$) among those with stage II; and an HR of 2.63 (95% CI, 1.58-4.39, *P* less than .001) in those with stage III and stage IV disease.

Biopsies taken in 251 cases resulted in 229 positive results for noncaseating granuloma, and just over half of patients had stage I disease. Stage II disease was found in 29%, stage III in 15%, and stage IV in 2%.

Patients in the sarcoidosis group who had not been exposed to immunosuppressive treatment had significantly higher risk of hospitalization with an HR of 1.73 (95% CI, 1.16-2.60; $P = .008$) when compared with controls. The risk was even higher in study patients who had received immunosuppressive therapy: an HR of 2.41 (95% CI, 1.60-3.64; *P* less than .001), when compared with controls. Less than half of all sarcoidosis patients required immunosuppressive therapy at any point during follow-up: about 37% by year 30 after original diagnosis. Oral glucocorticoids were the most commonly prescribed medication, used in 113 cases.

A baseline diffusing capacity of the lung for carbon monoxide was associated with an overall increased risk of hospitalized infection, with an HR of 1.15 per decrease of 10% predicted in diffusing capacity of the lung for carbon monoxide (95% CI, 1.01-1.32). A baseline forced vital capacity was associated with an increased hospitalized pneumonia risk with an HR of 1.15 per decrease of 10% predicted in forced vital capacity (95% CI, 1.01-1.32).

Although the use of immunosuppressive agents was not significantly associated with the risk of hospitalized infection (HR, 1.43; 95% CI, 0.94-2.19), current use of oral glucocorticoids, whether alone or as adjunct to immunosuppressive therapy, significantly predicted risk of infection in patients with sarcoidosis, with an HR of 3.03 (95% CI, 1.33-6.90) for oral glucocorticoids up to 10 mg per day, and an HR of 4.48 (95% CI, 1.33-6.90) in patients taking oral glucocorticoids at more than 10 mg per day, when compared with controls.

In an interview, Dr. Ungprasert said the results were not surprising, but provided the following takeaways from this study for physicians caring for patients with sarcoidosis.

"These patients are at an increased risk of serious infection and should seek medical attention as soon as possible when they develop symptoms of infection, such as fever or chills," he said in an interview. "Keeping current with vaccinations is also important for them."

Dr. Ungprasert also said the study serves as a reminder to use oral glucocorticoids judiciously. "When considering their use, the physician should keep in mind that a large number of patients with sarcoidosis will have a spontaneous resolution of the disease."

There were no relevant disclosures. The study was funded in part by the National Institute on Aging.

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SAVR an option for elderly with aortic stenosis

BY DOUG BRUNK
Frontline Medical News

HOUSTON – Surgical aortic valve replacement (SAVR) can be performed in intermediate-risk elderly patients with an operative mortality rate of 4.1%, which is better than expected, according to results from a large multicenter analysis. However, the rate of in-hospital stroke was 5.4% – twice what was expected.

"This is most likely secondary to neurologic assessment [that was conducted] for all patients postoperatively," Vinod H. Thourani, MD, said at the annual meeting of the Society of Thoracic Surgeons.

DOUG BRUNK/FRONTLINE MEDICAL NEWS

For intermediate-risk patients, mortality was commensurate with national benchmarks, Dr. Vinod H. Thourani said.

The findings come from an in-depth analysis of SAVR outcomes in patients who participated in the Placement of Aortic Transcatheter Valves trial, known as PARTNER 2A. Conducted from December 2011 to November 2013, PARTNER 2A evaluated 2,032 medium-risk patients with aortic stenosis who were randomized to SAVR or transcatheter aortic valve replacement (TAVR) in 57 North American centers and found no significant difference in the 2-year rate of death or disabling stroke (N Engl J Med. 2016 Apr 28;3749[17]:1609-20).

Dr. Thourani's analysis focused on the 937 patients who underwent SAVR. The main objectives were to describe operative mortality and hospital morbidities compared with STS benchmarks, describe time-related mortality and stroke including preoperative predictors for these outcomes, evaluate the effect of concomitant procedures on mortality and hospital morbidities, and evaluate longitudinal valve performance after SAVR.

The average age of these patients was 82 years, 45% were female, and their mean STS risk score was 5.8. In addition, 26% had prior coronary artery bypass (CABG) surgery, 10% had a previous stroke, and 12% had previous pacemaker placement. Of the 30% of patients with chronic obstructive pulmonary disease, 9.6% were oxygen dependent going into the operating room, reported Dr. Thourani, one of the PARTNER 2A investigators, and a cardiothoracic surgeon at Emory University, Atlanta.

Most of the patients (85%) had a full sternotomy, while 15% had a mini sternotomy. Isolated AVR was done in 79% of patients, 15% of patients had AVR plus CABG, and 6% had AVR and other concomitant procedures. The mean coronary bypass time for isolated AVR was 98 minutes, and rose to a mean of 129 minutes when a concomitant procedure was added. The mean cross-clamp time was 69 minutes, and rose to a mean of 95 minutes when a concomitant procedure was added.

The investigators observed that all-cause operative mortality was 4.1%, which is lower than STS predicted-risk models. At the same time, mortality for AVR plus a concomitant procedure was 5%, followed by isolated AVR (4.2%) and AVR plus CABG plus a concomitant procedure (2.9%). The rate of in-hospital stroke was 5.4% and the rate of in-hospital deep sternal wound infection was 0.8%. At 2 years postoperatively, mortality was 17% among those who underwent isolated AVR, 18% among those who underwent AVR plus CABG, and 21% among those who underwent AVR plus a concomitant procedure, differences that did not reach statistical significance. The rate of stroke at 2 years also was similar between groups: 12% among those who underwent isolated AVR, 11% in those who underwent AVR plus a concomitant procedure, and 8.2% in those who underwent AVR plus CABG.

The main risk factor for early death after SAVR was longer procedure time (P less than .0001), while risk factors for later deaths included cachexia ($P = .02$), lower ejection fraction ($P = .01$), higher creatinine ($P = .03$), coronary artery disease ($P = .03$), and smaller prostheses ($P = .01$)

Dr. Thourani and his associates also found that 33% of patients had severe prosthesis-patient mismatch, yet they had survival rates similar to the rates of those without severe prosthesis-patient mismatch.

"From this adjudicated, prospectively collected data in the contemporary era, SAVR can be performed in intermediate-risk elderly patients with mortality commensurate with national benchmarks," he concluded. "Continued surveillance of these patients remains extremely important."

Dr. Thourani disclosed that he is a consultant for and has received research support from Edwards Lifesciences. Other authors of the study reported having numerous relevant financial disclosures.

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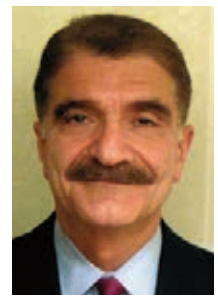
VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: This analysis of the surgical arm of the PARTNER 2A trial reveals respectable outcome for those so-called intermediate-risk patients with severe symptomatic aortic stenosis. The fact that mortality at 2 years was similar between the surgical and the catheter arm of the trial (upward of 17%), speaks of the multiple comorbidities present in these patients (N Engl J Med. 2016;374:1609-20). The trial proved the noninferiority of the catheter-based aortic valve implantation as compared with surgical AVR. With further refinement and advances in technology and design of these valves, and, more importantly, patients' demand, the TAVR is destined to become the main stay of the AVR for patients with severe aortic stenosis.

Can bioprosthetics work for large airway defects?

BY RICHARD MARK KIRKNER
Frontline Medical News

Large and complex airway defects that primary repair cannot fully close require alternative surgical approaches and techniques that are far more difficult to perform, but bioprosthetic materials may be an option to repair large tracheal and bronchial defects that has achieved good results, without postoperative death or defect recurrence, in a small cohort of patients at Massachusetts General Hospital, Boston.

Brooks Udelsman, MD, and coauthors reported their results of bioprosthetic repair of central airway defects in eight patients in the Journal of Thoracic and Cardiovascular Surgery (2016;152:1388-97). "Although our results are derived from a limited number of heterogeneous patients, they suggest that closure of non-circumferential large airway defects with bioprosthetic materials is feasible, safe and reliable," Dr. Udelsman said. He previously reported the results at the annual meeting of the American Association for Thoracic Surgery, May 14-18, 2016, in Baltimore.

These complex defects typically exceed 5 cm and can involve communication with the esophagus. For repair of smaller defects, surgeons can use a more conventional approach that involves neck flexion, laryngeal release, airway mobilization, and hilar release, but in larger defects these techniques increase the risk of too much tension on the anastomosis and dehiscence along with airway failure. Large and complex defects occur in patients who have had a previous airway operation or radiation exposure, requiring alternative strategies, Dr. Udelsman and coauthors said. "Patients in this rare category should be referred to a high-volume center for careful evaluation by a surgeon experienced in complex airway reconstruction before the decision to abandon primary repair is made," he said. Among the advantages that bioprosthetic materials have over synthetic materials for airway defect repair are easier handling, minimal immunogenic response, and potential for tissue ingrowth, Dr. Udelsman and coauthors said.

All eight patients in this study, who underwent repair from 2008 to 2015, had significant comorbidities, including previous surgery of the trachea, esophagus, or thyroid. The etiology of the airway defect included HIV/AIDS-associated esophagitis,

Continued on page 18

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

WARNING: (B) SPINAL/EPIDURAL HEMATOMA

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

- Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- Strong Dual Inducers of CYP3A4 and P-gp: Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
- Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

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

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

ELIQUIS is the #1 most prescribed oral anticoagulant among cardiologists for new patient starts*

Explore the efficacy and safety data

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*Based on IMS SDI VECTOR New-to-brand Prescription Database (NBRx). Oral anticoagulant prescriptions were written by cardiologists and filled by patients who did not have any prescriptions filled for that same oral anticoagulant in the previous 6 months. Claims valid as of 1/3/14 to 8/12/16.

INDICATIONS

ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

ELIQUIS is indicated for the treatment of DVT and PE, and to reduce the risk of recurrent DVT and PE following initial therapy.

SELECTED IMPORTANT SAFETY INFORMATION

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

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

Please see additional Important Safety Information, including continued Boxed WARNINGS, on adjacent page.

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

Reversal of Anticoagulant Effect

A specific antidote for ELIQUIS is not available, and there is no established way to reverse the bleeding in patients taking ELIQUIS. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

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

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

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

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

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

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.

† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

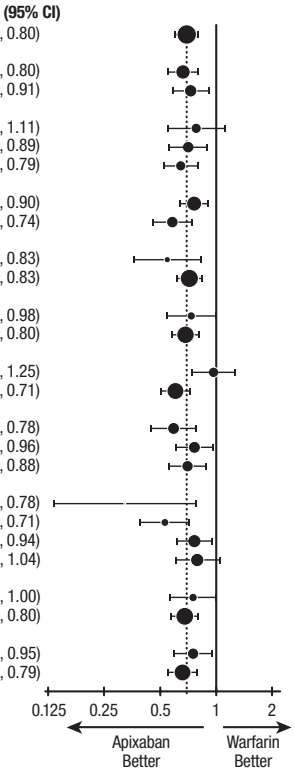
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

¶ CRNM = clinically relevant nonmajor.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

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

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1) in full Prescribing Information]*:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1) in full Prescribing Information]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1) in full Prescribing Information]*.

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in full Prescribing Information]*.

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Most lung recipients gain 2-year survival benefit

BY BIANCA NOGRADY
Frontline Medical News

Nearly three-quarters of lung transplant recipients are likely to gain at least 2 years of survival, according to new research.

In a study published in the February issue of the Annals of the American Thoracic Society, researchers used data from 13,040 adults listed for lung transplantation between May 2005 and September 2011 to develop a structural nested accelerated failure time model of the survival benefit of lung transplantation over time.

These results reinforce that lung transplantation should be considered an appropriate treatment option for patients with most advanced lung diseases, the researchers noted.

"A 'structural nested model' is [used to] compare the distribution of counterfactual residual survival if a patient were to receive a transplanted organ with the survival distribution if the patient did not receive that organ and never received one subsequently," wrote David M. Vock, PhD, from the University of Minnesota, Minneapolis, and coauthors.

Using this approach, they calculated that 73.8% of transplant recipients were predicted to achieve a 2-year survival benefit with transplantation. At 1 year post transplantation, the relative survival benefit was 1.59, at 2 years it was 1.93, and at 3 years it was 2.23 (Ann Am Thorac Soc. 2017;14:172-81. doi: 10.1513/AnnalsATS.201606-507OC).

Patients' lung allocation score at transplantation (LAS-T) – the score used to prioritize donated lungs for transplantation – had a significant impact on the survival benefit from transplantation. The relative survival benefit of transplantation increased by 59.4% as the lung allocation score increased from 30 to 35, and increased by 45.1% as the lung allocation score increased from 50 to 55.

However patients with a lung allocation score of 32.5 or less were more likely to die with a transplant than without, even over the long term, while patients with a score of 35 or more always gained a survival advantage from transplantation, even if their scores were as high as 50-100. The authors said this showed there should be no upper limit for the lung allocation score.

"It has been suggested that the LAS system may encourage patients who have clinically deteriorated to undergo transplantation even though it would be futile," they wrote. "Our results reinforce the notion that lung transplantation should be considered an appropriate treatment option for patients with most advanced lung diseases and is expected to confer survival benefit in appropriately selected patients."

Researchers also observed an interesting, borderline significant association between disease group and survival benefit, with individuals with obstructive lung disease showing the lowest relative survival gains and those with cystic fibrosis showing the highest. Head to head, the relative survival benefit of transplantation for those with cystic fibrosis was 54.4% greater than for those with obstructive lung disease.

Other factors such as transplant type, age, smoking, and center volume also influenced relative survival benefit. Bilateral transplants were associated with a 13.4% greater relative survival benefit, lungs from donors aged under 55 years showed a 17.9% relative survival benefit, and lungs from donors without a history of smoking showed a 10.5% increase in relative survival benefit.

However the researchers noted that their modeling focused on only the survival benefit of transplantation and did not take into account improvements in quality of life. This was likely to be particularly relevant in conditions such as chronic obstructive pulmonary disease where the quality of life benefits might justify transplantation even in the absence of a clear survival benefit.

"A comprehensive understanding of the survival benefit of lung transplantation and how that benefit varies by recipient characteristics is imperative to inform recipient selection, to justify the intensive health care resources allocated to this treatment, and to achieve an equitable allocation of donor lungs," the researchers said.

The study was supported by the National Heart, Lung, and Blood Institute; the National Cancer Institute; and the National Institute of Allergy and Infectious Diseases. One author declared grants and personal fees from private industry for consultation on lung transplantation. No other conflicts of interest were declared.

VIEW ON THE NEWS

Lung transplantation prolongs survival

Lung transplantation is the only option available for patients with treatment-resistant end-stage lung disease. However, the ability of this intervention to extend survival is still actively debated. The authors demonstrate that most adults undergoing lung transplantation experience a survival benefit that is mainly driven by the value of the lung allocation score at the time of transplantation and by the underlying lung disease.

It is reassuring to see that the two studies published so far that accounted for the course of patient disease after placement on a wait list reached essentially the same conclusions: Most of the patients experienced a survival benefit from lung transplantation.

Gabriel Thabut, MD, is from the service de pneumologie B and transplantation pulmonaire at the University of Paris. These comments are taken from an accompanying editorial (Ann Am Thorac Soc. 2017;14:163-4. doi: 10.1513/AnnalsATS.201611-853ED). No conflicts of interest were declared.

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malignancy, mesh erosion, and complications from extended intubation. Three patients had previous radiation therapy to the neck or chest. Five patients had defects localized to the membranous tracheal wall, two had defects of the mainstem bronchus or bronchus intermedius, and one patient had a defect of the anterior wall of the trachea.

Dr. Udelsman and coauthors used both aortic homograft and acellular dermal matrix to repair large defects. Their experience confirmed previous reports of the formation of granulation tissue with aortic autografts, underscoring the importance of frequent bronchoscopy and debridement when necessary. And while previous reports have claimed human acellular dermis resists granulation formation, that wasn't the case in this study. "The exact histologic basis of bioprosthetic incorporation and reepithelialization in these patients is still elusive and will require further study," Dr. Udelsman and coauthors said.

This study also employed the controversial muscle buttress repair in six patients, which helped, at least theoretically, to secure the repairs when leaks occur, to separate suture lines when both the airway and esophagus were repaired, and to support the bioprosthetic material to prevent tissue softening, Dr. Udelsman and coauthors said.

Postoperative examinations confirmed that the operations successfully closed the airway defects in all eight patients. Long term, most resumed oral intake, but three did not for various reasons: One had a paryngostomy; another had neurocognitive issues preoperatively; and a third with a tracheoesophageal fistula repair and cervical esophagostomy could resume oral intake but depended on tube feeds to meet caloric needs.

All patients developed granulation at the repair site, two of whom required further debridement and one who underwent balloon dilation. Pneumonia was the most common complication within 30 days of surgery, occurring in two patients. Three patients died within 120 days from metastatic disease, and a fourth patient progressed to end-stage AIDS 6 years after the operation and eventually died.

Dr. Udelsman and coauthors reported having no financial disclosures.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: This is a small series of 8 patients out of 342 total patients requiring airway repair who underwent repair of complicated major airway defects at a well-known tertiary referral center for airway surgery. The message is clear that complicated airway defects, as defined by the authors, should be referred to a high-volume specialty center with expertise in this field.

Medicare patients often need pacemaker after TAVR

BY DOUG BRUNK
Frontline Medical News

HOUSTON – About 1 in 10 Medicare patients require implantation of a permanent pacemaker after transcatheter aortic valve replacement, results from a large analysis showed.

"There is conflicting evidence and some debate over permanent pacemaker placement following transcatheter aortic valve replacement – whether it has a protective or adverse effect, and how often it takes place," study investigator Fenton H. McCarthy, MD, said in an interview at the annual meeting of the Society of Thoracic Surgeons.

There is some debate over whether a permanent pacemaker is protective following TAVR.

DR. MCCARTHY

To evaluate the relationship between permanent pacemaker implantation and long-term patient outcomes among Medicare beneficiaries undergoing TAVR, Dr. McCarthy, a cardiothoracic surgery fellow at the University of Pennsylvania, Philadelphia, and his associates used Medicare carrier claims and Medicare Provider Analysis and Review files to identify 14,305 TAVR patients between January 2011 and December 2013.

The mean age of the 14,305 TAVR patients studied was 83 years, and 11% received a permanent pacemaker after TAVR. Of these, 9% received the pacemaker at index hospitalization, 1% at 30 days after implant, 0.5% at 90 days after implant, and 1% at 1 year after implant. Patient age of greater than 90 years was a significant predictor of pacemaker placement, with an odds ratio of 1.7 (*P* less than .01).

Dr. McCarthy and his associates observed that the readmission rates for pacemaker placement and no pacemaker placement at index hospitalization were similar at 30 days (21% vs. 19%, respectively), at 90 days (33% vs. 31%) and at 1 year (43% in both groups of patients).

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VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The need for new permanent pacemaker implantation in TAVR patients has been higher as compared with surgical AVR. The current analysis on the administrative database of Medicare patients undergoing TAVR has the advantage of a large sample size but lacks details at the patient level. The PARTNER 2A trial in medium-risk patients (N Engl J Med. 2016;374:1609-20) found no statistical difference between TAVR and surgical AVR for the need for permanent pacemaker implantation at 30 days (8.5% and 6.9%, respectively; $P = 0.17$).

Maintain conjugate vaccine schedule with preemies

BY DAN WATSON
Frontline Medical News

There should be no hesitation in administering the routine vaccination schedule for 13-valent pneumococcal conjugate vaccine (PCV13) on account of gestational age or birth weight in preterm infants, researchers concluded.

In a phase IV study, researchers compared 100 term with 100 preterm infants; both groups were vaccinated on the routine schedule at ages 2, 3, 4, and 12 months. After the 12-month (toddler) dose of the PCV13, the infants were evaluated for serum antibody persistence at 12 and 24 months. "To date, no studies have examined the long-term persistence of immune responses to PCV13 in formerly preterm infants," noted Federico Martinón-Torres, MD, PhD, of Hospital Clínico Universitario de

Santiago de Compostela, Spain, and his coauthors.

In the study, at six sites in Spain and five sites in Poland between October 2010 and January 2014, both groups were checked for geometric mean concentrations (GMC) of serotype-specific anticapsular immunoglobulin G–binding antibodies and for opsonophagocytic activity. All 200 subjects were white and were generally healthy; the preterm infants were grouped by gestational age at birth of less than 29 weeks (n = 25), 29 weeks to less than 32 weeks (n = 50), or 32 weeks to less than 37 weeks (n = 25). Twelve subjects dropped out of the study by the first year's evaluation, and another eight of the term subjects and seven of preterm subjects dropped out by the second year's evaluation (Ped Infect Dis J. 2017. doi: 10.1097/INF.0000000000001428).

At both follow-up time points, no discernible patterns were observed in IgG GMCs for any serotype or in opsonophagocytic activity geometric mean titers across preterm subgroups based on gestational age.

"The vaccination phase of the study demonstrated that preterm infants are able to generate an immune response to PCV13 that is likely to

Continued on page 25

Shunts often fail rapidly in neonates and infants

BY DOUG BRUNK
Frontline Medical News

HOUSTON – Among neonates and infants who underwent shunt construction as a source of pulmonary blood flow, early, in-hospital shunt failure occurred in 7.3% of cases, results from a large retrospective study showed.

"Approximately one in seven patients who experiences cardiac surgery in the first year of life undergoes construction of a systemic to pulmonary artery shunt of some type," one of the study investigators, Marshall L. Jacobs, MD, said in an interview. The study was presented at the annual meeting of the Society of Thoracic Surgeons.

"Early failure of such shunts is an incompletely understood phenomenon which accounts for important morbidity and mortality among in-

Of the at-risk neonates and infants, 7.3% experienced early, in-hospital shunt failure.

DR. DO

fants and neonates. Much of what is known about shunt failure is based on experiences reported from individual institutions. The few multicenter studies to date have been clinical trials that focused primarily on pharmacologic strategies intended to reduce the risk of shunt failure due to thrombosis. Their utility for guiding clinical decision making has been limited. Some have been underpowered; some have had limited risk adjustment of subjects."

The current investigation, which began when Nhue Do, MD, was a cardiac surgery chief resident at Johns Hopkins Hospital, Baltimore, is the largest reported analysis of factors associated with postoperative in-hospital shunt failure in neonates and infants with congenital heart disease. It is the first multicenter study to define preoperative risk factors and patient characteristics associated with early shunt failure.

Dr. Do, who presented the find-

Continued on following page

Continued from previous page

ings at the meeting and is currently a Congenital Heart Surgery Fellow at the Children's Hospital of Philadelphia, and a team of 11 other investigators utilized the STS Congenital Heart Surgery Database to identify 9,172 neonates and infants who underwent shunt construction as a source of pulmonary blood flow at 118 institutions from 2010 to 2015. Criteria for shunt failure included a documented diagnosis of in-hospital shunt failure, shunt revision, or catheter-based shunt intervention. The investigators used multivariable logistic regression to evaluate risk factors for in-hospital shunt failure.

Of the 9,172 at-risk neonates and infants, 674 (7.3%) experienced early, in-hospital shunt failure. "The observed rate of early shunt failure varied across the many specific types of shunts, and was lower with systemic ventricle to pulmonary artery shunts (as in the Sano modification of the Norwood procedure) than with the systemic artery to pulmonary artery shunts," said Dr. Jacobs, who is a cardiothoracic surgeon at Johns Hopkins University, Baltimore.

In multivariable analysis, risk factors for in-hospital shunt failure included lower weight at operation for both neonates and infants, preoperative hypercoagulable state, and the collective presence of any other STS Congenital Heart Surgery Database preoperative risk factors. Neither cardiopulmonary bypass nor single ventricle diagnosis were risk factors for shunt failure. The investigators also observed that patients with in-hospital shunt failure had significantly higher rates of operative mortality (31.9% vs. 11.1%) and major morbidity (84.4% vs. 29.4%), and longer postoperative length of stay among survivors (a median of 45 vs. 22 days).

"The observed rate of early shunt failure varied across the many specific types of shunts, and was lower with systemic ventricle to pulmonary artery shunts ... than with the systemic artery to pulmonary artery shunts," said Dr. Jacobs.

"Understanding the characteristics of the patient groups found to be at highest risk for early shunt failure is helpful in identifying individual patients that may warrant expectant surveillance, enhanced pharmacologic management, or other strategies to reduce the risk of shunt failure," Dr. Jacobs concluded.

"But perhaps more importantly it provides key information that may be helpful in the design and development of future clinical trials and/or collaborative quality improvement initiatives designed to reduce the cost in lives and resources that is associated with early shunt dysfunction."

He acknowledged certain limitations of the study, including its retrospective observational design and the voluntary nature of the STS Congenital Heart Surgery Database. "In addition, some potentially important variables, such as detailed data concerning preoperative test results of coagulation assays are not collected in the STS Congenital Heart Surgery Database," he said.

The research was supported by the STS Access & Publications Research program. The investigators reported having no financial disclosures.

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Double-dose influenza vaccine gives best protection

BY DEEPAK CHITNIS
Frontline Medical News

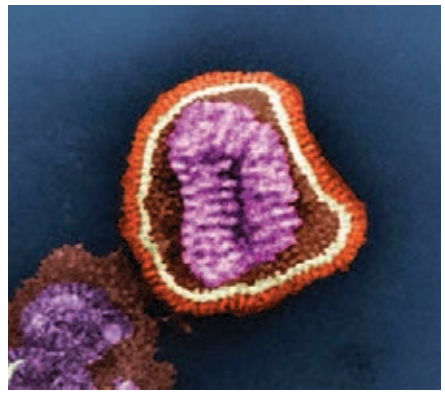
A double-dose inactivated quadrivalent influenza vaccine (IIV4) could be administered to all children aged 6-35 months, as it not only offers the best protection against influenza type B but also allows for simplifying the current vaccination schedule considerably.

"The introduction of IIV4 provides an opportunity to review long-accepted practices in administration of influenza vaccines," explained Varsha K. Jain, MD, formerly employed by GlaxoSmithKline Vaccines, King of Prussia, Pa., and associates.

"If the double-dose vaccine could be administered in young children without adverse effects on tolerability, this age group may benefit from potentially improved immunogenicity," they wrote.

Giving a lower dose to young children was planned to reduce reactogenicity and febrile convulsions observed with the whole virus vaccines that were in use in the 1970s. But young children have a variable immune response to lower doses, especially against vaccine B strains, they noted (J Ped Infect Dis. 2017 Jan 6. doi: 10.1093/jpids/piw068).

Dr. Jain and coauthors enrolled 2,430 children aged 6-35 months during the 2014-2015 influenza season in the United States and Mexico in this phase III study. Children were



CYNTHIA GOLDSMITH/CDC PHOTO #10073

randomized into one of two cohorts: one cohort received a standard-dose IIV4 vaccination, while the other received a double dose. Data on age (6-17 months, 18-35 months), health care center, and influenza primer status also were taken into consideration.

The standard-dose vaccine contained 7.5 mcg of A/California/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Brisbane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata), while the double-dose vaccine contained 15 mcg, or twice the amount each, of the same strains. The former was developed by Sanofi Pasteur and the latter by GSK Vaccines.

Primed children who completed the study numbered 1,173; 586 received the standard dose and 587 received the double dose. On the unprimed side, 868 completed the study: 442 standard dose and 426 double dose. Each dose's immunogenic noninferiority was quantified by calculating the geometric mean titer (GMT) ratio.

"Immunogenicity was higher in the double-dose group compared with the standard-dose group, particularly against vaccine B strains in children 6-17 months of age and unprimed children," Dr. Vain and associates said. Both vaccines performed well against the influenza B strain, with the double dose yielding a GMT of 1.89 against the B/Yamagata strain and 2.13 against the B/Victoria in children aged 6-17 months. Across the entire age spectrum of the study population, unprimed children registered a GMT of 1.85 and 2.04 against the same strains, respectively. For comparison, none of the A strains in any cohort based on age or primed/unprimed registered a GMT above 1.5.

"Increased protection against influenza B [would] be a beneficial clinical outcome [and] use of the same vaccine dose for all eligible ages would also simplify the annual influenza vaccine campaign and reduce cost and logistic complexity," the authors concluded. "This study provides evidence to support a change in clinical practice to use [double-dose IIV4] in all children 6 months of age and older, once that dosing for a vaccine product has been approved."

Immunogenicity was higher in the double-dose group, particularly against vaccine B strains in children 6-17 months of age and unprimed children.

Dr. Jain now is employed by the Bill and Melinda Gates Foundation. Dr. Jain and several coauthors disclosed ties to GlaxoSmithKline, which funded the study.

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Bronchiolitis pathway adherence tied to reduced LOS, costs

BY LORI LAUBACH
Frontline Medical News

High adherence to bronchiolitis clinical pathway recommendations in health care settings is associated with shorter length of stay (LOS) and lower health care costs, according to Mersine A. Bryan, MD, of the University of Washington, Seattle and her associates.

In a retrospective cohort study, researchers looked at 267 patients less than 24 months old diagnosed with bronchiolitis from December 2009 to July 2012. Levels of adherence were then categorized into low, middle, and high tertiles. Results show that adherence was highest for the inpatient quality indicators (mean score, 95) and lowest for the emergency department quality indicators (mean score, 79). The mean ED LOS was significantly shorter for cases with ED adherence scores in the highest versus the lowest tertile (90 vs. 140 minutes; *P* less than .05). There were no significant differences in mean inpatient LOS by inpatient adherence score tertiles. "However, the mean inpatient LOS was approximately 17 hours shorter for cases with combined ED/inpatient adherence scores in the highest, compared with the lowest tertile," they said.

The mean ED costs for cases with ED adherence scores in the highest tertile were significantly lower than cases with scores in the lowest tertile (–$84; *P* less than .05). It is noted there were no significant differences in mean total costs by inpatient adherence score tertile, but "for cases where the combined ED/inpatient adherence scores were in the highest tertile, the mean total costs were significantly lower than for cases with combined adherence scores in the lowest tertile, the researchers noted. Also, cases with ED adherence scores in the highest tertile had lower odds of inpatient admission, compared with those with scores in the lowest tertile (odds ratio, 0.38). There were no significant differences in the odds of return ED visits or readmissions by adherence score tertile.

"Our study demonstrates that high adherence to evidence-based recommendations within a clinical pathway across the entire continuum of care, from the ED to the inpatient setting, is associated with lower costs and shorter LOS," Dr. Bryan and associates concluded. "By improving adherence to evidence-based recommendations within a clinical pathway, we may be able to provide higher-value care by optimizing the quality of bronchiolitis care at lower costs and with shorter LOS."

Read the full study in Pediatrics (doi: 10.1542/peds.2016-3432).

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protect against invasive pneumococcal disease.

However, IgG GMCs were lower in preterm than term infants for nearly half of the serotypes at all time points.

Antipneumococcal IgG levels in preterm infants were generally lower than in term infants, but fewer differences in opsonophagocytic activity were seen between the groups," Dr. Martinón-Torres and his associates reported.

They concluded by recommending "timely vaccination of infants against *Streptococcus pneumoniae* starting at the chronologic age of 2 months, regardless of gestational age or weight at birth," and "giving the toddler dose at the earliest possible opportunity."

Pfizer funded the study.

Dr. Martinón-Torres reported receiving research grants and/or honoraria as a consultant/adviser and/or speaker and for conducting vaccine trials for GlaxoSmithKline, MedImmune, Merck, Novartis, Pfizer/Wyeth, Sanofi Pasteur, and the Carlos III Health Institute.

Several coauthors disclosed ties with pharmaceutical companies; four are stock-holding employees of Pfizer, and another is an employee of a company contracted by Pfizer.

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48% of pediatric HA-VRIs caused by rhinovirus

BY KATIE WAGNER LENNON
Frontline Medical News

Health care–associated viral respiratory infections (HA-VRIs) were common in two pediatric hospitals, with rhinovirus the most frequent cause of the infections in a 3-year analysis.

The incidence rate of laboratory-confirmed HA-VRIs was 1.29/1,000 patient-days in an examination of the hospitals' patient data. Forty-eight percent of all 323 HA-VRI cases were caused by rhinovirus, with an overall incidence rate of 0.72/1,000 patient-days. Additionally, rhinovirus was the most frequently identified virus in cases of HA-VRI in almost all units of both hospitals, followed by parainfluenza virus and respiratory syncytial virus. The exception was the medical/surgical ward of Steven and Alexandra Cohen Children's Medical Center (CCMC) of New York; in this unit of the CCMC, the incidence rate of parainfluenza virus was higher than that of rhinovirus (0.21/1,000 patient-days vs. 0.15/1,000 patient-days) (J Ped Inf Dis. 2016. doi: 10.1093/jpids/piw072).

The researchers used infection prevention and control surveillance databases from Montreal Children's Hospital and the CCMC to identify HA-VRIs that occurred between April 1, 2010, and March 31, 2013, In both hospitals, HA-VRIs were attributed to the unit to which the patient was admitted at the time of transmission. Both hospitals used a multiplex nucleic acid amplification test for respiratory virus detection on nasopharyngeal swabs or aspirates.

"An HA-VRI with an onset of symptoms after hospital discharge would be detected and included only for patients who presented to the emergency department or were readmitted for VRI and tested," according to Caroline Quach, MD, of the Montreal Children's Hospital, McGill University Health Centre, and her colleagues.

The HA-VRI rate was 1.91/1,000 patient-days at Montreal Children's Hospital, compared with 0.80/1,000 patient-days at the CCMC (*P* less than .0001). At the CCMC, the HA-VRI incidence rate was lowest in the neonatal ICU, but at Montreal Children's Hospital, the hematology/oncology ward had the lowest rate of HA-VRI.

Having less than 50% single rooms in a given unit was associated with a statistically significantly higher rate of HA-VRI, after the investigators adjusted for unit type and took the correlation of HA-VRI rates within a hospital into consideration. The study authors' model predicted that units with less than 50% single rooms have 1.33 times higher HA-VRI rates than units with at least 50% single rooms, regardless of unit type.

Dr. Quach has received funding from GlaxoSmithKline, Pfizer, Sage, and AbbVie for an unrelated research project, while the other authors disclosed no financial relationships.

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RSV is preemies' top severe respiratory disease source

BY BIANCA NOGRADY
Frontline Medical News

Respiratory syncytial virus is the number one virus causing severe lower respiratory disease in preterm infants, while those of younger age and those exposed to young children are at greatest risk, Eric A. F. Simões, MD, of the University of Colorado at Denver, Aurora, and his coauthors reported in the Nov. 29 edition of PLOS ONE.

"These data demonstrate that higher risk for 32 to 35 wGA [weeks gestational age] infants can be easily identified by age or birth month and significant exposure to other young children," they wrote. "These infants would benefit from targeted efforts to prevent severe RSV disease."

The prospective RSV Respiratory Events Among Preterm Infants Out-

Continued on following page

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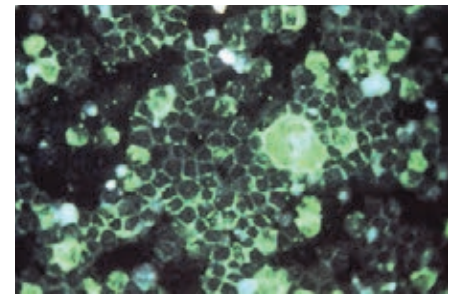
comes and Risk Tracking (REPORT) study in 38 states followed 1,642 preterm infants born at 32-35 weeks' gestational age who had medically attended acute respiratory illness.

The overall rates of lower respiratory infections per 100 infant-seasons – a season being 5 months of observation from November 1 to March 31 in 2009-2010 or 2010-2011 – were 13.7 for respiratory syncytial virus (RSV), 2.9 for adenovirus, 1.7 for parainfluenza virus type 2, 1.3 for human metapneumo virus, and 0.3 for parainfluenza virus type 2 (PLoS One. 2016 Nov 29. doi: 10.1371/journal.pone.0166226).

Infants who had been exposed to young children, either through attending day care or living with non–multiple birth preschool-age siblings, had a twofold higher risk of RSV and human metapneumovirus, and a 3.3-fold greater risk of adenovirus.

The youngest infants showed the highest rate of hospitalizations with



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Infants born in May, before the RSV season, had much lower rates of hospitalization and ICU admission, compared with infants born at the height of RSV season in February.

RSV: The incidence ranged from 8.2 per 100 infant-seasons in those aged less than 1 month to 2.3 per 100 infant-seasons in those aged 10 months of age. Similarly, the incidence of admission to ICU was significantly higher among younger infants.

Infants born in May, before the RSV season, had a much lower incidence of hospitalization, compared with those born in the height of RSV season in February. ICU admission rates also were higher among those born in February, compared with those born in May.

The highest overall rates of hospitalization with RSV – 19 per 100 infant-seasons – were among those born in February, and also those who were exposed to other young children.

"The current results are unique in that they provide continuous age-based risk models for outpatient and inpatient disease for infants with and without young child exposure," wrote Dr. Simões and his coauthors.

The study was supported by AstraZeneca, parent company of MedImmune. Two authors declared grant support and research funding from AstraZeneca, one author was a former employee of AstraZeneca, and one author was a former employee of MedImmune and now contractor to AstraZeneca. One author was a current employee of AstraZeneca and holds stock options. Two authors also declared funding and consultancies with AbbVie.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: The American Academy of Pediatrics has a consensus statement on the use of palivizumab (Synagis) in preterm infants and infants with congenital heart disease. It is important for pediatric primary care providers and subspecialists to review these guidelines in the Red Book.

Strokes cut by extended NOAC prophylaxis

BY MITCHEL L. ZOLER
Frontline Medical News

NEW ORLEANS – Thromboprophylaxis for 35-42 days with the new oral anticoagulant betrixaban led to a significant reduction in all-cause and ischemic strokes in medically ill patients who required hospitalization as compared with conventional prophylaxis for 10 days, based on a post-hoc analysis of data from a randomized trial with more than 7,500 patients.

But the trial's unusual design left it unclear whether the incremental benefit seen from prolonged prophylaxis with a NOAC resulted primarily from a longer period of treatment, the drug used, or both.

The Kaplan-Meier analysis showed that stroke incidence in the two intervention arms began to diverge during the first 10 days when all patients received an anticoagulant, suggesting that betrixaban surpassed enoxaparin when the two therapies went head to head, C. Michael Gibson, MD, said at the American Heart Association scientific sessions. Beyond the first 10 days and out to 77 days of follow up – during the period when standard enoxaparin prophylaxis in the control patients had ended but the novel regimen with betrixaban continued – the curve of strokes in the betrixaban group continued to separate sharply from that of the control group, indicating extended prophylaxis offered substantial benefit, said Dr. Gibson, a professor of medicine at Harvard Medical School and an interventional cardiologist at Beth Israel Deaconess Medical Center, both in Boston.

The safety analysis showed that prolonged treatment with betrixaban roughly doubled the rate of major or clinically relevant nonmajor bleeding events during the period of treatment and for the first 7 days after treatment stopped. The incidence of these bleeds was 1.6% among control patients on 10 days of enoxaparin treatment and 3.1% among patients who received extended treatment with betrixaban, a statistically significant difference. The rates of fatal bleeds and intracranial hemorrhages in the two study groups did not significantly differ.

The data Dr. Gibson reported came from the Multicenter, Randomized, Active-Controlled Efficacy and Safety Study Comparing Extended Duration Betrixaban With Standard of Care Enoxaparin for the Prevention of Venous Thromboembolism in Acute Medically Ill Patients (APEX). The study's primary aim was testing in 7,513 hospitalized medically ill patients the safety and efficacy of prolonged prophylaxis with the oral, factor Xa inhibitor betrixaban, compared with 10 days of prophylaxis with the low molecular weight heparin enoxaparin. The primary endpoint was the rate of venous thromboembolic events and deaths from venous thromboembolism (VTE) out to 47 days after the start of treatment.

APEX enrolled patients hospitalized for acute decompensated heart failure, chronic respiratory failure, acute infection without septic shock, acute rheumatic disorders, or acute ischemic stroke. All enrolled patients had to be expected to be immobilized for at least 24 hours following randomization and to be hospitalized for at least 3 days. Patients also had to have an additional risk marker for high thrombotic risk: They had to be at least 75 years old, or 60-74 years old with a d-dimer level at least twice the upper limit of normal, or 40-59 years old with a d-dimer level at least twice the upper limit of normal and a history of either VTE or cancer.


Mitchel L. Zoler/Frontline Medical News

Dr. Gibson: Betrixaban surpassed enoxaparin.

Results for the primary endpoint, reported in 2016, showed that prolonged betrixaban prophylaxis linked with an absolute 1.6% reduction in the combined endpoint, which resulted in a 19% relative risk reduction that fell just short of the trial's prespecified definition of statistical significance. The study's primary safety endpoint was the occurrence of major bleeding events through 7 days after the stop of treatment, which occurred in 0.7% of the betrixaban patients and in 0.6% of those on enoxaparin (N Engl J Med. 2016 Aug 11;375[6]:534-44).

Even though the primary results from this pivotal trial failed to meet the prespecified threshold for statistical significance, the company developing betrixaban, Portola, submitted an application to the Food and Drug Administration to approve marketing of extended-duration betrixaban for VTE prophylaxis in acute medically ill patients with VTE risk factors. In December 2016, Portola announced that the FDA had given the application priority status for a decision.

The post-hoc analysis that Dr. Gibson presented at the meeting looked at the impact of betrixaban compared with enoxaparin on the incidence of all-cause and ischemic stroke during 77 days of follow-up after the start of treatment in the 7,432 patients who received at least one dose of their assigned drug, two endpoints that weren't even secondary outcomes in APEX's original design.

Among the 3,716 treated with betrixaban, the all-cause stroke incidence was 0.54%; among the 3,716 patients treated with enoxaparin, the all-cause stroke incidence was 0.97%. The 56% relative risk reduction was statistically significant. The incidence of ischemic strokes was 0.48% with betrixaban and 0.91% with enoxaparin, a 53% relative risk reduction that was also statistically significant.

The post-hoc analysis also looked specifically at the comparison between betrixaban and enoxaparin for stroke prevention in a subgroup of patients who had the highest stroke rate, the patients who were hospitalized because of an index stroke or an index heart failure episode. In this high-risk subgroup, prophylaxis with betrixaban cut the all-cause stroke rate compared with enoxaparin by 49% and the ischemic stroke rate by 45%, both statistically significant effects.

Dr. Gibson has been a consultant to Eli Lilly, Gilead, The Medicines Company, Novo Nordisk, Pfizer, and St. Jude. He has received research support from Portola and several other companies.

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VIEW ON THE NEWS

Extended-duration thromboprophylaxis may help

The APEX study identified a group of patients hospitalized for medical reasons who were at high risk for both venous thromboembolism and for stroke. We are comfortable with the concept of thromboprophylaxis for hospitalized patients who are at high risk for venous thromboembolism, but we have generally not paid attention to prophylaxis against stroke during and immediately after hospitalization.

The results suggest that extending thromboprophylaxis beyond the standard period of 10 days may be a good idea. Because patients in the two treatment arms of the study differed in both the drugs they received and in the duration of prophylaxis, the results cannot distinguish which of these two variables was more important. Treating patients with enoxaparin for 35-42 days may provide a similar benefit to what was seen with extended-duration betrixaban. Although daily treatment at home with injected enoxaparin is less convenient than outpatient treatment with an oral drug like betrixaban, extended-duration enoxaparin is a feasible option. The Kaplan-Meier curves that Dr. Gibson presented indicate that most of the incremental benefit from betrixaban occurred after 10 days, once it was compared with no prophylaxis at all in the control arm with short-duration enoxaparin.

The findings are a wake-up call to the high thromboembolic risk faced by the types of patients enrolled in APEX, and they point to a new way to manage these patients. Guidelines already call for putting high-risk patients, such as those with heart failure, on anticoagulant prophylaxis if they have no contraindications. These new data suggest that thromboprophylaxis in appropriate patients should extend beyond 10 days and beyond acute hospitalization.

Steven R. Lentz, MD, is a professor of medicine and a hematologist oncologist at the University of Iowa in Iowa City. He has been a consultant to Novo Nordisk and Opko, has an ownership interest in Celgene, and has received research grants from Novo Nordisk. He made these comments in an interview.

Infections plummet with new catheter interventions

BY ABIGAIL CRUZ
Frontline Medical News

Quality improvement (QI) interventions related to the use of central venous catheters (CVCs) were, on average, associated with 57% fewer infections and $1.85 million in net savings to hospitals within 1-3 years of implementation, based on the results of a meta-analysis of data from 113 hospitals.

"Hospitals that have already attained very low infection rates (through the use of quality improvement checklists) would likely see smaller clinical benefits and savings than in the studies we have reviewed," said Dr. Teryl Nuckols of Cedars-Sinai Medical Center, Los Angeles. "Nonetheless, we found that QI interventions can be associated with declines in CLABSI (central line-associated bloodstream infection) and/or CRBSI (catheter-related bloodstream infection) and net savings when checklists are already in use, and when hospitals have CLABSI rates as low as 1.7-3.7 per 1,000 CVC-days."

Dr. Nuckols and colleagues did a literature search and examined results from 15 unique studies representing data from 113 acute care hospitals. All studies addressed quality improvement interventions designed to prevent CLABSI and/or CRBSI.

Studies were eligible for the analysis if they reported or estimated the quality improvement intervention's clinical effectiveness, measured or modeled its costs, compared alternatives to the intervention, and reported both program and infection-related costs.

Insertion checklists were examined in 12 studies, physician education in 11 studies, ultrasound-guided placement of catheters in 3 studies, all-inclusive catheter kits in 5 studies, sterile dressings in 5 studies, chlorhexidine gluconate sponge or antimicrobial dressing in 2 studies, and antimicrobial catheters in 2 studies.

Overall, the weighted mean incidence rate ratio was 0.43 (95% confidence interval, 0.35-0.51) and incremental net savings were $1.85 million (95% CI, $1.30 million to $2.40 million) per hospital over 3 years (2015 U.S. dollars). Each $100,000 increase in program cost was associated with $315,000 greater savings (95% CI, $166,000-$464,000; *P* less than .001). Infections and net costs declined when hospitals already used checklists or had baseline infection rates of 1.7-3.7 per 1,000 catheter-days (doi: 10.1001/jamainternmed.2016.6610).

Dr. Nuckols acknowledged that the price tag for achieving these savings "may be burdensome for hospitals with limited financial resources … wages and benefits account for two-thirds of all spending by hospitals, and a quarter of hospitals have had negative operating margins in recent years. We found that, for CLABSI- and CRBSI-prevention interventions, median program costs were about $270,000 per hospital over 3 years – but reached $500,000 to $750,000 in some studies."

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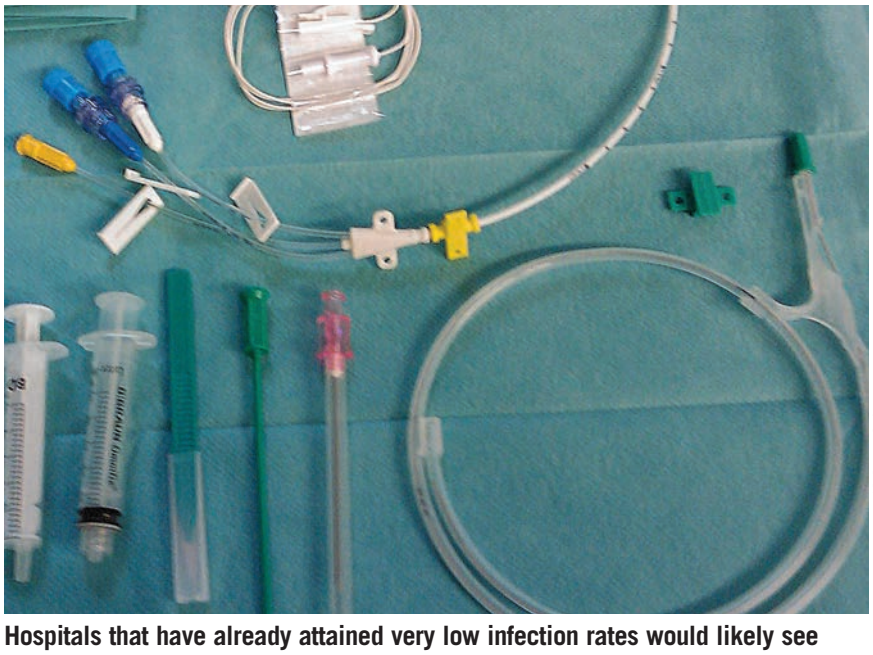

MR ARIFNAJAFOV/CC-BY-3.0

Hospitals that have already attained very low infection rates would likely see smaller clinical benefits than in the studies reviewed, noted Dr. Teryl Nuckols.

Moderate artery stenosis often becomes severe

BY DOUG BRUNK
Frontline Medical News

HOUSTON – Most nongrafted, moderately stenosed coronary arteries progress to severe stenosis or occlusion in the long term, results from a large, long-term study have shown.

"Not uncommonly, patients referred for coronary surgery have one or more coronary arteries with only moderate stenosis," Joseph F. Sabik III, MD, said at the annual meeting of the Society of Thoracic Surgeons.

DR. SABIK

"There is controversy as to whether arteries with only moderate stenosis should be grafted during coronary surgery, and if it should be grafted, with what conduit?" For example, the Fractional Flow Reserve-Guided PCI Versus Medical Therapy in Stable Coronary Disease study, known as FAME, suggests not intervening on moderate stenosis, since stenting non–ischemia-producing lesions led to worse outcomes (N Engl J Med. 2012 Sep 13;367:991-1001). However, Dr. Sabik, who chairs the department of surgery at University Hospitals Cleveland Medical Center, and his associates recently reported that grafting moderately stenosed coronary arteries during surgical revascularization is not harmful and can be beneficial by improving survival if an internal thoracic artery graft is used (J Thoracic Cardiovasc Surg. 2016 Mar;151[3]:806-11).

In an effort to determine how grafting moderately stenosed coronary arteries influences native-vessel disease progression, and whether grafting may be protective from late ischemia, Dr. Sabik and his associates evaluated the medical records of 55,567 patients who underwent primary isolated coronary artery bypass graft (CABG) surgery at the Cleveland Clinic from 1972 to 2011. Of the 55,567 patients, 1,902 had a single coronary artery with angiographically moderate stenosis (defined as a narrowing of 50%-69%) and results of at least one postoperative angiogram available. Of these moderately stenosed coronary arteries (MSCAs), 488 were not grafted, 385 were internal thoracic artery (ITA)–grafted, and 1,028 were saphenous vein (SV)–grafted. At follow-up angiograms, information about disease progression was available for 488 nongrafted, 371 ITA-grafted, and 957 SV-grafted MSCAs, and patency information was available for 376 ITA and 1,016 SV grafts to these MSCAs. Grafts were considered patent if they were not occluded. Severe occlusion was defined as a narrowing of more than 70%.

The researchers found that at 1, 5, 10, and 15 years, native-vessel disease progressed from moderate to severe stenosis/occlusion in 32%, 52%, 66%, and 72% of nongrafted MSCAs, respectively; in 55%, 73%, 84%, and 87% of ITA-grafted MSCAs, and in 67%, 82%, 90%, and 92% of SV-grafted MSCAs.

After Dr. Sabik and his associates adjusted for patient characteristics, disease progression in MSCAs was significantly higher with ITA and SV grafting, compared with nongrafting (odds ratios, 3.6 and 9.9, respectively). At 1, 5, 10, and 15 years, occlusion in grafts to MSCAs was 8%, 9%, 11%, and 15%, respectively, for ITA grafts and 13%, 32%, 46%, and 56% for SV grafts. At these same time points, protection from myocardial ischemia in ITA-grafted vs. nongrafted MSCAs was 29%, 47%, 59%, and 61%.

"Our opinion is you that shouldn't ignore moderate lesions," Dr. Sabik, surgeon-in-chief and vice president for surgical operations for the University Hospitals system, said in an interview at the meeting. "Although it may not help that patient over the next short period of time, over their lifespan it will. What works for intervention doesn't necessarily mean it's right for bypass surgery. If you have a vessel that's only moderately stenosed you should at least consider grafting it, because moderate lesions progress over time. Bypassing it helps people live longer when you use an internal thoracic artery graft, because they are likely to remain patent. You always have to individualize the therapy, but the key is to use your grafts in the best way possible."

Dr. Sabik disclosed that he has received research grants from Medtronic, Abbott Vascular, and Edwards Lifesciences.

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

For appropriate adult patients

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

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

BREO is for adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA.

BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

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

BOXED WARNING CONTINUED ON NEXT PAGE

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

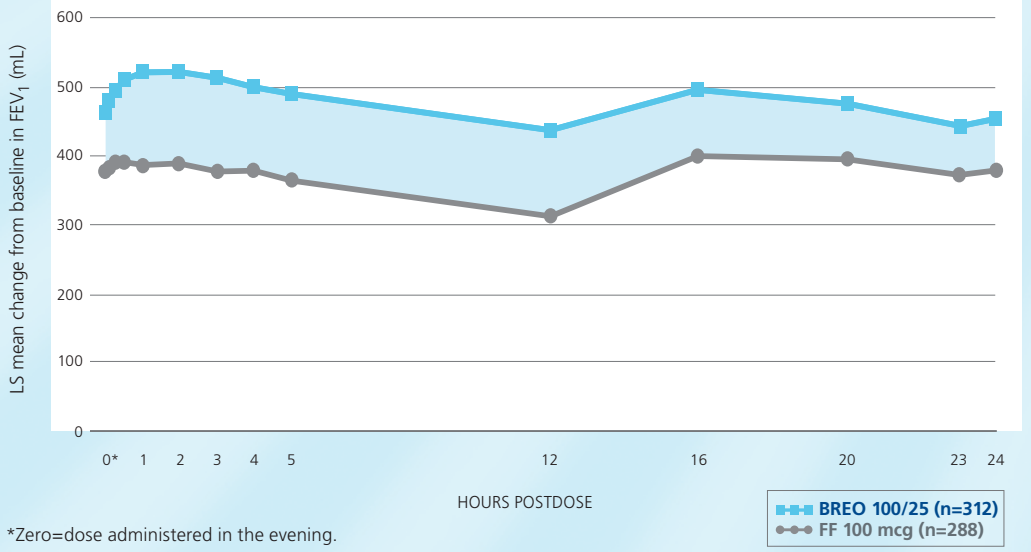
BREO:
CONTINUOUS LUNG FUNCTION IMPROVEMENT

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

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

BREO 100/25

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



*Zero=dose administered in the evening.

Study description

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

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

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

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

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

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

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

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

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

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

Important Safety Information (cont'd)

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

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

CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

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

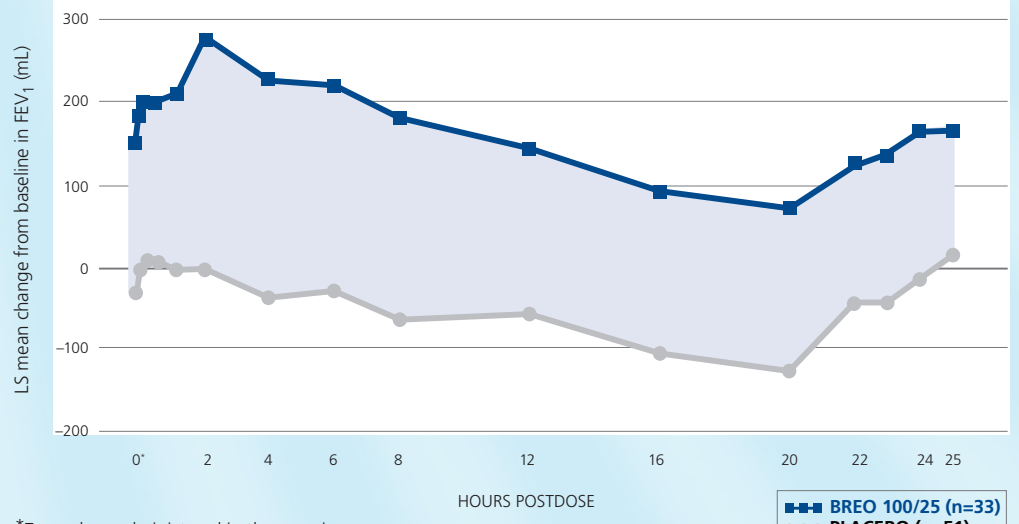
FOR A FULL 24 HOURS, WITH JUST ONE DAILY INHALATION

In patients with **COPD**

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

BREO 100/25

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



*Zero=dose administered in the morning.

Study description

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

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

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

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

FVC=forced vital capacity.

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

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

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

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

- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal.
  - In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO 100/25 (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and BREO 200/25 (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (<1% for each treatment group).

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

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

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

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

CONSIDER **24-HOUR BREO** TODAY

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

- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS: BREO 100/25 FOR COPD

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

ADVERSE REACTIONS: BREO FOR ASTHMA

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

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

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

Please see additional Important Safety Information for BREO on pages 1–3.
Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

BREO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

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

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease:
BREO 100/25 is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 once daily is the only strength indicated for the treatment of COPD.
Important Limitation of Use: BREO is NOT indicated for the relief of acute bronchospasm.

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death:
LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

5.2 Deterioration of Disease and Acute Episodes:
BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO 100/25 no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. For COPD, increasing the daily dose of BREO 100/25 is not appropriate in this situation.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO.

BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

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

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

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

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

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

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients from Systemic Corticosteroid Therapy:
Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression:
Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors:
Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin,

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troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information].*

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

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

5.12 Cardiovascular Effects:
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density:
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter. If significant reductions in BMD are seen and BREO is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

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

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

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

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

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. *[See Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: *Candida albicans* infection *[see Warnings and Precautions (5.4)]*; Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; Immunosuppression *[see Warnings and Precautions (5.6)]*; Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*; Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:
The clinical program for BREO included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects with COPD received at least 1 dose of BREO 100/25, and 1,087 subjects received a higher strength of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6- and 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with BREO 100/25 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n=1,224 and n=1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were white. They had a mean age of 62 years and an average smoking history of 44 pack-years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%). Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

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

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

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

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

In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis, 10% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dysphonia, 2% (1%, 0%). Oral candidiasis includes oral candidiasis and oropharyngeal candidiasis.

Trial 2 was a 12-week trial that evaluated the efficacy of BREO 100/25, BREO 200/25, and fluticasone furoate 100 mcg in adolescent and adult subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years.

In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/25 (n=346) (BREO 100/25 [n=346] or fluticasone furoate 100 mcg [n=347]) were: headache, 8% (8%, 9%); nasopharyngitis, 7% (6%, 7%); influenza, 3% (3%, 1%); upper respiratory tract infection, 2% (2%, 3%); oropharyngeal pain, 2% (2%, 1%); sinusitis, 2% (1%, <1%); bronchitis, 2% (<1%, 2%); and cough, 1% (2%, 1%).

24-Week Trial: Trial 3 was a 24-week trial that evaluated the efficacy of BREO 200/25 once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in adolescent and adult subjects with asthma. Of the 586 subjects, 59% were female and 84% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO 200/25 included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.

12-Month Trial: Long-term safety data is based on a 12-month trial that evaluated the safety of BREO 100/25 once daily (n=201), BREO 200/25 once daily (n=202), and fluticasone propionate 500 mcg twice daily (n=100) in adolescent and adult subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO 100/25 or BREO 200/25 for 12 months included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

Exacerbation Trial: In a 24- to 76-week trial, subjects received BREO 100/25 (n=1,009) or fluticasone furoate 100 mcg (n=1,010) (Trial 5). Subjects participating in this trial had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. Asthma-related hospitalizations occurred in 10 subjects (1%) treated with BREO 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 (n=151) compared with 0 subjects treated with fluticasone furoate 100 mcg (n=130). There were no asthma-related deaths or asthma-related intubations observed in this trial.

6.3 Postmarketing Experience:
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.
Cardiac Disorders: Palpitations, tachycardia.
Immune System Disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.
Musculoskeletal and Connective Tissue Disorders: Muscle spasms.
Nervous System Disorders: Tremor.
Psychiatric Disorders: Nervousness.
Respiratory, Thoracic, and Mediastinal Disorders: Paradoxical bronchospasm.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4:
Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information].*

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:
Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents:
Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents

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for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics:
The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy:
Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with BREO in pregnant women. Corticosteroids and $beta_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO.

Fluticasone Furoate and Vilanterol: There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day).

Fluticasone Furoate: There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery:
There are no adequate and well-controlled human trials that have investigated the effects of BREO during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers:
It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and $beta_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.4 Pediatric Use:
BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.

In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n=1,009) or fluticasone furoate 100 mcg (n=1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. *[See Clinical Studies (14.2) of full prescribing information.]* Adolescents aged 12 to 17 years made up 14% of the study population (n=281), with a mean exposure of 352 days for subjects in this age-group treated with BREO 100/25 (n=151) and 355 days for subjects in this age-group treated with fluticasone furoate 100 mcg (n=130). In this age-group, 10% of subjects treated with BREO 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age-group.

Effects on Growth: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of children and adolescents with ICS, including fluticasone furoate, on final adult height are not known. *[See Warnings and Precautions (5.17); Use in Special Populations (8.4) of full prescribing information.]*

8.5 Geriatric Use:
Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of BREO for COPD included 2,508 subjects aged 65 and older and 564 subjects aged 75 and older. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment*:*
Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment:
There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE
No human overdosage data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Fluticasone Furoate:
Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Vilanterol:
The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death
Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Also inform them that currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Not for Acute Symptoms:
Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting $beta_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following: decreasing effectiveness of inhaled, short-acting $beta_2$-agonists; need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists; significant decrease in lung function as outlined by the physician.

Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting $Beta_2$-agonists:
Instruct patients not to use other LABA for COPD and asthma.

Local Effects:
Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

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

Immunosuppression:
Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression:
Advise patients that BREO may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO.

Reduction in Bone Mineral Density:
Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Ocular Effects:
Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Risks Associated with Beta-agonist Therapy:
Inform patients of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Hypersensitivity Reactions, Including Anaphylaxis:
Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

GlaxoSmithKline
Research Triangle Park, NC 27709

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Nailfold can predict cardiopulmonary problems

BY JENNIE SMITH
Frontline Medical News

Nailfold videocapillaroscopy can help to predict which patients with systemic sclerosis may develop serious cardiopulmonary complications, according to findings from a Dutch cross-sectional study.

While individual autoantibodies seen in systemic sclerosis (SSc) are known to be associated with greater or lesser risk of cardiopulmonary involvement, in this study nailfold vascularization patterns independently predicted pulmonary artery hypertension or interstitial lung disease.

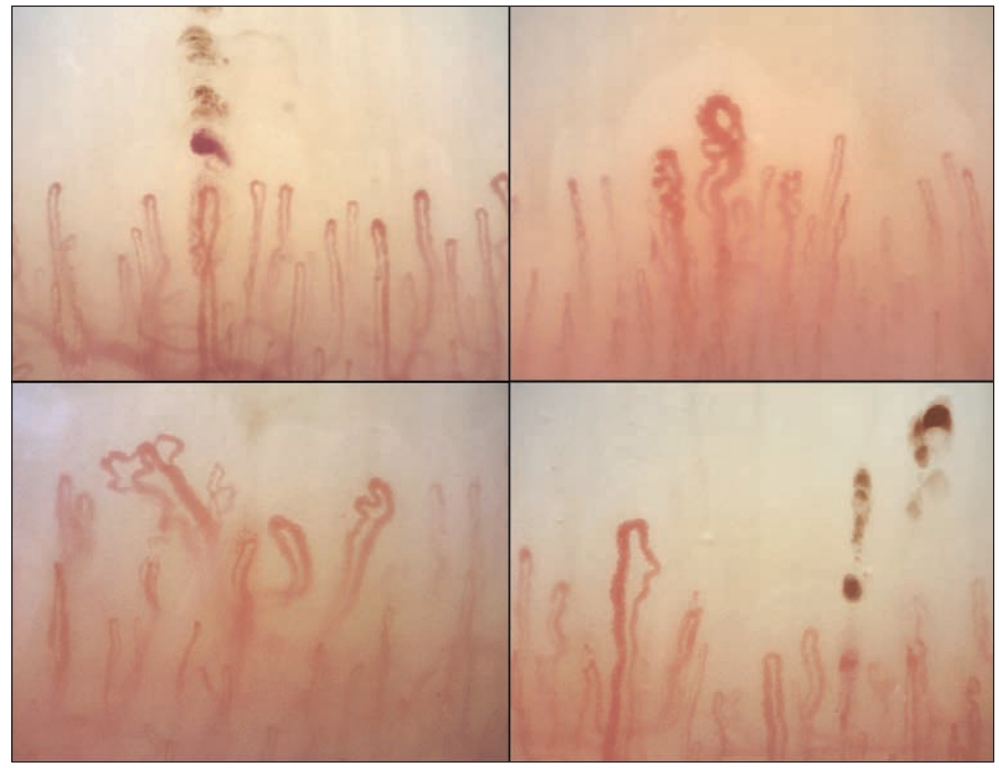
For their research, Iris M. Markusse, MD, PhD, and her colleagues at Leiden (the Netherlands) University Medical Center collected data on nailfold videocapillaroscopy (NVC) patterns and SSc-specific autoantibodies from a cross section of 287 patients in an established SSc cohort (Rheumatology [Oxford]. 2016 Dec 10. doi: 10.1093/rheumatology/kew402).

All patients in the study had NVC pattern data as well as anti-extractable nuclear antigen (anti-ENA) antibodies. The mean age of the patients was 54 years; 82% were female, and median disease duration was 3 years. Just over half the cohort had interstitial lung disease, and 16% had pulmonary artery hypertension.

Among the anti-ENA autoantibody subtypes, anti-ACA was seen in 37% of patients, anti-Scl-70 in 24%, anti-RNP in 9%, and anti-RNAPIII in 5%; other subtypes were rarer. SSc-specific NVC patterns were seen in 88% of patients, with 10% of the cohort showing an early (less severe microangiopathy) pattern, 42% an active pattern, and 36% a late pattern.

One of the study's objectives was to determine whether one or more mechanisms was responsible for both autoantibody production and the microangiopathy seen in SSc.

If a joint mechanism is implicated, "more severe NVC patterns would be determined in patients with autoantibodies (such as anti-Scl-70 and anti-RNAPIII) that are associated with more severe disease," wrote Dr. Markusse and her colleagues. "On the other hand, if specific autoantibodies and stage of microangiopathy reflect different processes in the disease, a combination of autoantibody status and NVC could be helpful for identifying patients at highest risk for cardiopulmonary involvement."



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Nailfold capillaroscopy images show progressively worsening damage: microhemorrhage and hemosiderin (top left), an isolated dilated loop (top right), lower capillary density and microhemorrhage (lower right), and architectural derangement (lower left).

The investigators reported finding a similar distribution of NVC abnormalities across the major SSc autoantibody subtypes (except for anti–RNP-positive patients), suggesting that combinations of the two variables would be most predictive of cardiopulmonary involvement. More severe NVC patterns were associated with a higher risk of cardiopulmonary involvement, independent of the presence of a specific autoantibody. Notably, the researchers wrote, "prevalence of ILD [interstitial lung disease] is generally lower among ACA-positive patients. According to our data, even among ACA-positive patients there was a trend for more ILD being associated with more severe NVC patterns (OR = 1.33)."

A similar pattern was seen for pulmonary artery hypertension. "Based on anti-RNP and anti-RNAPIII positivity, patients did not have an increased risk of a [systolic pulmonary artery pressure] greater than 35 mm Hg; however, with a severe NVC pattern, this risk was significantly increased (OR = 2.33)."

The investigators cautioned that their findings should be confirmed in larger cohorts. The study by Dr. Markusse and her colleagues was conducted without outside funding, though manufacturers donated diagnostic antibody tests. One of the 11 study coauthors disclosed receiving financial support from Actelion.

Macitentan boosts quality of life in PAH patients

BY RANDY DOTINGA
Frontline Medical News

FROM CHEST

Macitentan, a recent addition to the drugs that treat pulmonary arterial hypertension (PAH), improves and stabilizes quality of life for patients with the condition, according to an industry-funded study.

Macitentan (Opsumit) remains tremendously expensive, costing as much as $100,000 per year in the United States, and the study provides little in the way of direct comparison to other drugs in its class. Still, the drug's effects on quality of life are dramatic, said study lead author Sanjay Mehta, MD, FRCPC, FCCP, professor of medicine at the University of Western Ontario and director of the Southwest Ontario Pulmonary Hypertension Clinic at the London (Ont.) Health Sciences Center.

Researchers found that those who took the 10-mg dose, versus placebo, reported significant improvement in seven of eight quality-of-life domains, and in physical and mental components scores, as measured by the 36-item Short Form Health Survey (SF-36). In addition, the study linked 10-mg doses, versus placebo, to a lower risk of a decline of three points or more in the physical component score (hazard ratio, 0.60; 95% confidence interval, 0.47-0.76; *P* less than .0001] and the mental component scores (HR, 0.76; 95% CI, 0.61-0.95; *P* = .0173) until end of treatment.

"The drug has shown stability in patients' quality of life over 6 months and 12 months," Dr. Mehta said in an interview. "I can't cure anybody, and they'll get worse at some point, but I can improve them. They physically feel better, they're less short of breath with less body pain, and they feel better psychologically."

Macitentan, an endothelin receptor antagonist, received Food and Drug Administration approval in 2013 following a study that year (N Engl J Med. 2013 Aug 29;369[9]:809-18) that linked 10-mg doses to a significantly lower risk of death and various complications, compared with placebo and the 3-mg dose. The new study (Chest. 2017 Jan;151[1]:106-18) is an analysis of data from the 2013 study.

The PAH patients were randomly assigned to one of three groups: macitentan 10 mg once daily (234), macitentan 3 mg (237), and placebo (239). The study examined responses from 710 patients (76.9% were female, 55.2% were white, mean age was 45.5) to the SF-36 at baseline, 6 months, 12 months, and end of treatment.

Dr. Mehta noted that macitentan has not been clinically compared to the other drugs. The study, however, notes that it is the first PAH treatment to show improvement in seven of eight domains in the quality-of-life survey.

The study was funded by Actelion Pharmaceuticals, maker of macitentan. Dr. Mehta has received consulting and speaking fees and institutional support for clinical trials from Actelion, among other drug companies. The other authors report various disclosures, including relationships with Actelion.

Federal judge blocks Anthem-Cigna merger

BY ALICIA GALLEGOS
Frontline Medical News

A federal district court judge has blocked health insurer Anthem from acquiring Cigna, ruling the megamerger would violate antitrust laws and stifle competition.

The decision came weeks after another U.S. district court judge barred a merger between health insurance giants Aetna and Humana.

The U.S. Department of Justice praised the latest ruling, calling the decision a victory for patients.

"This merger would have stifled competition, harming consumers by increasing health insurance prices and slowing innovation aimed at lowering the costs of health care," Acting Assistant Attorney General Brent Snyder said in a statement.

Anthem intends to appeal the decision, said Joseph R. Swedish, Anthem's chair, president, and chief executive officer. "Anthem is significantly disappointed by the decision, as combining Anthem and Cigna would positively impact the health and well-being of millions of Americans – saving them more than $2 billion in medical costs annually," Mr. Swedish said in a statement. "If not overturned, the consequences of the decision are far reaching and will hurt American consumers by limiting their access to high-quality affordable care, slowing the industry's shift to value-based care and improved outcomes for patients, and restricting innovation, which is critical to meeting the evolving needs of health care consumers."

In a statement, a Cigna official said the company intends to carefully review the opinion and evaluate its options in accordance with the merger agreement.

"Cigna remains focused on helping to improve health care by delivering value to our customers and clients and expanding our business around the world," the statement said.

The DOJ, 11 states, and the District of Columbia sued Anthem and Cigna in July over their proposed $54 billion consolidation in what would have been the largest merger in history.

The DOJ argued the merger would substantially harm competition and negatively impact the entire insurance industry if allowed to proceed. The consolidation would enhance Anthem's power to profit at the expense of consumers and the doctors and hospitals who provide their medical care, DOJ attorneys said in their complaint.

Anthem and Cigna argued the proposed acquisition was "procompetitive," and that the merger would result in efficiencies that would directly benefit consumers via greater access to affordable health care. The benefits of the merger outweigh any alleged anticompetitive effects, according to Anthem.

A trial before Judge Amy Berman Jackson of the U.S. District Court for the District of Columbia ran from November through January.

Judge Berman's opinion is temporarily under seal to allow parties to review for confidentiality.

The ruling is the second victory for the DOJ in as many weeks. In a Jan. 23 decision, Judge John D. Bates of the U.S. District Court for the District of Columbia denied Aetna's $37 billion plan to purchase Humana, following a month-long trial that began in early December. Judge Bates ruled the consolidation would violate antitrust laws and reduce competition.

Aetna and Humana did not respond to requests for comment.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: Any business owner who has been required to absorb yearly double-digit increases in employee health insurance costs cannot help but wonder where Mr. Swedish learned his "new math." His second statement is even more incogitable – since when were insurers known for expanding access to health care. Anyone who has been unfortunate enough to participate in a peer-to-peer conference with an insurer in an attempt to get a patient needed care knows otherwise. Although health insurance companies did not exist in 1890, the Sherman Antitrust Act of the same year was perfectly scripted to proscribe this type of merger over a century later.

Trump travel policy may affect medical meetings

BY ALICIA GALLEGOS
Frontline Medical News

President's Trump's revised executive order blocking travelers from six Muslim-majority countries from entering the United States could land a damaging blow to global cooperation in scientific research and could impede assemblies of the world's top medical experts.

The March 6 executive order bars citizens of Iran, Libya, Somalia, Sudan, Syria, and Yemen from obtaining visas for 90 days and blocks refugees from those countries from entering the United States for 120 days. The measure, which takes effect March 16, supersedes President Trump's Jan. 27 travel ban. The new order exempts citizens of the six countries who are legal permanent U.S. residents or who have current visas.

The policy could have detrimental effects on future collaboration between U.S. and international scientists and may ultimately endanger the health and well-being of patients, said International Antiviral Society–U.S.A. executive director and president Donna M. Jacobsen.

There is "serious reason for concern" that the policy will dissuade scientists and researchers "from traveling to the [United States] in the future overall and sharing their work with colleagues here," she said.

Thousands of academics from around the world, including physicians, researchers, and professors, have vowed to boycott U.S.-based conferences in light of the Trump administration policy.

The new executive order comes nearly 2 months after President Trump's original travel ban caused nationwide protests and led to a series of legal challenges. The states of Washington and Minnesota, which sued President Trump over his original ban, argued that such a ban harms the teaching and research missions of their universities and prevents students and faculty from traveling for research and academic collaboration. In addition, the executive order restricts universities from hiring attractive candidates from countries affected by the ban, state officials said. A federal court temporarily blocked the original travel ban on Feb. 3, a decision upheld by the 9th U.S. Circuit Court of Appeals on Feb. 9. The circuit judges said the plaintiffs were likely to succeed in their arguments and that the president had demonstrated no evidence that his executive order advances national security.

The new executive order excludes Iraq and also removes language that had indefinitely banned Syrian refugees. In a March 6 memorandum, the White House said the purpose of the ban is to prevent "foreign nationals who may aid, support, or commit violent, criminal, or terrorist acts," while the administration enhances the screening and vetting protocols and procedures for granting visas and admission to the United States.

"This nation cannot delay the immediate implementation of additional heightened screening and vetting protocols and procedures for issuing visas to ensure that we strengthen the safety and security of our country," the memo states.

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Societies voice concern for travel ban

February 7, 2017
The Honorable John F. Kelly
Secretary
U.S. Department of Homeland Security
Washington, DC 20528

Dear Secretary Kelly:
The undersigned organizations are greatly concerned that the executive order signed by President Trump on January 27, 2017 will result in discrimination against foreign-born persons from certain predominantly Muslim countries. We are particularly concerned that by restricting entry of physicians and medical students from seven designated Muslim majority countries, the order will undermine medical education and result in patients losing access to their doctors. We are also greatly concerned that the 120 day ban on accepting refugees, and the indefinite ban on Syrian refugees, will contribute to an ongoing public health crisis for those affected, needlessly subjecting them to violence, injury, illness, deprivation and even death. While we are pleased that the courts have temporarily halted implementation of the executive order, the underlying issues of concern about the harm caused by the executive order remain.

The restrictions in the executive order will hinder the free exchange of information and travel among medical students, residents and physicians around the world and result in Americans having poorer access to care. In 2016, 3,769 non-U.S. citizen international medical graduates (IMGs) obtained first-year residency positions. More than half of internal medicine residency positions were filled by IMGs. Approximately 25% of the nation's physicians are IMGs and provide a disproportionate share of the care to Americans in underserved communities that have a shortage of U.S. born and trained physicians. They also add necessary diversity and cultural competency to our healthcare workforce. If the executive order prevents IMGs from being able to come to the U.S. this could potentially affect the care for thousands of patients.

Our organizations are also especially concerned about refugees with dire medical conditions who had been approved for visas to enter the U.S. but since the executive order, have been unable to enter the country to receive much needed medical care.

While we urge that the executive order be rescinded and replaced with non-discriminatory policies that support families, public health, and medical education, and are pleased that the courts have temporarily halted implementation, there are steps that DHS can take immediately to selectively ease travel restrictions that impact medical education, access to health care services, and public health for individuals who otherwise meet the criteria for immigration, including those from the seven countries identified in the executive order. Specifically, we urge the Department of Homeland Security to:

1. Reinstate the Visa Interview Waiver Program. Suspension of the program "risks creating substantial backlogs in the processing of new and renewal visas for trainees from any foreign country — delays that create substantial problems for residency programs with trainees on visas and that could interfere with the residency match process this year."
2. Remove restrictions on entering the U.S. for physicians from the seven designated countries who have been approved for J-1 or H-1B visas and students from those countries with F-1 visas who have been accepted to U.S. medical schools.
3. Develop and implement a plan to allow physicians from the seven designated countries to obtain travel visas to travel to the U.S. for medical conferences and other medical and research-related engagements.
4. Make it a priority to implement a process to admit refugees, without further delay, who had already been vetted and approved for entry prior to the executive order and who are in need of urgent medical care. We note that even with such revisions, the executive order will still inappropriately bar immigrants and refugees based on discriminatory criteria (religion and country of origin) including family members of physicians and medical students in the U.S.

Our organizations are committed to non-discrimination against physicians, medical students and others in immigration policies and offer our assistance in developing policies that support access to health care services, public health, and medical education while balancing the nation's security needs. Until or unless the executive order is completely rescinded or permanently blocked, it is essential that DHS move forward to ensure that restrictions on physicians and medical students are not reimposed, and that priority is given to refugees with medical conditions needing treatment.

Sincerely,
Alliance for Academic Internal Medicine
American College of Chest Physicians
American College of Physicians
American Society for Gastrointestinal Endoscopy
American Society of Hematology
American Society of Nephrology
American Thoracic Society
Infectious Diseases Society of America
Renal Physicians Association
Society for Adolescent Health and Medicine
Society of Critical Care Medicine
Society of General Internal Medicine

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THE LESS DIFFICULT THE CHOICE OF HOSPITAL.

The Mount Sinai Hospital - National Jewish Health Respiratory Institute brings together a strong, integrated program for diagnosis and treatment of respiratory illness and lung disease. Our pulmonologists collaborate with specialists in related disciplines and work closely with research scientists on precision medicine, genomics, and data-driven clinical protocols to enhance the quality and outcomes of the respiratory disease practice. Additionally, our experts are on the faculty of the Icahn School of Medicine at Mount Sinai, ranked among the nation's top medical schools by *U.S. News & World Report*.

- Asthma
- Bronchiectasis and NTM
- COPD
- Pulmonary Fibrosis/ILD
- Lung Nodule/Lung Cancer
- Pulmonary Hypertension
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HFNC bests conventional O_2 therapy

BY WHITNEY MCKNIGHT
Frontline Medical News

FROM CHEST

In patients with acute respiratory failure, high-flow nasal cannula (HFNC) is more reliable than is conventional oxygen therapy at reducing rates of endotracheal intubation, although no significant difference was found when HFNC was compared with noninvasive positive pressure ventilation, a new study found.

An increasing awareness of the high rate of adverse events and mortality rates associated with invasive mechanical ventilation in hospitals has led to a rise in the use of noninvasive positive pressure ventilation (NIPPV). While this has effectively cut the use of conventional oxygen therapy (COT), its application in clinical practice is limited by a host of complications such as interface intolerance, skin damage, and other hazards. HFNC, because of its demonstrated efficacy and relatively easier application, and better tolerance in patients, also has been gaining popularity. Despite the known benefits of HFNC, this therapy is not given to all adults with acute respiratory failure (ARF). This may be due to the lack of consistency in data regarding how HFNC's effectiveness at decreasing intubation and reintubation rates compares with COT's and NIPPV's.

Researchers in China conducted a meta-analysis and systematic review of all superiority and nonsuperiority data on the outcomes of using HFNC, COT, and NIPPV to treat ARF. Their examination included 18 trials comprising 3,881 patients, which compared the results of receiving HFNC with the results of receiving NIPPV or COT. The study is published in CHEST (10.1016/j.chest.2017.01.004).

The investigators concluded that HFNC was associated with significantly lower rates of the need for endotracheal intubation, compared with COT ($P = .01$). When HFNC was compared with NIPPV, however, the rates of patients needing intubation were not statistically different from each other ($P = .16$). HFNC was not associated with significant improvements in mortality rates or lengths of stay in the intensive care units, when compared with both COT and NIPPV.

According to the researchers' subgroup analysis conducted of HFNC in 2,741 patients following extubation, those patients who received HFNC had a significantly lower reintubation rate than that of those who received COT (odds ration, 0.39; $P = .0003$). In this analysis, again, no significant differences in outcomes were seen between patients who received HFNC and NIPPV (OR, 1.07; $P = .60$)

Bin-Miao Liang, MD, PhD, a researcher in the department of respiratory and critical care medicine at Sichuan (China) University, and coauthors noted that "concomitant complications such as acute kidney dysfunction and cardiac impairment may contribute to ICU mortality and ICU [lengths of stay] besides respiratory status itself." Factors such as available beds, a patient's insurance status, and other resources may also have impacted outcomes, they said.

The researchers wrote that they found "[significant] statistical heterogeneity" in the rates of endotracheal intubation and ICU mortality between HFNC and NIPPV. A lack of raw data, which prevented a sub analysis of individual respiratory failure from being performed, is one possible cause of the statistical heterogeneity, the authors concluded.

"The finding that rates of intubation in patients with acute respiratory failure are reduced with [HFNC] use when compared to standard oxygen administration has important implications for critical care practitioners," said Danielle R. Ouellette, MD, FCCP, of Henry Ford Hospital, Detroit, in an interview. "It seems likely that this effect is a result of improvement in not only oxygenation, but also ventilation by such catheters. HFNC may be a useful adjunct not only in patients with respiratory failure, but also post-extubation, and may be more tolerable than noninvasive ventilation."

China-Japan Friendship Hospital is continuing the search for more data on the success rates of HFNC and NIPPV at reducing intubation and mortality rates. The hospital is sponsoring a multicenter, randomized, noninferiority trial titled, "High Flow Nasal Cannula vs. NPPV in Moderate Chronic Obstructive Pulmonary Disease Exacerbation," according to ClinicalTrials.gov. No results were available for this trial as of March 1.

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VIEW ON THE NEWS

Is HFNC better than NIPPV? It depends

The introduction of high-flow nasal cannula (HFNC) fundamentally has changed how patients with acute respiratory failure are treated – both in avoidance of intubation and prevention of reintubation. Its use is supported by some very high quality studies over the last few years done in a variety of types of critically ill patients. While its clinical superiority to noninvasive ventilation (NIV) is still open to debate, the comfort and other attributes that HFNC provides increasingly are making it the first-choice modality (e.g., the patient can continue to eat, speak, and wear for longer periods of time).

Regarding this meta-analysis, given that most would agree that both HFNC and NIV are better than COT, the outcomes of interest are the comparisons between HFNC and noninvasive positive pressure ventilation (NIPPV). Given the heterogeneity in the included trials, populations, and study quality, there unsurprisingly is a significant I-squared statistic for high heterogeneity in outcomes between studies. As such, little conclusion can be drawn regarding whether HFNC would be more beneficial than NIPPV in a given patient. It is likely that HFNC is better in some patients, while NIPPV is more appropriate for others ... and this meta-analysis just doesn't offer much in that regard.

Eric J. Gartman, MD, FCCP, is assistant professor of medicine at Brown University, Providence, R.I. He is an editorial board member of CHEST Physician.

In ICU, pair MRSA testing method with isolation protocol

BY DAN WATSON
Frontline Medical News

An ICU's method of testing for methicillin-resistant *Staphylococcus aureus* (MRSA) should be paired with its patient isolation policy, according to researchers at the University of Colorado at Denver.

In an ICU with all patients preemptively isolated, it is worth the added expense to opt for the polymerase chain reaction (PCR) test – which generates results in a few hours – so that patients negative for the infection can be moved out of isolation more quickly, wrote Melanie D. Whittington, PhD, and her coauthors. But if the ICU is isolating only MRSA-positive patients, the authors instead recommend the less expensive but slower chromogenic agar 24-hour testing.

The other two MRSA tests the researchers assessed – conventional culture and chromogenic agar 48-hour testing – are less expensive. But when paired with either ICU isolation policy, those tests lead to excessive inappropriate isolation costs while waiting for the results, the study investigators cautioned (Am J Infect Control. 2017 Jan 23. doi: 10.1016/j.ajic.2016.12.014).

Adding together the cost per patient of the test, the "appropriate isolation costs," and "inappropriate isolation costs," the universal isolation policy is least expensive per patient with PCR, at $82.51 per patient. With conventional culture, which can take several days, this cost ballooned to $290.11 per patient, with high inappropriate isolation costs.

Doing the same math with the more targeted isolation policy, the least expensive screening method was the 24-hour chromogenic agar, at $8.54 per patient, while the expense of the PCR test made it the most expensive method when paired with this isolation policy, at $30.95 per patient.

"With knowledge of the screening test that minimizes inappropriate and total costs, hospitals can maximize the efficiency of their resource use and improve the health of their patients," Dr. Whittington and her coauthors wrote.

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High NIV volume not a predictor of good outcomes

BY MARY ANN MOON
Frontline Medical News

Hospitals that frequently treat acute chronic obstructive pulmonary disease (COPD) exacerbations using noninvasive ventilation – a practice known to reduce mortality, length of stay, and the need for more invasive treatment – did not have better patient outcomes than did hospitals that used noninvasive ventilation less frequently, according to a report published in Annals of the American Thoracic Society.

"Contrary to our hypothesis, we did not observe significantly lower COPD mortality" in hospitals with high volumes of noninvasive ventilation, the researchers noted.

Acute COPD exacerbations are "one of the few conditions with high-level evidence demonstrating the benefits of noninvasive ventilation in patients with respiratory distress," and the treatment has been widely adopted for this patient population. However, for noninvasive ventilation to succeed, patients must be carefully selected and closely monitored, and a multidisciplinary team of nurses, respiratory therapists, and physicians must coordinate the treatment, often across multiple hospital settings, said Anuj B. Mehta, MD, of The Pulmonary Center, Boston University, and his associates.

Until now, it was not known whether hospitals with a high volume of noninvasive ventilation develop specialized expertise and thus deliver superior patient outcomes, or whether a high volume results from suboptimal patient selection or otherwise puts a strain on a hospital's staff and thus produces poor outcomes. To examine this question, Dr. Mehta and his associates analyzed information in a database enrolling adults treated at 252 California hospitals for acute COPD exacerbation. They focused on 37,516 hospitalizations that occurred during a single year.

Overall, 9.3% of these patients received noninvasive ventilation. The

Continued on following page

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: It is unclear what conclusions can be drawn from this study given the likely heterogeneity between the included hospitals. For instance, hospitals with high volumes of NIV use also seemed to have patients with more significant comorbidities – and thus it would not be appropriate to compare these high-acuity hospitals to lower acuity hospitals. Further, as mentioned in the article there are many other support systems and monitoring that potentially can affect the outcomes of these patients – and such factors would be very difficult to control for in an analysis like this.

Continued from previous page

median annual case volume of noninvasive ventilation for any indication was 64 per hospital. But rates of noninvasive ventilation varied widely across hospitals, with 40% of facilities significantly deviating from this median rate.

"Contrary to our hypothesis, we did not observe significantly lower COPD mortality" in hospitals with high volumes of noninvasive ventilation. For individual patients, admission to a hospital with a high volume of noninvasive ventilation was associated with significantly higher odds of treatment failure (adjusted odds ratio, 1.95), and such failure was associated with significantly higher odds of death (adjusted OR, 1.81). In addition, at the hospital level, a high volume of noninvasive ventilation was associated with a significantly higher risk of treatment failure, which in turn was associated with higher patient mortality.

"Hospitals with higher total noninvasive ventilation case volume tended to use [it] in patients with more comorbidities and acute organ failures," the authors said.

"Hospitals with higher total nonin-

vasive ventilation case volume tended to use [it] in patients with more comorbidities and acute organ failures, suggesting potential overuse among patients at higher risk of treatment failure. [This] may partially explain why hospitals with high rates of using an evidence-based intervention did not achieve significant mortality benefits," Dr. Mehta and his associates said (Ann Am Thorac Soc. 2016;13[10]:1752-9).

They added that the wide variation between hospitals in failure rates for noninvasive ventilation were likely attributable to unmeasured hospital factors, speculating that the site of treatment (regular ward vs. ICU); staffing ratios for nurses, respiratory therapists, and physicians; and the intensity of patient monitoring, such as the frequency of blood-gas measurement, may contribute.

"High rates of treatment failure at some hospitals suggest that further work is needed to maximize the real-world effectiveness of noninvasive ventilation, even for an indication [backed by] strong evidence," the investigators said.

The National Institutes of Health; the National Heart, Lung, and Blood Institute; and Boston University supported the study. The investigators' financial disclosures are available at www.atsjournals.org.

Vitamin D reduces respiratory infection risk

BY DEEPAK CHITNIS
Frontline Medical News

Administering doses of a vitamin D supplement to patients can significantly mitigate their risk of developing acute respiratory tract infections, according to a recent study published by the BMJ.

"[Existing] epidemiological and in vitro data have prompted numerous randomized controlled trials to determine whether vitamin D supplementation can decrease the risk of acute respiratory tract infection," wrote the authors of the study, led by Adrian R. Martineau, PhD, of Queen Mary University of London. "A total of five aggregate data meta-analyses incorporating data from up to 15 primary trials have been conducted to date [but] all but one of these aggregate data meta-analyses reported statistically significant heterogeneity of

effect between primary trials."

Dr. Martineau and his colleagues conducted a search of the Medline, Embase, and Web of Science databases, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and the International Standard Randomized Controlled Trials Number registry to find trials that were randomized, double blind, and placebo controlled involving patients receiving vitamin D supplementation, either with D_2 or D_3.

A total of 532 studies were reviewed by a panel, of which 25 studies were ultimately selected for inclusion in this analysis. The studies included were of varying lengths in terms of trial periods and involved a total of 11,321 subjects ranging from 0 to 95 years of age. Of these, 10,933 (96.6%) subjects experienced at least one acute respiratory tract infection.

No significant benefit was found in subjects who had already experienced an infection, yielding an odds ratio of 0.98 (95% confidence internval, 0.80-1.20; $P = .83$). Analysis performed to quantify the risk of infection with or without vitamin D showed that taking vitamin D supplements significantly decreased infection risk, with an OR of 0.88 (95% CI, 0.81-0.96; P less than .001) after adjusting for age, sex, and the duration of the trial.

Continued on page 49

In suspected VAP, ultrashort antibiotics may work

BY AMY KARON
Frontline Medical News

Ultrashort courses of antibiotics led to similar outcomes as longer durations of therapy among adults with suspected ventilator-associated pneumonia but minimal and stable ventilator settings, according to a large retrospective observational study.

The duration of antibiotic therapy did not significantly affect the time to extubation alive (hazard ratio, 1.2; 95% confidence interval, 1.0-1.4), time to hospital discharge (HR, 1.1; 95% CI, 0.9-1.3), rates of ventilator death (HR, 0.8; 95% CI, 0.6-1.2), or rates of hospital death (HR, 1.0; 95% CI, 0.8-1.31), said Michael Klompas, MD, and his associates at Harvard Medical School in Boston. If confirmed, the findings would support surveillance of serial ventilator settings to "identify candidates for early antibiotic discontinuation," the investigators reported (Clin Infect Dis. 2016 Dec 29. doi: 10.1093/cid/ciw870).

Suspected respiratory infections account for up to 70% of ICU antibiotic prescriptions, a "substantial fraction" of which may be unnecessary, the researchers said. "The predilection to overprescribe antibiotics for patients with possible ventilator-associated pneumonia (VAP) is not due to poor clinical skills per se, but rather the tension between practice guidelines that encourage early and aggressive prescribing [and] the difficulty [of] accurately diagnosing VAP," they wrote. While withholding antibiotics in suspected VAP is "unrealistic" and can contribute to mortality, observing clinical trajectories and stopping antibiotics early when appropriate "may be more promising," they added.

To test that idea, the researchers studied 1,290 cases of suspected VAP treated at Brigham and Women's Hospital between 2006 and 2014. On the day antibiotics were started and during each of the next 2 days, all patients had a daily minimum positive end-expiratory pressure (PEEP) of no more than 5 cm H_2O and a daily minimum fraction of inspired oxygen (FiO_2) of no more than 40%.

A total of 259 patients received 1-3 days of antibiotics, while 1,031 patients received more than 3 days of therapy. These two groups were similar demographically, clinically, and in terms of comorbidities. Point estimates tended to favor ultrashort course antibiotics, but no association reached statistical significance in the overall analysis or in subgroups based on confirmed VAP diagnosis, confirmed pathogenic infection, or propensity-matched pairs.

The results suggest "that patients with suspected VAP but minimal and stable ventilator settings can be adequately managed with very short courses of antibiotics," Dr. Klompas and his associates concluded. "If these findings are confirmed, assessing ventilator settings may prove to be a simple and objective strategy to identify potential candidates for early antibiotic discontinuation."

The work was supported by the Centers for Disease Control and Prevention's Prevention Epicenters Program.

Smoking cessation drugs' warning labels are changing

BY WHITNEY MCKNIGHT
Frontline Medical News

Labels on two smoking cessation treatments will offer less severe warnings for mental health risk potentials in people with no history of psychiatric disorders, the Food and Drug Administration has announced.

Varenicline (Chantix) will no longer include a boxed warning for serious mental health side effects. The label for bupropion (Zyban) will still include a boxed warning, but language describing the potential for serious psychiatric adverse events will no longer appear within it. Updates will also be made to both labels to describe side effects on mood, behavior, or thinking.

"The risk of these mental health side effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past," FDA officials stated in an online notice.

In addition, varenicline's label will reflect trial data showing its superior efficacy, compared with oral bupropion or nicotine patch. Although a patient medication guide will still be included with each prescription, the risk evaluation and mitigation strategy that prompted the guide will no longer be in place.

Earlier this year, two FDA advisory committees voted in favor of updating varenicline's label, based on data from a randomized, controlled trial of more than 8,000 smokers, half of whom had a history of psychiatric disorders.

The trial showed no clinically significant difference in risk of adverse events across the smoking cessation treatments varenicline, bupropion, nicotine patch, or placebo study arms, although the risk was higher in the psychiatric cohorts in each. Overall, 2% of those without a history of mental illness experienced neuropsychiatric adverse events, compared with between 5% and 7% of those with such a history. Pfizer, maker of Chantix, and GlaxoSmithKline, maker of Zyban, cosponsored the trial.

FDA officials advised clinicians to guard against changes in mental health status in smokers using varenicline and bupropion, but noted that the results of the trial confirm the benefits of stopping smoking outweigh the risks of these medicines.

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Most smokers attempt quitting without meds

BY RICHARD FRANKI
Frontline Medical News

More than half of cigarette smokers have received advice to quit from a health care professional, but less than a third used medication or counseling in their cessation attempt, according to investigators from the Centers for Disease Control and Prevention.

In 2015, just over 57% of adult smokers said that a health care professional had advised them to quit in the past year. Of those who tried to quit, 29% used medication such as nicotine patches or gum, varenicline, or bupropion; 7% used counseling (including a stop-smoking clinic, class, or support group and a telephone help line); and 31% used counseling and/or medication, the investigators reported (MMWR. 2017;65[52]:1457-64).

Data from the 2015 National Health Interview Survey show that cigarette smokers who were white (60%) or of multiple races (70%) were the most likely to have a health professional tell them to quit, while Asians (34%) and American Indians/Alaska natives (38%) were the least likely. Whites were most likely to use counseling and/or medication (34%) and Hispanics were least likely (19%), although the rate for American Indians/Alaska Natives was not reported because of a small sample size or large margin of error.

"[It] is critical for health care providers to consistently identify smokers, advise them to quit, and offer evidence-based cessation treatments, and for insurers to cover and promote the use of these treatments and remove barriers to accessing them," the researchers noted.

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Continued from page 47

Results also demonstrated that bolus doses of vitamin D did not offer any beneficial value to subjects. Those who received daily or weekly doses without bolus had a better OR, compared with those who did receive at least one bolus dose: 0.81 (95% CI, 0.72-0.91) versus 0.97 (95% CI, 0.86-1.10), respectively ($P = .05$). Individuals whose baseline 25-hydroxyvitamin D levels were lower than 25 nanomols per liter experienced a greater benefit than those whose levels were above 25: OR of 0.30 (95% CI, 0.17-0.53) and OR of 0.75 (95% CI, 0.60-0.95), respectively ($P = .006$).

"Our study reports a major new indication for vitamin D supplementation: the prevention of acute respiratory tract infection," Dr. Martineau and his coauthors concluded, adding that a potential application for these findings would be "the introduction of public health measures such as food fortification to improve vitamin D status, particularly in settings where profound vitamin D deficiency is common."

The study was funded by a grant from the National Institute of Health Research.

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VIEW ON THE NEWS

Results are 'underwhelming'

While the work undertaken by Dr. Martineau et al. is commendable, the results themselves are ultimately underwhelming. The study's results are too heterogeneous and offer too slight a reduction in overall risk to justify a complete overhaul of clinical procedure and prescribing protocols. These findings should not change clinical practice in any significant way, and there are other groups of individuals, such as those with low serum concentrations of vitamin D, that were omitted from this analysis altogether.

Mark J. Bolland, PhD, is an associate professor of medicine at the University of Auckland (New Zealand). Alison Avenell, MD, is a professor at the University of Aberdeen.

PRESIDENT'S REPORT Strategic planning, travel ban, CHEST 2017

Dear Colleagues,

It doesn't seem possible, but I have just completed the first quarter of my term as your 79th President and recently returned from chairing my first board meeting – a scary experience to be sure. All in all, it went well. We officially offered Steve Welch the position of Executive Vice President, thereby ushering in one of our own to lead the organization. Steve has successfully served as CHEST's interim EVP/CEO since May 2016, after 22 years of service with this organization, most recently as Senior Vice President of Publications and Digital Content. I am utterly and completely confident in our choice and want you to know he has the full backing of the board, the Past Presidents, and nearly every doctor he has come in contact with.

DR. SILVESTRI

We also started the strategic planning process for the next 5 years. I am a big believer in planning and have confidence that the team of physicians and staff we have assembled to provide us with guidance will lead us through this process, and we will be a much stronger organization for it. I hope you will all take the opportunity to weigh in as we progress. Ideas from all parts of the organization will be needed so that we don't miss opportunities for improvement.

One of our strategic areas of focus for the past 5 years is how we serve our international members. CHEST is now truly a global organization. Our international membership continues to grow, and that impacts all areas of the College. In 2016, we provided education for more than 4,300 international members through our national meeting and courses provided all around the globe. In addition, the College has, in partnership with Chinese CHEST leadership and ministry of health officials, led the effort to begin the first pulmonary and critical care fellowship training programs in China. This was an amazing undertaking. The first four graduates were introduced and honored at CHEST 2016, and 20 more are scheduled to graduate next year. An additional 25 more fellowship training programs are to start this next year, and the Chinese National Health and Family Planning Commission recently approved the program as one of only three official fellowship training programs in China. I firmly believe we will look back on this endeavor as one of the greatest accomplishments in our organization's long and storied history. Countless lives of patients with pulmonary diseases and critical illness are likely to be saved or extended in that country because of this work.

This brings me to CHEST's position on the travel ban recently imposed and currently on hold in the United States. We, along with 11 other medical societies, sent a letter to the Secretary of Homeland Security underscoring our concern for such a ban, as it could most definitely adversely affect health-care delivery worldwide in ways not previously contemplated. For example, international medical graduates reportedly make up 25% of our physician workforce and provide a disproportionate amount of care to underserved communities. Should we not allow them to come and train here, we could be putting patients in those areas at risk. The ban could result in patients who need specialized health care being denied entrance to the country. We worry that our global physician colleagues will be unable to travel to the United States for educational programs meant to provide them with the tools they need to care for their patients back home. I encourage you to read the full letter if you are interested.

See letter on page 40.

On a brighter note, the program committee is busy planning CHEST 2017, which will be held in Toronto, Oct 28 to Nov 1. Our theme is Team-Based: Patient-Centered. Our advanced practice providers, critical care nurses, and respiratory therapists, among others, will participate in the planning and help shape different aspects of the program. We encourage our physician members to invite a friend, and come and enjoy the meeting. The traditional CHEST program with simulation and interactive, interdisciplinary symposia will be back by popular demand. There will be something in this meeting for everyone. I would be remiss if I didn't mention that we are working closely with the American Board of Internal Medicine on Maintenance of Certification (MOC) and getting credit by using CHEST products, such as CHEST SEEK, e-learning modules, and live learning opportunities. In fact, CHEST 2016 made getting MOC points easy. Much of the program this year will qualify for MOC, and I would encourage you to take advantage of it. For those who I have had the pleasure of working with and hearing from this year, I thank you for your comments, welcome all opinions, and hope to hear from any member who has something CHEST-related on their mind.

Gerard A. Silvestri, MD, MS, FCCP
President

This month in *CHEST*

Editor's picks

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

GIANTS IN CHEST MEDICINE
Paul M. O'Byrne, MBBCh, FCCP.
By S.E. Wenzel, MD.

ORIGINAL RESEARCH
Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A Systematic Review and Meta-Analysis.
By F.E. Aleva, MD, et al.

COMMENTARY
The American College of Radiology Lung Imaging Reporting and Data System: Potential Drawbacks and Need for Revision.
By H. J. Mehta, MD, et al.

SPECIAL FEATURE
Improving the Management of COPD in Women.
By C.R. Jenkins, MD, et al.

Plan to attend CHEST 2017 in Toronto

Oct 28 – Nov 1
Toronto, Ontario, Canada

Join us in wonderful Toronto for CHEST 2017, where we'll connect a global community in clinical chest medicine. Our program will deliver current pulmonary, critical care, and sleep medicine topics presented by world-renowned faculty in a variety of innovative instruction formats. Take advantage of these opportunities to get involved now:

Submit Abstracts and Case Reports

Submission deadline: March 31

Submit an abstract of your original investigative work, case reports, and clinical case puzzlers for presentation at CHEST 2017. Submission is free, and accepted abstracts become eligible for investigative awards from the CHEST Foundation. Accepted abstracts and case reports (excluding clinical case puzzlers) will be published in an online supplement to the journal *CHEST*. Slide or poster presentations will be considered, along with poster discussion presentations for abstracts. Four types of case reports will be considered:

- Fellow Case Reports.
- Medical Student/Resident Case Reports.
- Global Case Reports.
- Clinical Case Puzzlers.

Learn more and submit at chest2017.abstractcentral.com.

Apply for 2017 CHEST Foundation Grants

Application deadline: March 31

The CHEST Foundation has started accepting applications for its clinical research, distinguished scholar, and community service grants. Every year, the CHEST Foundation awards more than a half-million dollars to the next generation of lung health champions.

The grants available are:

- GlaxoSmithKline Distinguished Scholar Research Grant in Respiratory Health: $150,000 over 3 years
- CHEST Foundation Research Grant in Lung Cancer: $50,000-$100,000* over 2 years
- CHEST Foundation Research Grant in Pulmonary Arterial Hypertension: $25,000 1-year grant
- CHEST Foundation and Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency: $25,000 1-year grant
- CHEST Foundation Research Grant in Nontuberculous Mycobacteria: $10,000-$30,000* 1-year grant
- CHEST Foundation Research Grant in Venous Thromboembolism: $30,000 1-year grant

Continued on page 53

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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To learn more, please visit REVATIOHCP.com

Indication

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

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No dose adjustment required for renal impaired.

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

REVATIO is available in the following dosage forms:

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

The Revatio® Family

Available in OS, tablet, and injection forms.

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

Revatio® sildenafil

PP-REV-USA-0090-01

July 2016

Revatio® sildenafil 20 mg tablets

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

INDICATION AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

Rx only Rev. June 2015

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 Dr. Mathers.

James A.L. Mathers Jr., MD, FCCP
President 2008-2009


DR. MATHERS

It was a great honor to be inaugurated as President of the American College of Chest Physicians at the 2008 Annual Meeting in Philadelphia. My chosen vocation was community-based private practice, and from my early years in practice, I found the opportunity to interact with the clinically oriented scholars of CHEST invaluable. My wife Susan and I fondly remember activities with staff, others in leadership, and their families. My immediate goals for my presidential year were to ensure the financial security of the College, in light of the evolving restrictions on industry funding, and to raise the profile of telemedicine for the care of patients with chronic conditions and the critically ill. However, that year is probably most remembered for the unanticipated need to formulate a step-down agreement with then-CEO Alvin Lever, who had served the College for the preceding 17 years.

To assist with financial planning, we were able to engage Master's degree candidates from the Kellogg School of Business at Northwestern University in Evanston, Illinois, to perform a detailed cost and benefit analysis of our programs and to help develop recommendations for streamlining and improving our budgeting process. In partnership with the American Thoracic Society, the Society of Critical Care Medicine, and the American Association of Critical-Care Nurses, we developed a grant proposal to host a multisociety conference to examine the use of telemedicine for the care of critically ill patients. The grant was funded by the National Institutes of Health, and the results of the conference were published in CHEST. Following my presidential year, I continued to speak at numerous meetings about the potential for telemedicine to improve the care of patients with pulmonary disease.

I retired from my community-based private practice at the end of 2010. Susan and I divide our time between Richmond, Virginia., engaging with our grandchildren, and the west coast of Florida, where I am working on my saltwater fly-fishing credentials. Regular rounds of golf with former colleagues, some retired and some still in practice, keep me abreast of the pressures on and changes in the clinical environment.

Early in my practice, I became interested in addressing federal policies that interfered with the ability to provide state-of-the-art care to my patient population. My first committee appointment with CHEST was the Government Relations Committee. Our activities were closely coordinated with the National Association for Medical Direction of Respiratory Care (NAMDRC) and the American Thoracic Society. During my year as Immediate Past President of the College, I was approached by NAMDRC and invited to write their monthly publication, *The Washington Watchline*. I have continued to enjoy that opportunity, as well as interacting with their membership. When called upon by NAMDRC, I travel to Washington, DC, to meet with Medicare staff to discuss policy issues important in the care of pulmonary patients.

Continued from page 50

- CHEST Foundation Research Grant in Pulmonary Fibrosis: $30,000 1-year grant
- CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease: $50,000 1-year grant
- CHEST Foundation Research Grant in Women's Lung Health: $10,000 1-year grant
- CHEST Foundation Research Grant in Asthma: $15,000 - $30,000* 1-year grant
- CHEST Foundation Research Grant in Cystic Fibrosis: $30,000 1-year grant
- Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP: multiple awards up to $15,000 per 1-year grant

**Amount contingent on funding.*

Apply for grants at chestfoundation.org/grants.

Household air pollution: Foundation grantee champions lung health

BY CATHERINE OBERG, MD

In 2016, Catherine Oberg, MD, was awarded the CHEST Foundation Research Grant in Women's Lung Health for her project on household air pollution in Ghana. In this recent interview with Dr. Oberg, she describes how she is championing lung health.

How I got involved

In medical school, I was very interested in international medicine and took a trip to Tanzania to do primary care work when I was in my fourth year. I saw firsthand how the people, women especially, sleep, cook, eat, and take care of their children and animals all in one house. I saw how direct smoke exposure from cooking caused symptoms of cough, phlegm, and shortness of breath. I knew this was an area where I could make an impact.

When you're looking for grants to do this kind of work, it's a very nebulous area.

Fortunately, I learned about CHEST Foundation grants through my mentor, Alison Lee, MD, who was a CHEST Foundation grant recipient early in her career. With the help of the grant, I was able to furnish my own supplies, get everything to Ghana, train native health-care providers, and start doing assessments. I received the CHEST Foundation grant at the perfect time. I am so appreciative and honored to be a CHEST Foundation grant recipient. It's such a humbling experience to be able to act on these things that I've been looking into for so many months. I'm just excited and thankful, and can't wait to see what we're able to show.

Tackling a leading cause of lung disease

In rural areas around the world, people cook with ineffective fuels, such as animal dung, that cause damaging household air pollution. This is a leading cause of asthma, COPD, and lung cancer worldwide, and it preferentially affects women and children because of their roles in the household. My project focuses on household air pollution with a goal to measure the effectiveness of utilizing a clean burning stove as an intervention.

John Howington, MD, FCCP, then President of the CHEST Foundation, presenting the CHEST Foundation Research Grant in Women's Lung Health to Dr. Oberg during CHEST 2016.

We have a cohort of women in Ghana and have had randomized clusters using either a liquefied petroleum gas (LPG) clean burning stove or a traditional cook stove for 18 months now. We're going to look at their lung function, inflammatory markers, and respiratory symptoms and compare the groups to see if the intervention has made a difference.

The impact

Being able to breathe is a function many of us take for granted. The ability to impact something this vital to everyday life is a really exciting and important challenge. It's an area where I think we can make a big impact.

This grant is allowing us to run our entire inflammatory marker component. As we are learning more about asthma and COPD, we're seeing phenotypes of people that don't fit the standard. This cohort of women illustrates that heterogeneity of disease, as we're seeing more overlap in the symptoms they have. Currently, there are really no data looking at this, and we now have the resources to dive into this research.

The future

This project could bring about further research and hopefully provide evidence supporting these types of interventions. The impact could affect millions of people around the world. The CHEST Foundation grant is providing materials that are the foundation of our project. This grant allows us to design better studies in the future, to educate patients in a more effective manner, and to prevent these life-threatening diseases.

The next CHEST Foundation grants cycle is open from February 1 to March 31, 2017. How will you champion lung health? Learn more about foundation grants and how you can apply at https://chest.realmagnet.land/chest-foundation-grants.

Alternative to 10-year ABIM exam starts 2018

On December 14, the American Board of Internal Medicine (ABIM) announced an alternative to the 10-year Internal Medicine recertification exam, effective 2018. Currently, ABIM board–certified physicians can participate in Maintenance of Certification (MOC) by earning 100 MOC points every 5 years and passing a maintenance of certification exam every 10 years.

Beginning in 2018, physicians who are certified by the ABIM in Internal Medicine will have the option to take a lower-stakes exam every 2 years, rather than taking the current high-stakes exam every 10 years. The low-stakes exam option provides greater flexibility to the diplomate by allowing one to complete the examination at a convenient time set by the physician at home or in the office. While this new option will initially be available only to Internal Medicine diplomates, the ABIM intends to extend this alternative recertification model to subspecialties in the future.

CHEST is exploring how our education will evolve to address these key changes. For additional information, please visit ABIM's website.

Pulmonary Hypertension Care Center initiative moves forward

The Pulmonary Hypertension Association (PHA) launched its Pulmonary Hypertension Care Center (PHCC) initiative 2 years ago. This initiative was designed to raise the quality of care, as well as long-term outcomes for this disease that is often misdiagnosed and progressive. The PHCC program has designated 41 adult and 6 pediatric sites as Comprehensive Care Centers with ongoing accreditation of new sites. As part of this program, the PHA Registry was established to provide input to improve the care of PH patients. The PHA Registry (PHAR) is a multicenter, prospective observational registry of newly evaluated patients with pulmonary arterial hypertension (PAH) and has enrolled 200 patients to date. PHAR participation is open to any PHCC-accredited center.

PHCC accreditation has two pathways: Comprehensive Care Centers and Regional Care Centers. Accreditation is based on adherence "to consensus guidelines for the diagnosis and treatment of PH, the scope of PH-related services provided at the center, and the expertise of the center's PH Care Team members." PHCC accreditation is potentially available to all PH centers that meet the established criteria that can be found at the PHCC website.

Additional information may be found at the PHCC website (https://phassociation.org/PHCareCenters).

Calls for faculty participation in the CHEST PREP program

About PREP

The CHEST PREP Clinical Immersion program is an unbranded, disease-state program that educates industry members and partners to advance their knowledge into understanding that builds their confidence for engagement in clinical conversations with health-care teams.

We are seeking faculty for the following initiatives:

1. The CHEST PREP program is embarking on a curriculum and content development initiative and is seeking interested faculty members to consider participating in the development of content in the areas of **CTEPH**, **Alpha-1 Antitrypsin**, **and Bronchiectasis**.

2. The CHEST PREP program is seeking interested CHEST members in Chicago-based institutions to consider participating as faculty presenters in the following disease areas: **COPD**, **Asthma**, **PAH**, **CTEPH**, **IPF**, **SCLC**, **and NSCLC**.

Continued on following page

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Requirements for participation

1. PREP welcomes faculty who would be interested in creating two or more presentations and/or cases on an assigned topic using a flipped classroom, interactive design. A minimum of four faculty experts will be needed per disease state indicated previously. Honorarium provided.
2. PREP welcomes faculty from Chicago-based institutions who would be interested in participating as faculty presenters in the disease states indicated previously. Honorarium provided.

Selection criteria

To be considered, please indicate the disease area in which you are interested in participating as content developer or faculty presenter, as well as providing the best way to contact you. For the asthma curriculum, we have a specific need for expertise/interest in moderate to severe asthma and the use of biologics in treatment.

If you are interested in participating in this initiative, please contact Jasmine Turner (jturner@chestnet.org). Thank you.

Bipartisan Budget Act (BBA) of 2015 threatens growth of pulmonary rehab

BY PHIL PORTE
Executive Director, National Association for Medical Direction of Respiratory Care (NAMDRC)

A hospital that wishes to expand its current program and bill under the hospital outpatient methodology MUST do so by expanding at its current location. An expansion at a new location that is not within 250 yards of the main hospital campus triggers Section 603 provisions.

In late 2015, Congress passed the Bipartisan Budget Act (BBA) to address numerous wide-ranging budget concerns, including issues related to agriculture, pensions, the strategic petroleum reserve, along with some Medicare issues. Section 603 of BBA is now coming back to haunt pulmonary rehabilitation services.

The intent of Section 603 is reasonable – to address the phenomenon of hospitals purchasing physician practices to take advantage of payment differentials between identical or virtually identical services when comparing the hospital outpatient prospective payment system (HOPPS) and the physician fee schedule (PFS). For example, an orthopedic practice might own its own MRI and related support services. It will bill for those services under the PFS. However, if the practice sells that segment of the revenue stream (the MRI assets, etc) to a hospital, the hospital can bill Medicare for those same services under the hospital outpatient prospective payment system at an amount notably higher than the PFS payment.

To address this payment aberration, Congress instructed the Centers for Medicare & Medicaid Services to craft a system to preclude a hospital from such behavior. If a hospital offers new or expanded outpatient services, it could NOT bill Medicare under the hospital outpatient services methodology and would be required to bill under the PFS payment methodology. Importantly, a few exemptions exist. If the new or expanded service is within 250 yards

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Medicare Payments for HCPCS code G0424 through the physician fee schedule

	2012	2013	2014
TOTAL PAYMENTS	$688,489.27	$589,116.95	$535,512.81
Pulm Disease Specialty	$340,805.64	$310,065.29	$229,832.58

(Source: Physician Supplier Procedure Summary File)

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of the main hospital campus, the outpatient billing methodology is permitted. Likewise, if expansion of a current off-campus service occurs **at the same location of the current off-site service**, the hospital may continue to bill under the outpatient rules. Several other technical exceptions are permitted, for example construction planned prior to passage of BBA.

The implications for pulmonary rehabilitation are critical to its growth. A hospital that wishes to expand its current program and bill under the hospital outpatient methodology MUST do so by expanding at its current location. An expansion at a new location that is not within 250 yards of the main hospital campus triggers Section 603 provisions, and the hospital will bill at the physician fee schedule rate. Because the PFS payment rate is just over half of the payment rate for HOPPS payment, it is unlikely that a hospital would expand an existing program or establish a new one if it would be forced to bill under the lower rate.

While congressional logic may be relatively understandable, for pulmonary medicine, it is based on the premise that a hospital would purchase a pulmonary practice because that practice had a lucrative pulmonary rehabilitation services cash flow. NAMDRC and other societies were able to document major flaws in the basic premise, resulting in very problematic unintended consequences. A detailed review of Medicare claims data provides strong evidence that pulmonary practices simply do not provide pulmonary rehab services.

These data strongly indicate that **G0424** pulmonary practice physician office billing for the most recent year data are available ($230K), compared with hospital outpatient allowed charges ($119M), is **less than two-tenths of 1%** of billing through the hospital setting. To argue that hospitals are purchasing pulmonary practices for financial gain tied to pulmonary rehab services defies Medicare data, as well as financial logic. If the CMS premise was valid, one would expect the aggregate physician office billing to be much greater than $535K.

In discussions with CMS, the Agency did agree that there are likely to be unintended consequences related to Section 603 implementation. The Agency also emphasizes that it does not have the statutory authority for a "carve out" exemption. CMS stated that even if it agreed with us, it simply lacked the authority to exempt pulmonary rehab services. CMS also agreed that there is growing evidence that pulmonary rehab is a underutilized service that may very well save the program money through reduced hospitalizations and rehospitalizations, but it has little choice to implement the statute as Congress so mandated.

Therefore, the only solution is a legislative one. NAMDRC and other societies are seriously considering approaching Congress for such resolution.

While congressional logic may be relatively understandable, for pulmonary medicine, it is based on the premise that a hospital would purchase a pulmonary practice because that practice had a lucrative pulmonary rehabilitation services cash flow. NAMDRC and other societies were able to document major flaws in the basic premise, resulting in very problematic unintended consequences.

G0424 total allowed charges though hospital outpatient prospective payment

Year	Total Allowed Charges	Unique # of Providers
2012	$108,515,429	1,260
2013	$115,238,410	1,320
2014	$119,809,898	1,350

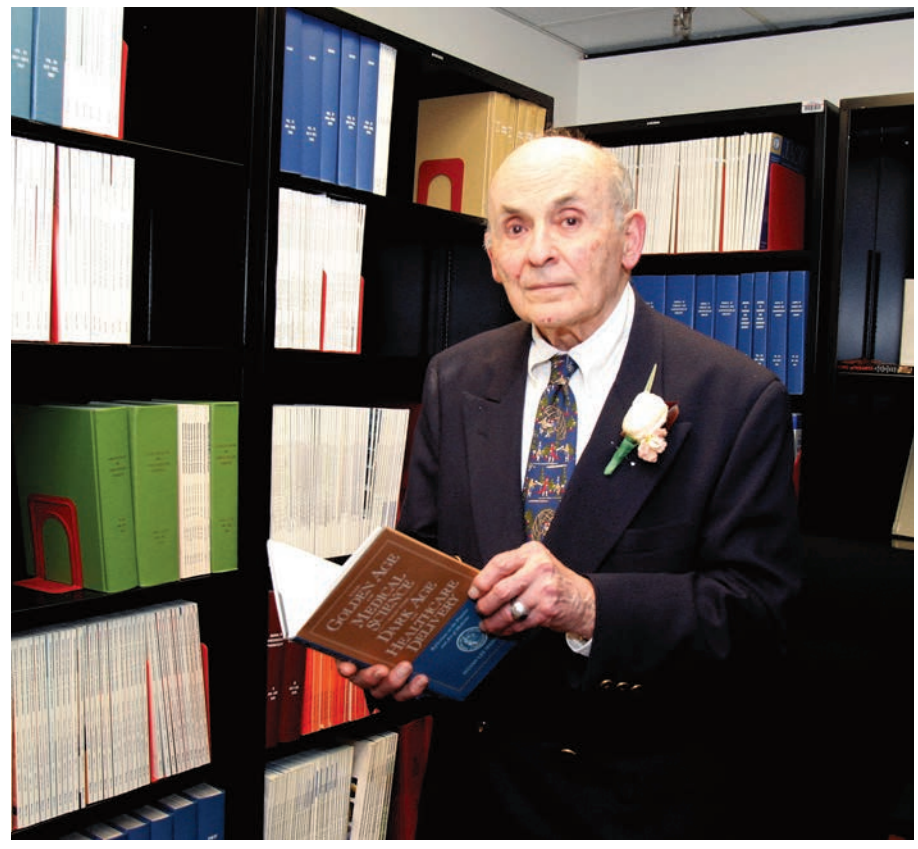
(Source: 100% Outpatient SAF)

In memoriam

Sylvan Lee Weinberg, MD, FCCP, MACC, a Past President of the American College of Chest Physicians (1983-1984), died Jan 17, 2017, in Dayton, Ohio. Dr. Weinberg was born in Nashville, TN, and received both his bachelor of science and doctor of medicine degrees from Northwestern University in Evanston, IL. He spent his time as an intern, medical resident, and fellow in cardiology at the Michael Reese Hospital in Chicago and went on to serve as a physician at Good Samaritan Hospital in Dayton, Ohio, for more than 40 years, ultimately becoming chief of cardiology and founder of the first coronary care unit in Ohio. Dr. Weinberg was also a clinical professor of medicine at the Wright State University School of Medicine in Dayton, and led a group cardiology practice until his retirement in 2000.

A past president also of the American College of Cardiology (ACC) and the Montgomery County Medical Society, Dr. Weinberg was the founding editor of the *American Heart Hospital Journal*, founding co-editor of *Heart & Lung*, and founding editor of the *Journal of The Heart Institute of Dayton*. He also was associate editor of the *AMA Archives of Internal Medicine*, the *ACC Review Journal*, and served on numerous editorial boards, including CHEST, the *Journal of the American College of Cardiology*, and the *Clinical Cardiology and Heart Journal*, formerly the *British Heart Journal*. He was editor-in-chief of ACC's *ACCEL* audio journal for 15 years, recognized and known as, "the voice of cardiology," traveling around the world and interviewing the world's leaders in cardiology.

CHEST extends its heartfelt condolences to Dr. Weinberg's family and friends.



Dr. Sylvan Lee Weinberg

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NetWorks: Mass shootings, MACRA, asthma in pregnancy

Disaster Response

Mass shootings

There are multiple definitions for a mass shooting. Some definitions require a certain number of people be killed. Some definitions require a certain number of people be shot. Some definitions do not include gang violence. Regardless of the definition used, the number of mass shootings in the United States is increasing.


DR. GAILLARD

There are also multiple definitions of what qualifies as a medical disaster. These definitions can be summarized with the statement that a medical disaster is an event that produces a number of casualties that overwhelms the local health system.

In the first 31 days of 2017, there have been 30 shootings in the United States, in which four or more people were injured (www.gunviolencearchive.org/reports/mass-shooting). On average, 309 people are shot every day in the United States. Ninety-three (30%) of those victims die of their injuries (www.bradycampaign.org/key-gun-violence-statistics).

Most mass shootings fit the definition of a medical disaster. When a mass shooting occurs, medical resources are diverted from current patients to those injured in the shooting. Patients with acute medical problems unrelated to the shooting must endure a prolonged wait for medical care.

The CHEST Disaster Response NetWork feels that it is necessary to take action to reduce the number of mass shootings. Unlike natural disasters, mass shootings are man-made. As such, we should proactively work to prevent them. Prevention is a large part of medicine. Working together with community leaders, law enforcement, and government officials, we can and should work to eliminate mass shootings so that we can minimize gun-related injury and death.

John Gaillard, MD, FCCP
Steering Committee Member

Most mass shootings fit the definition of a medical disaster. When a mass shooting occurs, medical resources are diverted from current patients to those injured in the shooting. Patients with acute medical problems unrelated to the shooting must endure a prolonged wait for medical care.

Practice Operations

MACRA: Reincarnation of Medicare physician reimbursement model

In April 2015, President Obama signed the Medicare Access and CHIP Reauthorization Act (MACRA) eradicating the detested sustainable growth rate (SGR) formula. If this is your first dive into MACRA as an eligible professional (EP), it may be a bit baffling trying to understand its impact on your practice. MACRA affects physician offices, not hospitals. For 2017-2018, EPs include physicians, physician-assistants, nurse practitioners, clinical nurse specialists, and nurse anesthetists. Providers in their first year of Medicare participation or with a low Medicare volume are excluded. Additionally, there are two participation pathways, Merit-Based Incentive Payment System (MIPS), which combines the current Physician Quality Reporting System, Value Modifier, and Meaningful Use programs into a single pay-for-performance payment system; or Alternative Payment Models (APMs) that provide incentives in certain alternative payment models based on proposed CMS criteria. Accountable Care Organizations, Patient-Centered Medical Homes,


DR. ANJUM

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PROFESSIONAL OPPORTUNITIES

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Pulmonary/Critical Care with Sleep Opportunity
Cambridge Health Alliance • Cambridge, MA

Cambridge Health Alliance (CHA) is a well respected, nationally recognized and award-winning public healthcare system, which receives recognition for clinical and academic innovations. We have an excellent opportunity for a Pulmonary/ Critical Care Physician to join our well established Pulmonary Division. Our system is comprised of three campuses and an integrated network of both primary and specialty care practices in Cambridge, Somerville and Boston's Metro North Region. CHA is a teaching affiliate of both Harvard Medical School (HMS) and Tufts University School of Medicine.

Ideal candidate will be FT, BC in Pulmonary, Critical Care and Sleep as well as possess a strong interest in resident and medical student teaching. Excellent clinical/communication skills as well as a strong commitment to serve our multicultural underserved patient population is required. This position has both inpatient and ambulatory responsibilities. We offer a supportive and collegial environment with a strong infrastructure, inclusive of an electronic medical records system (EPIC). Candidates will have the opportunity to work in a team environment with dedicated colleagues similarly committed to providing high quality healthcare. Our employees receive competitive salary and excellent benefits.

Please send CV's to Deanna Simolaris, Department of Physician & PA Recruitment, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge, MA 02139, via fax (617) 665-3553, call (617) 665-3555. or via e-mail: **dsimolaris@challiance.org**. We are an equal opportunity employer and all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability status, protected veteran status, or any other characteristic protected by law.

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BC Pulmonary/CC/Sleep Medicine physician opportunity, hospital-employed practice (Sleep Medicine optional). Base + wRVU, annual quality bonus available, plus incentives/benefits. Comprehensive Cancer Center & clinical trials. EBUS/ Navigational Bronchoscopy. No Visa Sponsorship. No firms. Send CV to:

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Continued from previous page

and Bundled Payment Models are a few examples of an APM.

Under MIPS, rules are divided into four categories. During the first year, each category will make up a certain percentage to the physician's overall score, which will result in a penalty or payment as a lump sum in 2019. If you are an Advanced APM in 2017 and receive 25% of Medicare payments or see 20% of your Medicare patients through this model, you can earn up to a 5% incentive payment in 2019.

MACRA affects physician offices, not hospitals. For 2017-2018, [eligible professionals] include physicians, physician-assistants, nurse practitioners, clinical nurse specialists, and nurse anesthetists.

The performance period started on January 1, 2017. Submission of performance data is due by March 31, 2018. MACRA is complicated and here to stay. Learn and educate yourself to avoid downward payment adjustment. For full details, please visit https://qpp.cms.gov/docs/QPP_Executive_Summary_of_Final_Rule.pdf.

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3. American Medical Association. http://bit.ly/1miEtBD
4. Policy and Medicine. MACRA http://bit.ly/1PTLkKa. MIPS http://bit.ly/20RoMzZ. APMs http://bit.ly/1Olx-oxH

Humayan Anjum, MBBS
Steering Committee Member

Transplant

Frailty in lung transplantation

Two of the greatest challenges in lung transplantation are to identify optimal transplant candidates and to help those transplant recipients thrive in the years following surgery. Frailty is emerging as a marker of increased posttransplant morbidity and may represent an area where both the recipient selection process and posttransplant outcomes can be optimized. Described by some as "biologic age" rather than "chronologic age," frailty is a syndrome of functional impairment and weakness that predisposes to adverse health outcomes. The adverse effects of frailty have been described in multiple clinical scenarios, including the ICU, chronic lung diseases, heart failure, liver transplant, kidney transplant, geriatrics, and others.

Approximately 10% to 45% of lung transplant patients are considered to be frail, depending on the measurement used. In a cohort of lung transplant recipients, frail patients had increased 1-year mortality (21.2% increase) and 3-year mortality (24.8% increase), compared with nonfrail patients (Wilson et al. *J Heart Lung Transplant*. 2016;35[2]:173-178). In a cohort of patients on the lung transplant waiting list, frailty was associated with an increased risk of delisting or death before lung transplant (Singer et al. *Am J Respir Crit Care Med*. 2015;192[11]:1325-1334). In addition, frailty may be associated with an increased risk of hospital readmissions and acute rejection following transplant (Wilson et al. *J Heart Lung Transplant*. 2016;35[4]:S317).


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Remaining challenges include determining which clinical assessments best define frailty in the lung transplant population, documenting the adverse effects of frailty in well-designed multicenter prospective studies, and developing interventions to mitigate the adverse effects of frailty.

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Women's Health

Asthma treatment during pregnancy

Asthma is common in pregnancy, occurring in 3% to 8% of pregnant women. While the course of asthma during pregnancy is variable, the objectives of asthma treatment do not change and aim to prevent acute exacerbations and optimize management. Uncontrolled asthma is associated with an increased risk of perinatal morbidity. Published guidelines on pharmacologic therapies during pregnancy recommend the same step-wise approach as in nonpregnant women. Despite this, many providers are reluctant to prescribe medications during pregnancy, and data show a reduction of refills of asthma medications during pregnancy, likely due to safety concerns. Some recent studies have suggested an increase in major congenital anomalies among pregnant asthmatics using ICS (Garne E et al. *BJOG*. 2016;123[10]:1609-18), albeit with large confidence intervals. These findings have not been consistently confirmed (Kallen B et al. *Eur J Clin Pharmacol*. 2007;63:383-8). Furthermore, studies showing a dose response association of ICS with congenital anomalies (Blais L et al. *J Allergy Clin Immunol*. 2009;124[6]:1229-34) suggest that disease severity may be a confounder in these associations.


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The diagnosis of asthma, the use of other concurrent medications, and medication compliance may all be potential confounders. ICS use in pregnancy was associated with endocrine and metabolic disturbances in the offspring in a national cohort (Tegethoff M et al. *Am J Respir Crit Care Med*. 2012;185[5]:557-63). However, this study did not report on systemic steroid use, asthma severity, or details of these disturbances. In summary, ICS use remains justifiable in pregnancy (Smy L et al. *Can Fam Physician*. 2014;60[9]:809-12) as the risk of untreated or poorly treated asthma outweighs the possible risk of ICS use, especially when alternative drugs such as systemic steroids are not without risk. Ultimately, it should be stressed that asthma control is the goal of treatment. This should be achieved with close interaction between the pregnant woman and her health-care provider.

Ghada Bourjeily, MD, FCCP
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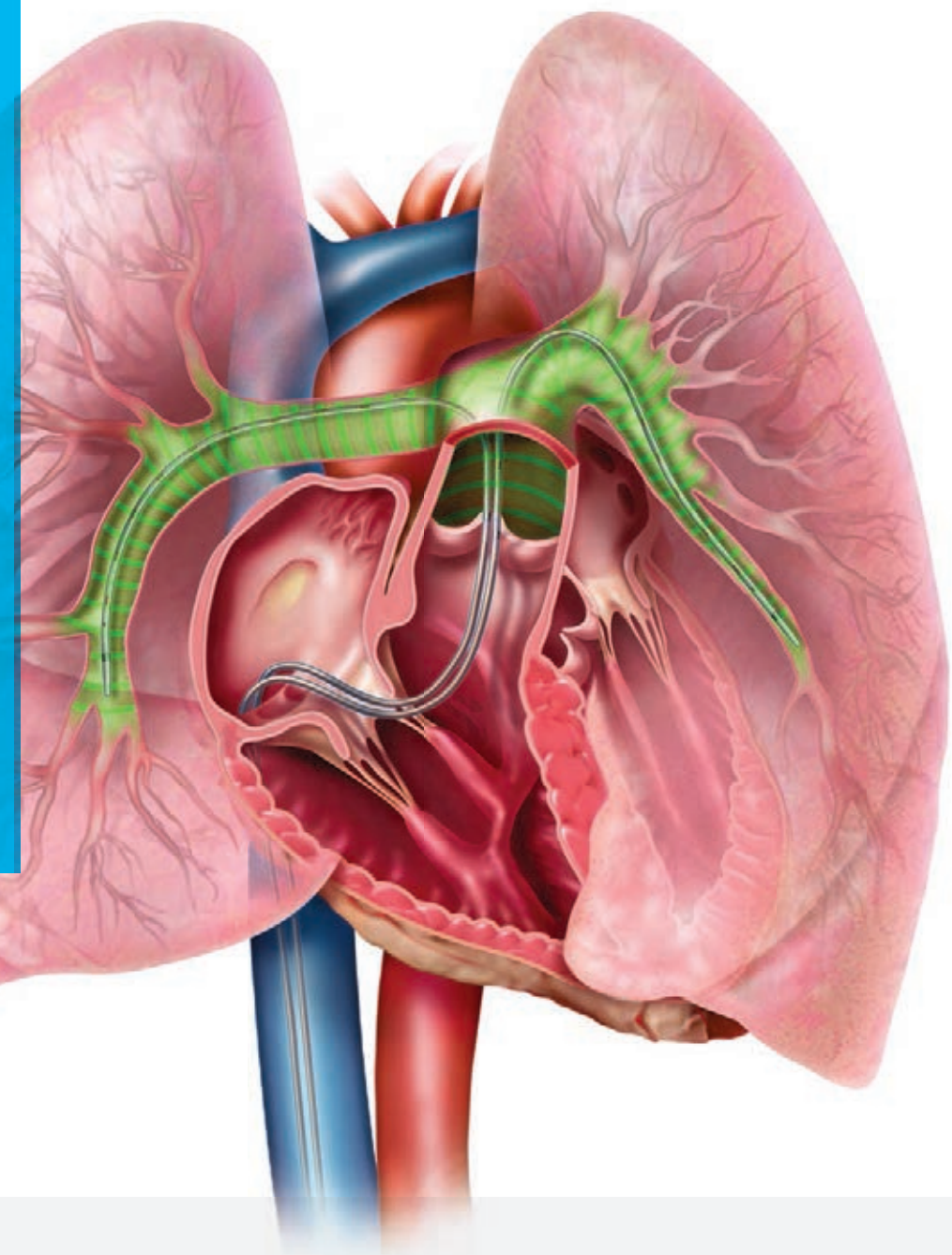

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2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

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

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

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