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CHEST™ Physician

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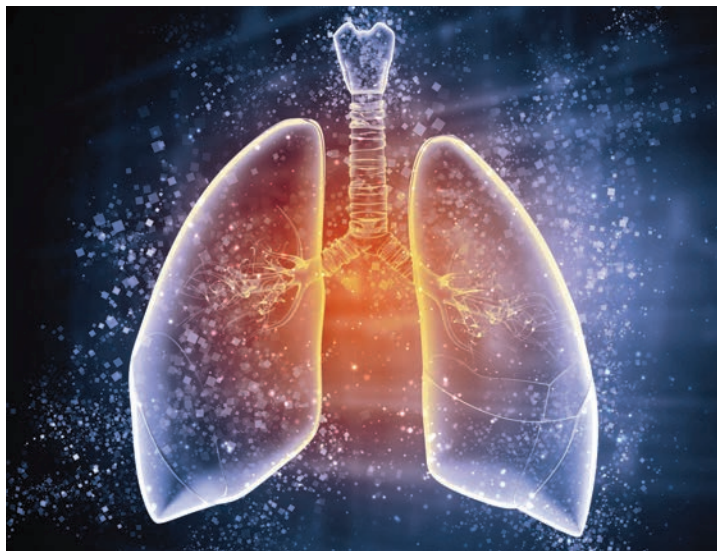

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Six-minute walk distance grew from 358 meters to 423 meters 6 months after PADN, a clinically important 23.9% improvement.

Denervation bettered drugs in PAH study

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – Percutaneous pulmonary artery denervation for the treatment of pulmonary arterial hypertension safely resulted in significantly greater improvement in functional capacity and hemodynamics compared with medication, in a controlled before-and-after study.

A particularly noteworthy secondary finding in the study was that rehospitalizations during the first 6 months after pulmonary artery denervation (PADN) occurred just one-third as frequently as in the 6-month preprocedural period on standard medications, Dr. Shao-Liang Chen said at the annual meeting of the American College of Cardiology.

He and his coinvestigators, including Dr. Gregg W. Stone of Columbia University in New York, developed a percutaneous catheter-based method of destroying the pulmonary baroreceptor structure located at the bifurcation area of the middle pulmonary artery. Along the way, they redefined the understanding of the pathogenesis of pulmonary artery hypertension (PAH) by demonstrating that local sympathetic nerve activity plays a pivotal role in modulating the elevations of mean pulmonary artery pressure

See **PAH** • *page 6*

CHEST issues guideline on COPD exacerbations

In partnership with the Canadian Thoracic Society

BY MARY ANN MOON
Frontline Medical News

FROM CHEST

The American College of Chest Physicians (CHEST) and the Canadian Thoracic Society have issued new recommendations for reducing the risk of acute exacerbations of COPD.

The guideline includes 33 recommendations based on "an up-to-date, rigorous, evidence-based analysis of current randomized controlled trial data," according to Dr. Gerard J. Criner, FCCP, professor of pulmonary and critical care medicine, Temple University, Philadelphia, and his associates on the guideline's expert panel.

"Exacerbations are to COPD what myocardial infarctions are to coronary artery disease: They are acute, trajectory changing, and often deadly manifestations of a chronic disease. Exacerbations cause frequent hospital admissions, relapses, and readmissions; contribute to death during hospitalization or shortly thereafter; reduce quality of life dramatically; consume

See **Guidelines** • *page 12*

Bronchial thermoplasty in asthma

BY BRUCE JANCIN
Frontline Medical News

HOUSTON – Bronchial thermoplasty has emerged as an important treatment option for patients with severe asthma at specialized centers, Dr. Mario Castro, FCCP, observed at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The most recent international European Respiratory Society/American Thoracic Society practice guidelines on severe asthma recommend that bronchial thermoplasty for severe persistent asthma be utilized only in the setting of a clinical study or independent registry. The guidelines cited "very low confidence" in the available estimates of the novel treatment's longer-term benefits and harms, as well as the lack of data regarding the phenotypes of asthma patients most likely to benefit (Eur. Respir. J. 2014 Feb;43:343-73).

Dr. Castro, a member

See **Asthma** • *page 11*

INSIDE

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Reduce lung function decline

Delay IPF progression with Esbriet

Indication

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

Select Important Safety Information

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

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.

Esbriet®
(pirfenidone) capsules 267 mg

Proven to delay progression in IPF[1]

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had ≥10% decline in %FVC, $P<0.001$). Treatment effect was evident at 13 weeks ($P<0.001$) and increased through trial duration[1,2,*,†]
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)[2,*,‡]
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet[2]
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide[3]

Learn more about Esbriet and how to access medication at Esbriet.com.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled 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 $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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.

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

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the ≥10% decline category.
‡Stable was defined as no decline in lung function.

References: 1. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. **2.** Esbriet full Prescribing Information. InterMune, Inc. October 2014. **3.** InterMune, Inc. Data on file.

Genentech
A Member of the Roche Group

Esbriet®
(pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.

INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

Photosensitivity Reaction or Rash

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

Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

ADVERSE REACTIONS

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

- Liver Enzyme Elevations *[see Warnings and Precautions]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions]*
- Gastrointestinal Disorders *[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.

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

Table 1. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

DRUG INTERACTIONS

CYP1A2 Inhibitors

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

Strong CYP1A Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration section 2.4 in full Prescribing Information]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

ESBRIET® (pirfenidone)

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.2 in full Prescribing Information]*.

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 *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Renal 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 *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information],* 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.

OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005 USA

INTERMUNE®

Denervation bettered drugs

PAH *from page 1*

(mPAP) and pulmonary vascular resistance (PVR), which are the disease hallmarks.

Dr. Chen and coinvestigators previously reported the first-in-man study of PADN, which demonstrated safety and short-term efficacy

Local sympathetic nerve activity plays a pivotal role in modulating the elevations of mPAP and PVR, which are disease hallmarks of PAH.

(J. Am. Coll. Cardiol. 2013;62:1092-100). At ACC 15, Dr. Chen presented the findings of the new PADN-2 study, which expands upon the first study by including more patients and longer and more comprehensive follow-up.

The study comprised 28 patients with PAH, including 11 with idiopathic PAH and 8 with pulmonary hypertension caused by left ventricular disease. All of them underwent medication washout followed by right heart catheterization and echocardiography for baseline off-drug hemodynamic measurements as well as a 6-minute walk distance test of their functional capacity. Then they went back on medications for 6 months, after which they underwent repeat testing. Then their medications were discontinued and they underwent PADN. Six months after the procedure, still off medications, they were retested once again.

The primary study endpoint was change in 6-minute walk distance. After 6 months of medication it improved from 361 to 373 meters, a modest 3.9% gain over off-drug baseline. In contrast, 6-minute walk distance grew from 358 to 423 meters 6 months after PADN, a clinically important 23.9% improvement, reported Dr. Chen, a cardiologist at First Hospital of Nanjing (China) Medical University.

Multiple secondary hemodynamic endpoints also showed significantly greater improvement with PADN than medical therapy.

Twelve predefined clinical events – mostly involving worsening PAH – occurred during medical management, compared with three in the 6 months following PADN.

In addition, there were 12 hospitalizations during the 6 months on medical management compared with only 4 after the same patients underwent PADN. Health care costs averaged $35,000 per patient during the 6-month study period on medication compared with $6,000 per patient in the first 6 months after PADN.

There were no deaths, aneurysms, access site hematomas, or thrombotic events during either study period.

Further randomized, controlled trials are planned to explore the possibility that the benefits seen in the PADN-2 trial will result in reduced mortality in patients with PAH, according to Dr. Chen.

The PADN-2 trial was sponsored by Nanjing Medical University. Dr. Chen reported serving as a consultant to MicroPort.

bjancin@frontlinemedcom.com

Hemodynamic outcomes at 6-month follow-up

	Change after 6 months on medication	After pulmonary artery denervation
As assessed via right heart catheterization		
Cardiac output (L/min)	+0.06	+0.67
Mean PAP (mm Hg)	–0.14	–7.85
Systolic PAP	–0.46	–13.75
Mean right atrial pressure	+0.8	–2.6
Pulmonary vascular resistance (Wood units)	–0.17	–4.59
As assessed via cardiac echocardiography		
Mean PAP	–0.7	–2.9
Percutaneous fluid volume (mm)	+0.11	–0.74
Right ventricular Tei index	–0.04%	–0.34%

Frontline Medical News

Notes: Based on data from 28 patients with pulmonary artery hypertension. All differences between groups were statistically significant. PAP = pulmonary artery pressure.

Source: Dr. Chen

IN THIS ISSUE

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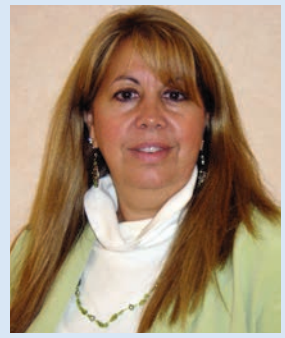

Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of *CHEST* Physician.

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Implantable filter doesn't cut rate of recurrent PE

BY MARY ANN MOON
Frontline Medical News

Implanting a retrievable filter in the inferior vena cava did not reduce the rate of recurrent pulmonary embolism or mortality in high-risk patients.

In recent years, there has been a sharp increase in the use of these devices as an add-on to anticoagulant therapy among patients hospitalized for acute PE associated with lower-limb deep or superficial vein thrombosis. Several clinical guidelines advocate this strategy, though others do not, citing the paucity of reliable data concerning both risks and benefits.

The findings in this study "do not support the use of this type of filter in patients who can be treated with anticoagulation alone," and clinical guidelines recommending this approach should be reexamined, Dr. Patrick Mismetti of the University Hospital of Saint-Etienne, France, and his associates said.

Recurrent PE developed in 6 of 200 patients assigned to receive an implantable filter and 3 of 199 assigned to the control group. All but one of these episodes of recurrent PE were fatal.

They performed a randomized, open-label clinical study at 17 French medical centers to compare anticoagulation alone against anticoagulation plus implanting a filter to be retrieved 3 months later. The study participants were 399 adults enrolled during a 6-year period who were deemed at high risk for recurrent PE because of advanced age, active cancer, chronic cardiac or respiratory insufficiency, ischemic stroke with leg paralysis, DVT that was bilateral or affected the iliocaval segment, or signs of right ventricular dysfunction or myocardial injury.

The primary efficacy outcome, recurrent PE within 3 months of hospitalization, developed in 6 of 200 patients assigned to receive an implantable filter (3%) and 3 of the 199 assigned to the control group (1.5%). All but one of these episodes of recurrent PE were fatal. One additional PE developed in each study group between 3 and 6 months. There were no differences between patients who received an inferior vena cava filter and those who did not in the incidence of DVT, major bleeding, or death from any cause at 3 or 6 months, the investigators said (JAMA 2015 April 28 [doi:10.1001/jama.2015.3780]).

Besides failing to prevent recurrent PE, the filter implantation caused access site hematomas in five patients, and the filter itself caused thrombosis formation in three. One patient developed cardiac arrest during the procedure. In addition, retrieval of the device failed because of mechanical problems in 11 patients.

Ivabradine approved to reduce HF hospitalizations

BY M. ALEXANDER OTTO
Frontline Medical News

The heart rate–lowering agent ivabradine was approved by the Food and Drug Administration on April 15 to reduce hospitalizations in patients with worsening heart failure.

The new indication, the result of a fast-track evaluation process, is for patients with chronic, stable, symptomatic heart failure and left ventricular ejection fractions at or below 35% and resting heart rates of at least 70 beats per minute and who are on maximum beta-blocker doses or have beta-blocker contraindications, according to an FDA statement.

Ivabradine "is thought to work by decreasing heart rate and represents the first approved product in [its] drug class," according to Dr. Norman Stockbridge, director of the FDA's

division of cardiovascular and renal products.

The drug was given priority review based on the results of SHIFT (Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial), which involved 6,505 clinically stable patients, all hospitalized for heart failure in the preceding year and all on standard background therapy, including beta-blockers (89%), ACE inhibitors and/or angiotensin II receptor blockers (91%), diuretics (83%), and antialdosterone agents (60%) (Lancet 2010;376:875-85).

There was a 4.7% absolute risk reduction and a 26% relative risk reduction for hospitalizations as a result of deteriorating heart failure in the 3,241 ivabradine patients, but the drug did not reduce mortality, according to a statement from the drug's manufacturer, Amgen.

The most common adverse events were bradycardia (10% vs. 2.2% with placebo), hypertension or increased blood pressure (8.9% vs. 7.8% with placebo), atrial fibrillation (8.3% vs. 6.6%), and luminous phenomena or visual brightness (2.8% vs. 0.5%).

Ivabradine is a specific inhibitor of the I_f ("funny") current in the sinoatrial node, but not other currents. The drug is contraindicated in patients with acute decompensated heart failure, blood pressure below 90/50 mm Hg, sick sinus syndrome, sinoatrial block, third-degree AV block (unless a functioning demand pacemaker is present), resting heart rate below 60 bpm prior to treatment, severe hepatic impairment, pacemaker dependence, and use of strong cytochrome P450 3A4 inhibitors. Ivabradine increases the risk of atrial fibrillation and can cause fetal toxicity. Bradycardia, sinus arrest, and heart block have been reported with its use, according to Amgen.

Absolute risk of hospitalization for deterioration of heart failure was reduced by 4.7% in ivabradine patients; relative risk was reduced by 26%.

Concurrent use of the calcium channel blockers verapamil or diltiazem increases exposure to the drug and should be avoided. Ivabradine also should be avoided in patients with second-degree AV block unless a functioning demand pacemaker is present.

Ivabradine will be available in 5-mg and 7.5-mg tablets, according to the product's label. The recommended starting dose is a 5-mg tablet twice daily with meals. After 2 weeks of treatment, the dose should be adjusted depending on heart rate. In patients with a history of conduction defects or others in whom bradycardia could lead to hemodynamic compromise, Amgen said to initiate therapy at 2.5 mg twice daily.

Patients should alert their physician if they develop an irregular heartbeat, a pounding or racing heart, chest pressure, worse shortness of breath, dizziness, weakness, or fatigue, Amgen said.

Ivabradine will be available within about a week of the approval under the trade name Corlanor, and will come with a patient medication guide. Wholesale acquisition cost will be $4,500 per year, or $375 per month, and patient costs will vary according to insurance coverage, said Amgen spokesman Cuyler Mayer.

Ivabradine has been available in Europe as Procoralan for several years.

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Aspirin desensitization making headway in U.S.

BY BRUCE JANCIN
Frontline Medical News

HOUSTON – About 63% of allergists and fellows in training perform aspirin desensitization for aspirin-exacerbated respiratory disease, according to a national survey.

That figure is lower than it should be, given the wealth of published evidence that aspirin desensitization is a safe and effective component of the treatment of aspirin-exacerbated respiratory disease (AERD), Dr. Jeremy D. Waldram asserted in presenting the survey findings at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Desensitizations are done in the outpatient setting. None of 1,500 patients has needed to be transferred.

DR. WALDRAM

Moreover, the figure likely overcalls the true rate, since participation in the survey was voluntary, and fans of aspirin desensitization were probably more inclined to complete the 16-item questionnaire, added Dr. Waldram, a fellow in allergy and immunology at the Scripps Clinic in San Diego.

Was he surprised to find that aspirin desensitization isn't more widely utilized?

"I think the number that surprised me more was that among the 37.5% of allergists who don't do aspirin desensitization, almost 30% of them don't even refer their patients to others who do the procedure. We don't know why they don't refer out; it wasn't a question included in the survey. Perhaps they see patients who are of a less severe phenotype," he said in an interview.

The 684 survey responses represented a 15% response rate. While 37.5% of respondents indicated they don't perform aspirin desensitization, 73% of those who reported doing the procedure said they do an average of 1-5 cases annually.

Among allergists who don't perform aspirin desensitization, safety concerns were the leading reason cited. Indeed, 70% of those who don't do aspirin desensitization indicated safety risks were the main reason. More than one reason could be given, however, and 30% of allergists cited poor compensation for the procedure as a deterrent, nearly 60% said the logistics of monitoring care were too onerous, and one-third said they didn't perform aspirin desensitization because they hadn't been trained to do it.

Of allergists who reported doing aspirin desensitization, 52% perform the procedure in an outpatient setting unattached to a hospital. Another 21% do so in an outpatient clinic that's physically attached to a hospital.

Within the past 5 years, 9% of respondents said that they've had a patient react severely to aspirin desensitization, requiring an unanticipated transfer to a higher level of care. That's contrary to the experience among allergists at the Scripps Clinic, which is widely credited with pioneering the outpatient approach.

"We essentially do all our aspirin desensitizations for AERD in the outpatient setting. In 1,500 treated patients we've never had one that we had to transfer to a higher level of care. We don't have any special setup. It's a typical outpatient clinic. We usually don't start IVs or do anything above and beyond," Dr. Waldram said.

While 26% of respondents reported they generally recommend aspirin desensitization immediately upon identifying a patient history that supports the diagnosis of AERD, another 54% said they usually recommend the procedure to patients only after they've failed to improve on typical medical therapy.

Twenty percent of physicians rated aspirin desensitization as "extremely helpful for the majority of patients," and another 49% said they find it most beneficial as an adjuvant to ongoing medical therapy.

Forty-four percent of allergists who perform aspirin desensitization reported that they learned to do the procedure during fellowship training. Fourteen percent said they learned to do the procedure at an annual meeting, and 36% picked it up by reviewing the relevant literature.

Several allergists commented that had Dr. Waldram's survey been conducted even a couple of years ago the rate of utilization of aspirin desensitization would have been far lower.

They interpreted his reported 62.5% rate as a sign of progress. Dr. Waldram said he believes the key to further boosting utilization of aspirin desensitization lies in increasing exposure to the procedure during fellowship training.

He noted that internal medicine-trained fellows who responded to the survey had a significantly higher aspirin desensitization utilization rate than those who came to their allergy fellowship with a background in pediatrics.

The hallmarks of AERD are difficult-to-treat nasal polyps, chronic eosinophilic sinusitis, and asthma in a patient with sensitivity to aspirin and other COX-1 inhibitors.

Dr. Waldram reported having no financial conflicts with regard to his study, which was conducted free of commercial support.

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VITALS

Key clinical point: Aspirin desensitization is catching on for patients with aspirin-exacerbated respiratory disease.

Major finding: Roughly 63% of allergists and allergy fellows who responded to a national survey indicated they perform aspirin desensitization for aspirin-exacerbated respiratory disease.

Data source: This was a 16-question survey of aspirin desensitization practices among U.S. allergists and allergy fellows. The national survey drew 684 responses.

Disclosures: The presenter reported having no financial conflicts with regard to his study, which was funded without commercial support.

No increased risk of lung disease with methotrexate

BY BIANCA NOGRADY
Frontline Medical News

Methotrexate is not associated with an increased risk of pulmonary disease in patients taking the drug for the treatment of psoriatic arthritis, psoriasis, or inflammatory bowel disease, the results of a meta-analysis have concluded.

The findings suggest methotrexate-related lung disease is rare, if it exists at all.

DR. CONWAY

The analysis was based on the results from seven double-blind, randomized, controlled studies.

The studies involved a total of 1,640 participants taking methotrexate.

The findings showed no increased risk of total adverse respiratory events – infectious or noninfectious – or pulmonary deaths in patients taking methotrexate, compared with controls, according to Dr. Richard Conway of the department of rheumatology at Galway (Ireland) University Hospitals and his coauthors.

Methotrexate has previously been implicated as a cause of lung toxicity.

Further, the prevalence of methotrexate-related interstitial lung disease has been reported as high as 11.6% in rheumatoid arthritis.

Studies of methotrexate-induced lung disease, however, are confounded by the higher risk of pulmonary infections that are seen among patients with rheumatoid arthritis, the authors said (BMJ 2015 [doi:10.1136/bmj.h1269]).

"These findings, coupled with those of a previous study in rheumatoid arthritis, suggest that methotrexate-related lung disease is rare, if it exists at all," the investigators wrote in their conclusions from their study.

VITALS

Key clinical point: Methotrexate is not associated with an increased risk of pulmonary disease.

Major finding: There was no increased risk of total adverse respiratory events – infectious or noninfectious – or pulmonary deaths in patients taking methotrexate, compared with controls.

Data source: Meta-analysis of seven double-blind, randomized, controlled studies, involving a total of 1,640 participants.

Disclosures: The investigators had no specific source of funding for the study and had no conflicts of interest to declare.

Bronchial thermoplasty

Asthma *from page 1*

of the task force that developed the ERS/ATS guidelines, said the group's cautious stance was appropriate given the evidence available at the time of deliberations. However, at the AAAAI meeting, he highlighted more recent study results that address many of the task force's concerns and that he said might lead to a more enthusiastic recommendation for bronchial thermoplasty in the future.

One key piece of evidence unavailable to the task force comes from 5-year prospective follow-up of 162 bronchial thermoplasty-treated patients in the international Asthma Intervention Research 2 (AIR2) trial.

"It's quite striking that the exacerbation rate did not start to creep back up over time in this severe asthma population. We believe this study shows for the first time that this therapy may actually be a disease modifier, and that you can do this procedure in an identified population and the benefits of this one-time treatment are sustained over at least a 5-year time period," said Dr. Castro, an AIR2 investigator and professor of pulmonary and critical care medicine and pediatrics at Washington University in St. Louis.

Compared with the baseline established during the year prior to the procedure, at 5 years post procedure, there was a 44% decrease in the percentage of AIR2 participants with severe exacerbations requiring oral corticosteroids, and a 48% reduction in the severe exacerbation event rate.

It's quite striking that the exacerbation rate did not start to creep back up over time in this population.

DR. CASTRO

Moreover, there was a 78% reduction in the percentage of patients with an emergency department visit for asthma and an 88% drop in the ED visit event rate (J. Allergy Clin. Immunol. 2013;132:1295-302).

With regard to safety, annual high-resolution CT scans showed no structural abnormalities from baseline to 5 years post-bronchial thermoplasty that could be attributed to the procedure. Prebronchodilator forced expiratory volume in 1 second (FEV_1) values remained steady between years 1 and 5 post procedure despite an 18% decrease in the average daily dose of inhaled corticosteroids.

In a separate study, Dr. Castro and coinvestigators at Washington University identified a number of predictors of who will respond best to bronchial thermoplasty. This was a small study of 42 patients with severe persistent asthma as reflected in their baseline mean inhaled corticosteroid dose of 2,185 mcg/day. Eighty percent of patients required bursts of oral corticosteroids during the year prior to the procedure. Their average baseline Asthma Quality of Life Questionnaire (AQLQ) score was 3.42. Baseline FEV_1 postbronchodilator averaged 70% (range 44%-121%).

Predictors of clinically meaningful improvement as defined by at least a 0.5-point improvement in AQLQ score 1 year post procedure included a shorter duration of asthma – 19 years, as compared with an average of 45 years in nonresponders – and a greater number of severe exacerbations during the year prior to bronchial thermoplasty.

Using another important yardstick of clinical improvement – at least a 240 mcg/day dose reduction in inhaled corticosteroids or a 2.5 mg/day decrease in oral corticosteroids at 1 year post procedure – significant predictors of benefit included older age (55 vs. 43 years), a lower baseline AQLQ score (2.4 vs. 4.0), and greater need for oral corticosteroids.

Several quantitative metrics obtained through multidetector CT scans of the chest showed promise as predictors of a corticosteroid dose reduction. Responders showed less baseline air trapping, with an average of 6.1% of the lung having a density below –850 Hounsfield units, compared with 12.1% in nonresponders. Responders also had less baseline emphysema-like lung, with 3.2% of the lung having a density below –950 Hounsfield units at total lung capacity, compared with 5.8% in nonresponders, according to Dr. Castro.

The study was funded by the National Institutes of Health. AIR2 was sponsored by Boston Scientific. Dr. Castro reported research grants from the NIH, the American Lung Association, Boston Scientific, and other companies.

An estimated 5% of asthma patients are categorized as having severe disease. Bronchial thermoplasty has been FDA approved for severe asthma since 2010. The outpatient procedure entails delivery of radiofrequency energy to the lungs in three sessions several weeks apart.

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With SGR repeal, Medicare refocuses on value

BY GREGORY TWACHTMAN
Frontline Medical News

It's value over volume for Medicare now that the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) is law.

The new law repeals the Medicare Sustainable Growth Rate formula, negating the 21% physician fee cut that was to go into effect April 1. In its place, the law provides a 0.5% pay increase yearly for 5 years as the Medicare program makes the transition away from fee-for-service and to value-based payment.

To help get to a point of value over volume, the bill consolidates existing quality programs – including those regarding the meaningful use of electronic health records – into a single value-based performance program.

The new law also incentivizes physicians to use alternate payment models that focus on care coordination and preventive care with a 5% payment bonus. It pushes for more transparency of Medicare data for physicians, providers, and patients.

MACRA also includes funding to help smaller practices participate in alternative payment models or the streamlined quality measurement program, as well as funding to help in the development of quality measures.

"The provisions that allow for continued funding of the quality measurement enterprise in [MACRA] are a key building block of this important transition," the National Quality Forum said in a statement. "These efforts will not only help people get better health care, but also will reduce costs that strain patients, purchasers, and the system."

The new law also reauthorizes the Children's Health Insurance Program (CHIP), the Community Health Center program, the National Health Service Corps, and the Teaching Health Centers program for 2 years. Additionally, the law continues a partial delay of the Medicare two-midnights rule until Sept. 30.

Other MACRA provisions allay malpractice concerns. The law specifies that the development, recognition, or implementation of any federal health care guideline or standard does not establish a duty of care in medical malpractice claims. The provision helps distinguish government quality guidelines and payment rules from medical liability standards, according to Brian K. Atchinson, president and CEO of PIAA, a national trade association for medical malpractice liability insurers.

"None of these rules or guidelines were created with the intent to establish a legal standard for negligence, and so it makes sense for Congress to clarify that fact," Mr. Atchinson said. "The standard of care provision in the SGR fix bill does just that, and nothing more. It ensures that these federal rules are not misused for purposes for which they were never intended."

The Congressional Budget Office estimated that enactment of the law will increase the deficit by $141 billion over 10 years and will save money, compared with the price of continued patches. A total of $73 billion of the $214 billion cost of package is offset through spending reductions and revenue increases such as income-related premium adjustments for Medicare Parts B and D, Medigap reforms, adjustments to inpatient hospital payment rates, and a delay of Medicaid Disproportionate Share Hospital changes until 2018.

VIEW ON THE NEWS

Dr. Michael Nelson, FCCP, comments: It is not entirely clear what finally motivated our legislators to eliminate the SGR, but some thanks should be given to those who contacted their representatives. This legislation finally removes the threat to physicians' remuneration present for the last decade, while endeavoring to enhance quality care for Medicare patients.

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COPD exacerbations

Guidelines *from page 1*

financial resources; and hasten a progressive decline in pulmonary function, a cardinal feature of COPD," Dr. Criner and his associates wrote (CHEST 2015;147:894-942).

Current COPD treatment guidelines state that prevention of exacerbations is possible, but they provide little guidance to clinicians regarding available therapies.

COPD exacerbations cause frequent hospital admissions, relapses, and readmissions; contribute to death during hospitalization or shortly thereafter; and reduce quality of life dramatically.

The ACCP and CTS jointly commissioned their guideline to address "this important void in COPD management."

Among their recommendations are the following:

- Patients with moderate, severe, or very severe COPD who had an exacerbation within the preceding 4 weeks should undergo pulmonary rehabilitation to prevent further exacerbations. In contrast, the data do not support pulmonary rehabilitation for those whose most recent exacerbation was more than 4 weeks earlier.
- Smoking cessation counseling and treatment are suggested as a component of a comprehensive clinical strategy to prevent COPD exacerbations. Quitting smoking is the only evidence-based intervention that actually improves COPD prognosis, because it mitigates further declines in lung function and reduces symptoms.
- Education plus case management together, to include direct contact with a health care specialist at least monthly, are recommended to prevent acute exacerbations; either measure alone is insufficient to reduce exacerbations.
- Administration of the 23-valent pneumococcal vaccine is suggested even though evidence does not specifically support the vaccine for preventing acute exacerbations. Rather, the vaccine benefits the general health of people aged 65 and older and of all adults who have underlying chronic medical conditions such as COPD.
- Annual administration of the influenza vaccine is recommended because of its benefit regarding general health and the fact that existing guidelines recommend it for COPD patients.

The guideline also addresses the use of numerous medications, alone or in combination, in great detail, including short- and long-acting beta-2 agonists, short- and long-acting muscarinic antagonists, inhaled corticosteroids, inhaled long-acting anticholinergics, long-term macrolides, oral and IV systemic corticosteroids, roflumilast (when chronic bronchitis is present), oral slow-release theophylline, oral N-acetylcysteine, oral carbocysteine, and statins.

There is also a section in the guideline addressing novel therapies, including agents that target airway inflammation such as adenosine A2A-receptor agonists, inhibitors of proinflammatory pathways, and activators of anti-inflammatory pathways.

Other new approaches include drugs with antioxidant effects, drugs that facilitate lung regeneration, and mucoactive agents.

VITALS

Key clinical point: The American College of Chest Physicians and the Canadian Thoracic Society have issued a guideline for prevention of acute exacerbations of COPD.

Major finding: COPD exacerbations are acute, trajectory changing, and often deadly manifestations of a chronic disease.

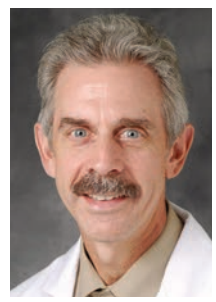
Data source: A comprehensive literature review on prevention of acute COPD exacerbations and a compilation of 33 recommendations and suggestions for physicians in clinical practice.

Disclosures: The American College of Chest Physicians, the Canadian Thoracic Society, and the American Thoracic Society supported the project. Dr. Criner reported having no relevant financial disclosures; his associates reported ties to numerous industry sources.

VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: As one of pulmonary medicine's most common chronic diseases, COPD places a heavy burden on patients, on health care systems, and on society's population health in general. The exacerbation often results in a reduction of baseline functionality for patients and, in end-stage disease, the exacerbation can be a frequent cause of health system utilization. These collaborative guidelines have the potential of ensuring that COPD patients benefit from a standardized approach to improve their health, to potentially limit the occurrence of the trajectory-challenging exacerbation, and to reduce morbidity and mortality.

DR. DEPALO



DR. OUELLETTE

Dr. Daniel Ouellette, FCCP, comments: One of the first patients that I saw in my clinic 30 years ago as a new first year internal medicine resident had COPD. An old man, he lived alone in a small home in the desert outside of El Paso, Texas. I treated him with albuterol inhalers, oral theophylline, and domiciliary oxygen. My mentors taught me to treat him for his bronchitic exacerbations with oral corticosteroids and antibiotics, and to administer the influenza vaccine yearly, in order to prevent him from being hospitalized. This prevention plan seemed to work anecdotally for my patients.

However, I was able to find little evidence in the medical literature at that time demonstrating improved clinical outcomes from this prevention strategy. I would have been surprised to hear of a government directive concerning the management of my COPD patients, and shocked to see a television advertisement concerning their treatment.

Since then, an augmented array of pharmaceutical agents and medical strategies has emerged for treating and preventing COPD exacerbations and reducing hospitalization rates. Prospective trials and meta-analyses demonstrated benefit from agents historically used to treat COPD exacerbations, such as oral corticosteroids and antibiotics.

The use of inhaled corticosteroids was analogously extended by pulmonologists from asthma to COPD. This practice became increasingly supported by clinical trial data demonstrating reduced exacerbation rates, improved respiratory physiology, or both. New agents such as short- and long-acting inhaled anticholinergics, and long-acting inhaled beta-agonists, became available. Older agents, such as theophylline, fell out of favor because of a narrow therapeutic window and a belief that the treatment afforded only modest efficacy.

Today, COPD is known to be the third leading cause of death in America. Nearly 24 million Americans may have COPD. Once thought to be a disease of men, COPD claimed the lives of 70,000 women in 2010, as opposed to 64,000 men. The burden on the U.S. health care system from COPD is enormous, with 715,000 hospital discharges in 2010, and a staggering total health care cost of $49.9 billion. In an effort to reduce health care spending, new Medicare rules in 2014 have created penalties for hospitals targeting 30-day readmissions for COPD. Once a strange acronym relegated to the physicians' lingua-franca, COPD is now on the tip of the tongue of hospital administrators, politicians, and health-care strategists.

CHEST stands ready to help physicians confront the challenges of COPD in the years to come. Central to this effort will be the effective, evidence-based, treatment and prevention of acute exacerbations of COPD. With this in mind, experts in COPD and evidence-based medicine from CHEST and the Canadian Thoracic Society have issued a clinical practice guideline concerning Prevention of Acute Exacerbations of COPD. Recommendations are graded in accordance with the strength of the supporting evidence, and take into account physician and patient preferences. Text and evidence tables provide information concerning supporting data for the thoughtful physician. Topics covered include pharmacologic treatments, nonpharmacologic treatments, and management strategies. Easy online access makes this guideline a useful, daily tool for the busy CHEST clinician.

Dr. Ouellette was one of the authors of the COPD guidelines.

What if your PAH patient may not have PAH?

A ventilation-perfusion (V/Q) scan can rule out chronic thromboembolic pulmonary hypertension (CTEPH) in patients diagnosed with PAH, which is the only form of pulmonary hypertension that can be potentially cured by surgery.[1]

If you know what to look for, a V/Q scan makes it relatively easy to spot.[1]

1 in 25*

As many as **1 out of every 25** of your previously treated PE patients (>3 months of anticoagulation[2]) may develop CTEPH.[3,4*]

*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5). CTEPH did not develop after two years in any of the 132 remaining patients with more than 2 years of follow up.

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Screening for CTEPH in Patients With Suspected Pulmonary Hypertension

presented by

RICHARD CHANNICK, MD

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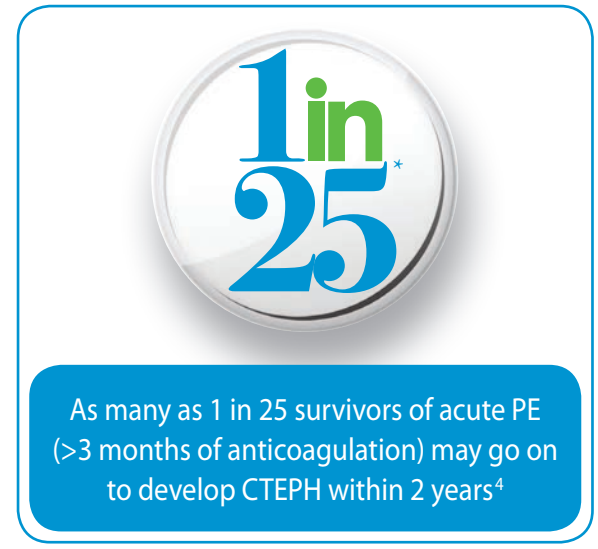

CTEPH IS A FORM OF PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension is a form of pulmonary hypertension (PH), designated by the World Health Organization as Group 4 PH. There are 5 WHO Groups of PH[1]:

1: Pulmonary arterial hypertension

2: PH due to left heart disease

3: PH due to lung diseases and/or hypoxia

4: CTEPH

5: PH with unclear multifactorial mechanisms

Recently, Klok et al have coined the term "post-pulmonary embolism syndrome" to describe chronic complications of pulmonary embolism (PE), involving permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function which are associated with symptoms of dyspnea and decreased exercise capacity.[2] The most serious manifestation of this syndrome—and the most serious complication of acute PE—is chronic thromboembolic pulmonary hypertension, or CTEPH.[2,3] As many as 1 in 25 survivors of acute PE may go on to develop CTEPH within 2 years.[4]

Hemodynamically, CTEPH is most often defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. These levels must be obtained via right heart catheterization, and they must be observed in the presence of multiple chronic/organized, occlusive thrombi/emboli in the pulmonary arteries after at least 3 months of effective anticoagulation.[5]

Symptoms of CTEPH are nonspecific[6] and include dyspnea on exertion, fatigue, weakness, chest pain, syncope, hemoptysis, and lower-extremity edema.[7] Among the risk factors for CTEPH are unprovoked or recurrent PE, young age at the time of first PE, and splenectomy.[7]

CTEPH is unique among the five groups of PH insofar as it is the only form that is potentially curable—via pulmonary thromboendarterectomy (PTE, also known as pulmonary endarterectomy [PEA]), the treatment of choice for surgical candidates with CTEPH.[8-10] It is this potential to effect a curative treatment that makes it imperative to suspect and screen for CTEPH—and to differentiate CTEPH from other forms of PH—when patients present with symptoms consistent with PH.

HOW DOES CTEPH DEVELOP?

CTEPH results after a single PE or recurrent PEs that create endothelialized residua that obstruct or substantially narrow pulmonary arteries.[11] The absence or depletion of endogenous nitric oxide may contribute to endothelial dysfunction in CTEPH.[12] Obstruction and narrowing of the pulmonary arteries drives pulmonary arterial pressures to abnormal levels and increases pulmonary vascular resistance (PVR).[11] Over time, developing small vessel vasculopathy can lead to right ventricular afterload, progression of PH, and CTEPH.[13] If CTEPH is unrecognized or left untreated, right ventricular dysfunction can progress, ultimately resulting in right heart failure.[13]

HOW COMMON IS CTEPH?

Based on data from small observational studies that followed survivors of acute PE, incidence of CTEPH has been estimated to be 0.57% (N=866 survivors of acute PE observed) to 3.8% (N=314 survivors of acute PE observed)—or almost 1 in 25—within 2 years of the first acute event.[3,13] A more recent, but smaller (N=146 acute PE survivors followed for 26 months) study found that 8 survivors of acute PE were suspected to have CTEPH, and 7 of these—or 4.8% of the study population—were confirmed to have CTEPH.[14] Yet another study of survivors of acute PE (N=104) saw 5.8% of patients develop CTEPH within 2 years. Further follow-up saw an additional 4 cases develop beyond 2 years (time period not specified) for a total of 9.1% of the original study population.[15]

> The absence of prior acute PE does not exclude a diagnosis of CTEPH[9,16,17]

Applying even the lower end of this range of estimates to the annual population of survivors of acute PE suggests there could be thousands of incident cases of CTEPH each year in the US. Further, though CTEPH is a complication of acute PE, as many as 25% to 30% of patients who have CTEPH may never have had an overt PE or a history suggestive of PE.[9,16,17] The true incidence of CTEPH may, therefore, be underestimated, because postembolism observational studies do not include patients who have no history of venous thromboembolism.[13]

HOW DO WE SCREEN FOR CTEPH?

As noted, symptoms of CTEPH are nonspecific, and as a result, CTEPH is often misdiagnosed and is under recognized in practice.[6] If after at least 3 months of anticoagulation following an episode of acute PE a patient still has or develops symptoms of dyspnea, fatigue, decreased exercise capacity, or another of the symptoms of PH, one should suspect and either screen for CTEPH or refer the patient to a PH specialist who can perform CTEPH screening.[18,19]
As noted above, as many as 30% of patients who are ultimately diagnosed with CTEPH may have no history of overt acute PE, so any patient who has unexplained dyspnea should also be screened for CTEPH.[9, 16,17]

> If after 3 months of anticoagulation following an episode of acute PE a patient still has or develops such symptoms, CTEPH should be suspected and the patient referred to a PH specialist who can perform CTEPH screening[17]

Computed tomographic pulmonary angiography (CTPA) has become the standard diagnostic test for acute PE, and a good-quality CTPA that is negative for acute PE effectively rules the diagnosis out.[19] Unlike for acute PE, though, CTPA is not a preferred diagnostic test for CTEPH.[8] Instead, the ventilation/perfusion, or V/Q, scan is the preferred and recommended screening test for CTEPH.[8] Tunariu et al demonstrated that as a screening test for CTEPH, the V/Q scan had >96% sensitivity, meaning that a negative (ie, normal) V/Q scan essentially rules out the presence of CTEPH.[20] Conversely, Tunariu et al also showed that CTPA had a sensitivity of only 51% as a screening test for CTEPH, with a falsely negative finding in 38 of 78 cases studied.[20] Multiple national and international guidelines recommend the use of the V/Q scan as the CTEPH screening tool of choice.[5,8,21-23] Though it can detect chronic thromboembolic disease in segmental, lobar, or main pulmonary arteries, CTPA may miss disease that is

confined to very distal segmental or subsegmental pulmonary arteries.[8,24]

The V/Q scan has many attributes that contribute to its utility as a screening tool for CTEPH.[8] It is easy to read—suspected perfusion defects, regardless of origin, are readily recognizable. V/Q scanning also requires less radiation exposure than CTPA, and it avoids complications from administration of IV contrast. Finally, it offers a lower likelihood of incidental findings.

PTE surgery is the first-line treatment of choice for surgical candidates who have CTEPH[15]

Many patients who have been diagnosed with pulmonary arterial hypertension (PAH) have never had a V/Q scan to rule out potentially curable CTEPH. Findings from the Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QuERI, N=786) demonstrated that 43% of patients who had been diagnosed with PAH had been so diagnosed despite never having received a V/Q scan to screen for, and potentially rule out, CTEPH.[25] This finding suggests that patients who have been previously diagnosed with PAH without having had a V/Q scan and who are not meeting their PAH treatment goals should receive a V/Q scan to screen for CTEPH.

To stress the importance of the V/Q scan as a screening tool for CTEPH, the World Symposium on Pulmonary Hypertension observed that "underutilization of V/Q scans in screening PH invites potential misdiagnosis of PAH."[8] Such misdiagnosis can result in delay of assessment for potentially curative surgery for CTEPH.[6,26] If V/Q scanning is not readily available, the patient should be referred to a center that can perform a V/Q scan.

CONFIRMATION OF CTEPH DIAGNOSIS

An abnormal V/Q scan showing perfusion defects is not enough on its own to diagnose CTEPH. To confirm CTEPH, right heart catheterization (RHC) must be performed to confirm mean PAP ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. Selective pulmonary angiography is typically used to confirm presence of CTEPH lesions.[8] CTPA and magnetic resonance angiography can contribute complementary information on the lesions, their surroundings, and their accessibility.[5,8]

Once the diagnosis of CTEPH is confirmed, all CTEPH patients must be assessed for operability by an experienced CTEPH team that would plan, perform, and follow-up the patient's surgery. Operability assessment must consider the patient's risk, including quality of and accessibility of lesions, hemodynamic assessment, and consideration of comorbidities and patient characteristics.[8] If one experienced CTEPH team determines that a patient has inoperable disease, a corroborating opinion from a second experienced CTEPH team should be secured, if possible.[8] This is because operability assessment is subjective, and what may be deemed by one CTEPH team as inoperable disease may well be deemed operable by another experienced CTEPH team.

CTEPH TREATMENT IN SURGICAL CANDIDATES: PULMONARY THROMBOENDARTERECTOMY

Referral of CTEPH patients to PH centers for confirmation of diagnosis, operability assessment, and comprehensive care is essential.[5] Because it is potentially curative, PTE surgery is considered the first-line treatment of choice for patients diagnosed with CTEPH who are appropriate surgical candidates.[8-10] Rather than reserving PTE surgery as a "last-ditch" treatment option, patients who have operable CTEPH should be referred for surgery without delay.[8] Though all CTEPH patients require lifelong anticoagulation to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism,[8] anticoagulation is not sufficient to treat the progressive right ventricular dysfunction that results from CTEPH. PTE surgery allows for the removal of central obstructing lesions, resulting in improvement and often normalization of pulmonary hemodynamics.[7] About two-thirds of patients have normal hemodynamics following PTE.[27]

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*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5).[4]

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Heart failure may trigger onset of type 2 diabetes

BY MITCHEL L. ZOLER
Frontline Medical News

SAN DIEGO – Reports from several independent groups implicate heart failure as a trigger of type 2 diabetes; findings also suggest that relief of congestion can result in rapid resolution of the diabetes.

The best way to manage new-onset diabetes in heart failure patients is to "minimize the congestion" and to "try to achieve as good control of the heart failure as possible," said Dr. Maya Guglin during a talk at the annual meeting of the American College of Cardiology, in which she laid out the evidence for this newly recognized form of type 2 diabetes. In a review she published in 2014, Dr. Guglin coined the term "cardiogenic diabetes" to describe the condition (Heart Fail. Rev. 2014;19:595-602).

Dr. Guglin traced the data trail for cardiogenic diabetes starting in a 2011 retrospective study of 15 patients with advanced heart failure who received a left ventricular assist device (LVAD) at Columbia University in New York (Eur. J. Heart Fail. 2011;13:195-9).

These 15, about a third of the 43 total LVAD recipients at Columbia at the time, had been diagnosed with type 2 diabetes for an average of 6 years before receiving the device. Just before they got their device, their average hemoglobin A_{1c} (HbA_{1c}) level was 7.7%, and their average fasting plasma glucose level was 158 mg/dL. An average of 4 months later, their mean HbA_{1c} had dropped to 6%, and their mean fasting glucose had fallen to 104 mg/dL. Six patients were completely off any diabetes medication.

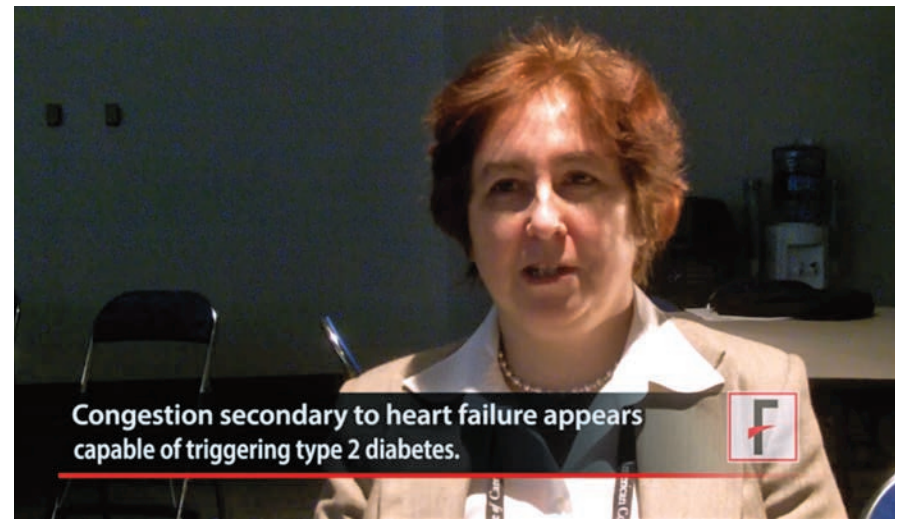
All this occurred while patients had a small increase in their body mass index, which Dr. Guglin attributed to their better physical condition and improved appetite.

Last year, another four reports appeared from four independent U.S. heart failure groups with results that mirrored the Columbia experience.

Dr. Guglin and her associates at the University of Kentucky, Lexington, reported their experience with 50 patients who received an LVAD during 2002-2012 and had type 2 diabetes just before they received a device, with an average HbA_{1c} of 7.6%. Three months after LVAD placement, their average HbA_{1c} had dropped to 5.7%, and 9-12 months after device placement, their average HbA_{1c} level was 5.3% (ASAIO J. 2014;60:290-3). As in the Columbia series, these improvements in hyperglycemia occurred without any significant change in body mass index.

Dr. Guglin also cited similar findings in 50 LVAD patients treated at the University of Rochester (N.Y.) (ASAIO J. 2014;60:675-80), 28 LVAD patients at Penn State Medical College in Hershey, Pa. (Heart Surg. Forum 2014;17:E98-102), and 66 LVAD patients from the University of Illinois in Chicago (Eur. J. Heart Fail. 2014;16:1120-4).

In these reports type 2 diabetes existed in roughly a quarter to a third of patients with advanced heart failure who qualified for an LVAD just prior to the time they received the device.



FRONTLINE MEDICAL NEWS

In a video interview, Dr. Maya Guglin discusses "cardiogenic diabetes" and the multiple benefits of reducing congestion in heart failure. Scan the QR code or visit www.chestphysician.org.

Dr. Guglin and her associates reviewed data from 3,165 elderly Americans free from diabetes enrolled in the Cardiovascular Health Study. This cohort included 80 patients with heart failure and 3,085 without heart failure.

During 3-4 years of follow-up, 6% of the heart failure patients developed new-onset diabetes, and an additional 10% developed new-onset impaired fasting glucose. In contrast, these incidence rates were 1.5% and 5%, respectively, in the enrollees without heart failure at baseline.

In an analysis that controlled for several demographic and biomedical factors, heart failure linked with a statistically significant, 2.4-fold increased risk for the development of diabetes (Cardiology 2014;129:84-92).

And a Danish nationwide cohort study of more than 99,000 residents discharged from a first-time hospitalization for heart failure during 1997-2010 showed a statistically significant link between heart failure severity and an increased rate of development of incident diabetes using diuretic treatment dosage as a surrogate measure of heart failure severity (Diabetologia 2014;57:1595-1600).

"It all boils down to congestion," Dr. Guglin said in an interview. "Control congestion as much as possible to control the diabetes."

Dr. Guglin had no relevant financial disclosures.

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Novel anticoagulants best for AF in heart failure

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – The novel oral anticoagulants clearly outperformed warfarin for stroke prevention and safety endpoints in patients with atrial fibrillation and comorbid heart failure in a meta-analysis of four recent landmark Phase III clinical trials.

Collectively, the four novel oral anticoagulants (NOACs) approved for stroke prophylaxis in nonvalvular atrial fibrillation (AF) reduced the risk of stroke and systemic embolism by 14%, compared with patients randomized to warfarin.

Moreover, the NOACs decreased the risks of major bleeding and intracranial bleeding by 23% and 45%, respectively, Dr. Gianluigi Savarese reported at the annual meeting of the American College of Cardiology.

"NOACs represent a valuable therapeutic option in patients with nonvalvular atrial fibrillation and heart failure," concluded Dr. Savarese of Federico II University, Naples.

There has never been a randomized trial comparing a NOAC to warfarin specifically in patients with these dual diagnoses.

In the meta-analysis, major bleeding, and intracranial bleeding, they showed a 12% decrease in total bleeding and an 8% reduction in cardiovascular death, compared with warfarin-treated controls.

In the absence of such a definitive study, the next best thing is a meta-analysis of the pivotal Phase 3 trials in which warfarin was compared to dabigatran (Pradaxa, the RE-LY study), apixaban (Eliquis, ARISTOTLE), rivaroxaban (Xarelto, ROCKET AF), and edoxaban (Savaysa, ENGAGE AF-TIMI 48).

The meta-analysis focused on a subset population of 26,384 randomized patients with AF and heart failure.

It's important to know how the NOACs stack up against warfarin in this population because symptomatic heart failure is common: indeed, it's present in 30% of patients with AF.

Patients with AF and comorbid heart failure are generally older and frailer, have more comorbidities, and are at higher risk of both stroke and bleeding, compared with AF patients without heart failure.

Since heart failure is a recognized risk factor for reduced time in the therapeutic international normalized ratio (INR) range for patients on

Continued on following page

Ventricular gel improved advanced heart failure

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – Beefing up a sick left ventricle via a set of injections of an inert alginate hydrogel resulted in significantly improved functional capacity, compared with optimal medical therapy through 6 months of follow-up in patients with advanced heart failure in the randomized AUGMENT-HF trial.

Investigators also noted "an interesting and striking reduction" in hospitalizations for worsening heart failure in the group that received left ventricular (LV) augmentation with the material, known as Algisyl-LVR, Dr. Stefan D. Anker reported at the annual meeting of the American College of Cardiology.

Indeed, among 78 patients with advanced heart failure randomized to hydrogel injections plus optimal medical therapy or to optimal medical therapy alone, there were 14 hospitalizations for worsening heart failure in eight controls, compared with 5 hospitalizations in four patients in the LV augmentation group. The between-group difference is large, but the number of hospitalizations is still small. AUGMENT-HF will continue for 2 years of follow-up.

"This gives us hope for the future," said Dr. Anker, professor of cardiology and cachexia research at Charité Medical School, Berlin.

In addition, based upon the favorable 6-month study results, planning is underway for a larger, pivotal phase III U.S. trial of Algisyl-LVR, classified as a medical device, to start later this year.

At present, surgeons implant the hydrogel through a minithoracotomy. The procedure involves 10-20 injections totaling 4-5 mL of the inert, permanent material, which is placed as a ring of beads along a circumferential line at the left ventricular midwall.

"We make the wall thicker and the cavity of the ventricle a little smaller, thereby reducing wall stress. We basically try to change the physics of the pump action of the heart to improve patient status and perhaps patient outcome," Dr. Anker explained.

Surgeons say it's an easily learned procedure. The surgical morbidity and mortality seen in AUGMENT-HF were deemed acceptable by investigators and the study sponsor, so this new therapy will initially be developed as a surgical procedure. But it's certainly a treatment that lends itself to delivery by percutaneous catheter in the future, according to the cardiologist.

Study participants had moderate to severe heart failure, with an average LV ejection fraction of 25%. Most were New York Heart Association (NYHA) functional class III.

The primary study endpoint was change in peak oxygen uptake (VO_2) at 6 months from a baseline of 12.2 mL/kg/min.

The value improved to 13.5 mL/kg/min in the LV augmentation group, compared with 12.4 mL/kg/min in controls, a between-group difference that Dr. Anker characterized as clinically relevant. He noted that one of the study's strengths was that each peak VO_2 result was the average of two tests performed on the same occasion, a method that markedly improves test reproducibility.

Also, 6-minute walk distance improved in the LV augmentation group by a mean of 84.7 meters from a baseline 280 meters, while decreasing by 15.4 meters in controls.

"This is quite a positive result rarely seen with other therapies. For everybody involved, this was a very positive finding," Dr. Anker said.

Among controls, NYHC class stayed steady over the course of 6 months while showing a 0.9-class improvement in the LV augmentation group.

Heart failure etiology – ischemic versus nonischemic – had no bearing on LV augmentation's effectiveness. Baseline 6-minute walk distance did, though. Patients with a baseline walk distance of less than 287 meters experienced a much larger treatment effect: a mean 2.42 mL/kg/min greater improvement from baseline to 6 months with LV augmentation than in controls, as compared with a nonsignificant 0.4 mL/kg/min advantage among patients who covered more than 287 meters at baseline.

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

We make the wall thicker and the ventricle cavity smaller, Dr. Anker said.

The mean procedure time was 80 minutes, with 190 minutes of anesthesia time. Patients spent an average of 2 days in the ICU.

Three deaths occurred in the surgical group within the first 30 days. Excluding the index hospitalization, there were 22 major adverse cardiovascular events in the control group and 9 in the LV augmentation group. Among these were three cardiovascular deaths in each study arm, for a total of six deaths through 6 months in the LV augmentation patients. However, with additional study follow-up beyond the 6 months presented at ACC 15, mortality has evened out in the two groups, according to Dr. Anker.

Sustained ventricular tachycardia occurred in four controls and one patient who received LV augmentation.

Several audience members expressed surprise at the low arrhythmia rate in the LV augmentation group, but Dr. Anker's coinvestigator Dr. Douglas L. Mann explained that the implantation doesn't create an isthmus, thus there is no nidus for arrhythmia formation.

"No arrhythmia signal has been seen. There is actually a reduction in both atrial and ventricular arrhythmias," said Dr. Mann, professor of internal medicine and chief of the division of cardiovascular medicine at Washington University in St. Louis.

The AUGMENT-HF trial was sponsored by LoneStar Heart. Dr. Anker reported having no financial relationship with LoneStar, although he serves as a consultant to half a dozen other health care companies.

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Continued from previous page

warfarin, it's likely that warfarin-treated dual diagnosis patients would be exposed to further increased risks of stroke and bleeding, according to Dr. Savarese.

In the meta-analysis, in addition to the NOAC-treated patients' significantly reduced risks of stroke, major bleeding, and intracranial bleeding, they showed a 12% decrease in total bleeding and an 8% reduction in cardiovascular death, compared with warfarin-treated controls, although neither of those latter two favorable trends achieved statistical significance.

The four NOACs didn't differ significantly on any of the prespecified outcomes in the meta-analysis, Dr. Savarese said.

One audience member noted that while the relative risk reductions for stroke and major bleeding seen with the NOACs in the meta-analysis were large and impressive, the absolute risk reductions were actually quite small. For example, warfarin-treated controls in RE-LY, the first of the major trials, had a stroke/systemic embolism rate of 1.69%/year and a major bleeding rate of 3.4%/year (N. Engl. J. Med. 2009;361:1139-51), while controls in ENGAGE AF-TIMI 48 had annualized stroke and major bleeding rates of 1.5% and 3.4%, respectively (N. Engl. J. Med. 2013;369:2093-2104).

Dr. Savarese replied that he and his coinvestigators consider those absolute risk reductions to be clinically meaningful, especially in light of the enormous and rapidly growing number of patients with both AF and heart failure.

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VITALS

Key clinical point: Patients with nonvalvular atrial fibrillation and heart failure clearly fare better on any of the novel oral anticoagulants than with warfarin for stroke prophylaxis.

Major finding: Dual diagnosis patients randomized to a novel oral anticoagulant had a 14% reduction in stroke/systemic embolism and a 23% decrease in major bleeding compared with those on warfarin.

Data source: This was a meta-analysis of the 26,384 patients with both atrial fibrillation and heart failure who were included in four pivotal Phase 3 clinical trials that led to approval of dabigatran, apixaban, rivaroxaban, and edoxaban.

Disclosures: The presenter reported having no financial conflicts regarding this meta-analysis, which was carried out free of commercial support.

BREO ELLIPTA

The first and only once-daily ICS/LABA for the maintenance treatment of COPD

Improves patients' lung function for a full 24 hours with one inhalation, once daily[1]*

Also approved to reduce COPD exacerbations in patients with a history of exacerbations

Indications

- BREO ELLIPTA 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 ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.
- BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABAs), such as vilanterol, one of the active ingredients in BREO ELLIPTA, 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 vilanterol.**
- **The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

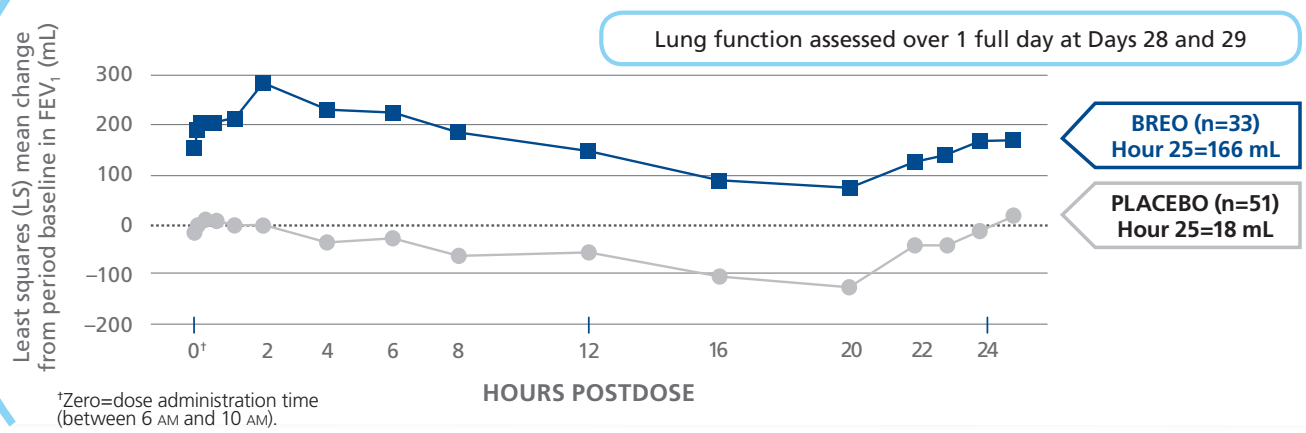
WARNINGS AND PRECAUTIONS

- BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- BREO ELLIPTA 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 ELLIPTA 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 drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO ELLIPTA. Advise patients to rinse the mouth 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 ELLIPTA. 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 ELLIPTA 100/25 mcg (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and FF/VI 200/25 mcg (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 ELLIPTA at the approved strength (100/25 mcg) and in 7 subjects receiving FF/VI 200/25 mcg (<1% for each treatment group).
- 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 ELLIPTA.
- 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 ELLIPTA slowly.
- Caution should be exercised when considering the coadministration of BREO ELLIPTA 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 ELLIPTA and institute alternative therapy.
- 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 ELLIPTA may need to be discontinued. BREO ELLIPTA 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 ELLIPTA and periodically thereafter.

Once-daily BREO ELLIPTA provided sustained improvement in lung function for a full 24 hours

PRIMARY ENDPOINT: BREO ELLIPTA provided a 220 mL improvement in weighted mean FEV_1 (0-24 hours) from period baseline compared with placebo ($P<0.001$) at end of the 28-day treatment period.[1]

SECONDARY ENDPOINT: SERIAL FEV_1 (0-25 HOURS)[1,2]



†Zero=dose administration time (between 6 AM and 10 AM).

*A multicenter, randomized, double-blind, placebo-controlled, crossover study evaluated the effect of 28 days of treatment with BREO ELLIPTA on lung function over 24 hours in 54 patients (mean age: 57.9 years) with COPD.‡ The primary endpoint was weighted mean FEV_1 (0-24 hours) at the end of the 28-day treatment period (period Days 28 and 29). This was calculated from predose FEV_1 (mean of –30- and –5-minute measurements) and postdose FEV_1 after 5, 15, 30, and 60 minutes and 2, 4, 6, 8, 12, 16, 20, 22, 23, and 24 hours. The secondary endpoint was serial FEV_1 (0-25 hours) at period Days 28 and 29.

‡At screening, patients had a mean postbronchodilator % predicted FEV_1 of 49.8%, a mean postbronchodilator FEV_1/FVC ratio of 52.9%, and a mean % reversibility of 8.8%.
FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

In a separate 6-month lung-function study: a multicenter, randomized, double-blind, parallel-group study compared the effect of BREO vs fluticasone furoate (FF) 100 mcg and vs placebo (each administered once daily by the ELLIPTA inhaler) on lung function in 1030 patients (mean age: 62.7 years) with COPD.§ For the co-primary endpoints, BREO significantly improved weighted mean 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 25 mcg¶ did not achieve statistical significance (95% CI: –6, 102; $P=0.082$).[2,3]

§At screening, patients had a mean postbronchodilator % predicted FEV_1 of 48.3%, a mean postbronchodilator FEV_1/FVC ratio of 47.6%, and a mean % reversibility of 15.9%.
‖The weighted mean comparison of BREO with FF, the ICS component, was assessed to evaluate the contribution of vilanterol to BREO. ICSs are not approved as monotherapy for COPD.
¶The trough FEV_1 comparison of BREO with vilanterol, the LABA component, was assessed to evaluate the contribution of FF to BREO. Vilanterol is not approved as monotherapy.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD 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.

ADVERSE REACTIONS

- The most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO ELLIPTA (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 treated with BREO ELLIPTA in two 1-year studies included COPD, back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema, and pyrexia.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO ELLIPTA 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 ELLIPTA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with reversible obstructive airways disease.
- 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

- Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate exposure may increase in these patients. Monitor for systemic corticosteroid effects.

References: 1. 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. **2.** Data on file, GSK. **3.** 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 Brief Summary of Prescribing Information, including Boxed Warning, for BREO ELLIPTA on the following pages.

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BREO ELLIPTA was developed in collaboration with Theravance

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

BREO ELLIPTA **BRIEF SUMMARY**
(fluticasone furoate and vilanterol inhalation powder)
FOR ORAL INHALATION USE
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) 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, including vilanterol, an active ingredient in BREO® ELLIPTA® *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
BREO ELLIPTA 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 ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.
Important Limitations of Use: BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either 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 Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA. A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO ELLIPTA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO ELLIPTA has been conducted. The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.
5.2 Deterioration of Disease and Acute Episodes BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. BREO ELLIPTA has not been studied in patients with acutely deteriorating COPD. The initiation of BREO ELLIPTA in this setting is not appropriate. BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist. When beginning treatment with BREO ELLIPTA, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of BREO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of BREO ELLIPTA and Use With Other Long-Acting $Beta_2$-Agonists BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Local Effects of Inhaled Corticosteroids In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO ELLIPTA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO ELLIPTA continues, but at times therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth 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 the fluticasone furoate/vilanterol combination, including BREO ELLIPTA 100 mcg/25 mcg, 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 the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 6% [48 of 820 subjects]; 100 mcg/25 mcg: 6% [51 of 806 subjects]; or 200 mcg/25 mcg: 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 fluticasone furoate/vilanterol 100 mcg/25 mcg and in 7 subjects receiving fluticasone furoate/vilanterol 200 mcg/25 mcg (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. Inhaled corticosteroids 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 inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more 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 ELLIPTA may control COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amount of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress or a severe COPD exacerbation, 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 or severe COPD exacerbation. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO ELLIPTA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO ELLIPTA. Lung function (mean forced expiratory volume in 1 second [FEV_1]), beta-agonist use, and COPD 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 ELLIPTA 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 dose of BREO ELLIPTA. 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 inhaled corticosteroids in sensitive patients, patients treated with BREO ELLIPTA 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 ELLIPTA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD symptoms should be considered.
5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.
5.10 Paradoxical Bronchospasm As with other inhaled medicines, BREO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO ELLIPTA 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 ELLIPTA. Discontinue BREO ELLIPTA 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 ELLIPTA *[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 ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12-fold higher systemic exposure than seen in patients with COPD) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO ELLIPTA, 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 inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, 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 ELLIPTA and periodically thereafter. If significant reductions in BMD are seen and BREO ELLIPTA is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered. In replicate 12-month trials in 3,255 subjects with COPD, bone fractures were reported by 2% of subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 2% [14 of 820 subjects]; 100 mcg/25 mcg: 2% [19 of 806 subjects]; or 200 mcg/25 mcg: 2% [14 of 811 subjects]) than in subjects receiving vilanterol 25 mcg alone (less than 1% [8 of 818 subjects]).
5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD 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. In replicate 12-month trials in 3,255 subjects with COPD, similar incidences of ocular effects (including glaucoma and cataracts) were reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: less than 1% [7 of 820 subjects]; 100 mcg/25 mcg: 1% [12 of 806 subjects]; 200 mcg/25 mcg: less than 1% [7 of 811 subjects]) as those receiving vilanterol 25 mcg alone (1% [9 of 818 subjects]).
5.15 Coexisting Conditions BREO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.16 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 4 clinical trials of 6- and 12-month duration evaluating BREO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warnings and Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; Increased risk for decrease in bone mineral density *[see Warnings and Precautions (5.13)]*.
6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The clinical program for BREO ELLIPTA 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 have received at least 1 dose of BREO ELLIPTA 100 mcg/25 mcg, and 1,087 subjects have received higher doses of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6-month 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 ELLIPTA in Table 1 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 Caucasian. 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 ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

Table 1. Adverse Reactions With ≥3% Incidence and More Common Than Placebo With BREO ELLIPTA in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Event	BREO ELLIPTA 100 mcg/25 mcg (n = 410) %	Vilanterol 25 mcg (n = 408) %	Fluticasone Furoate 100 mcg (n = 410) %	Placebo (n = 412) %
Infections and infestations				
Nasopharyngitis	9	10	8	8
Upper respiratory tract infection	7	5	4	3
Oropharyngeal candidiasis[a]	5	2	3	2
Nervous system disorders				
Headache	7	9	7	5

[a]Includes terms oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal.

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 Caucasian. 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 ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, or vilanterol 25 mcg. In addition to the events shown in Table 1, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO ELLIPTA (N = 806) for 12 months included COPD, back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema, and pyrexia.

6.2 Postmarketing Experience In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO ELLIPTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO ELLIPTA or a combination of these factors. Immune System Disorders: Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO ELLIPTA, are both substrates of CYP3A4. Concomitant administration of the potent CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO ELLIPTA 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) and 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 ELLIPTA, but may produce severe bronchospasm in patients with reversible obstructive airways disease. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, 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 ELLIPTA 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 studies are not always predictive of human response, BREO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO ELLIPTA.

Fluticasone Furoate and Vilanterol: There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 9 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 9 and 2 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 3 times 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 ELLIPTA during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO ELLIPTA 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 ELLIPTA by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO ELLIPTA for COPD included 2,508 subjects aged 65 and older and 564 subjects aged 75 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 ELLIPTA 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<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 ELLIPTA. BREO ELLIPTA contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO ELLIPTA.

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., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol. Treatment of overdosage consists of discontinuation of BREO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Fluticasone Furoate: Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (approximately equal to the MRHDID in adults on a mcg/m^2 basis). Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats. No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 9 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 8,750 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 530 times the MRHDID in adults on an AUC basis). In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID in adults on an AUC basis). These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown. Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay. No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,000 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

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

17.1 Asthma-Related Death Patients should be informed that LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma.

17.2 Not for Acute Symptoms BREO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with a rescue inhaler such as albuterol. The physician should provide the patient with such medicine and instruct the patient in how it should be used. Patients should be instructed to notify their physicians immediately if they experience any of the following: Symptoms get worse; Need for more inhalations than usual of their rescue inhaler; Significant decrease in lung function as outlined by the physician. Patients should not stop therapy with BREO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

17.3 Do Not Use Additional Long-Acting $Beta_2$-Agonists When patients are prescribed BREO ELLIPTA, other medicines containing a LABA should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised 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 ELLIPTA, but at times therapy with BREO ELLIPTA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth without swallowing after inhalation is advised to help reduce the risk of thrush.

Pneumonia: Patients with COPD who have received BREO ELLIPTA have a higher risk of pneumonia and should be instructed to contact their healthcare providers if they develop symptoms of pneumonia (e.g., fever, chills, change in sputum color, increase in breathing problems).

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

Hypercorticism and Adrenal Suppression: Patients should be advised that BREO ELLIPTA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids.

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

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

17.6 Hypersensitivity Reactions, Including Anaphylaxis Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO ELLIPTA. Instruct patients to discontinue BREO ELLIPTA 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 ELLIPTA.

BREO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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SLEEP STRATEGIES: An Asthma-OSA Connection? Very Likely!

BY DR. OCTAVIAN C. IOACHIMESCU, FCCP

Starting with a case and closing a circle

In 1979, Hudgel and Shucard published a case report titled "Coexistence of Sleep Apnea and Asthma Resulting in Severe Sleep Hypoxemia" (*JAMA*. 1979;242[25]:2789). The authors described a 66-year-old man with a body mass index (BMI) of 29.6, with asthma, hypertension, and erectile dysfunction. The patient had a history of "daytime somnolence while driving his automobile and during business meetings" and "loud snoring accompanied by fitful sleep, which had caused his spouse to sleep in another bedroom." Interestingly, the patient started to have similar symptoms at the age of 12 years, when he was hospitalized because of snoring and restless sleep. Tonsillectomy and adenoidectomy was performed at that time, with resolution of his symptoms. The patient was studied extensively with an indwelling arterial catheter, oxygen saturation by ear oximetry, thoracic respiratory movements, nasal airflow, continuous monitoring of EEG and ECG, chin electromyogram, and oculogram. The authors found that the deepest sleep stage during the monitoring was non-REM II (N2)

Personalized medicine is continuing its journey from big promise to a more palpable reality.

DR. IOACHIMESCU

and that the patient had frequent episodes of oxygen desaturations and premature ventricular contractions preceded by apneas. The authors stated: "A tracheostomy was performed and the patient immediately had restful sleep without obstructive sleep apnea. Daytime somnolence no longer occurred; his depression and related symptoms rapidly cleared. Nine months after tracheostomy, the patient's blood pressure was consistently 140/70 mm Hg." The authors concluded in their report: "in the examination of asthmatic patients with worsening respiratory complaints during nighttime hours, it is important to obtain information about the presence of snoring, irregular or interrupted respiration during sleep, daytime somnolence, and other behavioral disturbances." Simple coincidence or comorbid association of two prevalent conditions?

Fast forward to 2015: a group of investigators performed another analysis of the Wisconsin Sleep Cohort and showed that asthma was associated with an increased risk of new-onset OSA (Teodorescu et al. *JAMA*. 2015;313[2]:156). A population-based prospective epidemiologic study (called Wisconsin Sleep Cohort Study because it included adult Wisconsin state employees) was started in 1988. Since then, these subjects have undergone overnight polysomnographic studies at about 4-year intervals and completed several standardized questionnaires. In this paper, information on asthma and other variables that was gathered between 1988 and 2013 was analyzed. Presence and duration of self-reported, physician-diagnosed asthma were assessed by specific questionnaires administered during these visits. The authors found that 22 out of 81 subjects with asthma (27%) experienced incident or new OSA over their first 4-year follow-up interval, vs 75 out of 466 participants (16%) without asthma. Using all 4-year intervals, the adjusted risk of developing OSA was about 39% higher in asthmatics, controlling for sex, age, baseline, and change in BMI and other factors. Asthma was also associated with new-onset OSA and habitual sleepiness (a variant of OSA syndrome), a risk higher by 172%. Asthma duration was related to both incident OSA (7% risk increase) and incident OSA associated with habitual sleepiness (18% risk increase) per 5-year increments in asthma duration.

In a prior epidemiologic study (Busselton Health Survey) on 967 nonsnoring adults evaluated in 1981 who completed follow-up surveys in 1994-1995, the authors found that approximately 13% of subjects had become habitual snorers in the meantime. Male gender and baseline BMI were significant predictors of habitual snoring. However, changes in BMI over the 14-year follow-up period (odds ratio, 1.55 per 2.3 kg/m^2), development of asthma (OR, 2.8), and commencement of smoking (OR, 2.2) were found to be additional significant, independent risk factors for development of habitual snoring. This study confirmed that male gender, obesity, and weight gain are key determinants of habitual snoring, and indicated that smoking and development of asthma may also play a role (Knuiman et al. *CHEST*. 2006;130[6]:1779).

An analysis of the Wisconsin Sleep Cohort showed that asthma was associated with an increased risk of new-onset OSA.

Similar to these epidemiologic longitudinal studies, multiple cross-sectional and clinic-based studies found that the prevalence of sleepiness, snoring, and apnea was significantly higher in subjects with asthma. Only a few studies assessed for the presence of OSA by polysomnography; a couple of them reported very high prevalence of OSA (88%-95%) in patients with difficult-to-control asthma (Julien et al. J *Allergy Clin Immunol*. 2009;124[2]:371; Yigla et al. *J Asthma*. 2003; 40[8]:865). Even in pediatric populations, a recent systematic review found an OR for sleep-disordered breathing (SDB) of 1.9 (1.49 if polysomnography is used) in children with asthma (Brockman. *Sleep Med Rev*. 2014;18:393).

What are the connections?

Accumulating evidence suggests a bidirectional relationship between asthma and OSA, each condition influencing the other, both in development and severity (Puthalapattu and Ioachimescu. *J Investig Med*. 2014. 62[4]:665). Given the many clinical phenotypes and endotypes of asthma, a logical lumping approach may be to call the association of asthma and OSA "alternative overlap syndrome" (Ioachimescu and Teodorescu. *Respirology*. 2013;18[3]:421). While many pathogenic theories exist, several factors seem to be involved:

Asthma is manifested biologically by acute and chronic airway and systemic inflammation, which could affect the strength (ie, contractile force generation) of the respiratory muscles, including the upper airway dilators. The mechanisms linking lower airway inflammation with sleep-related upper airway collapse are likely multiple and may explain a unified airway hypothesis: hypervagotonia, spillover of inflammatory cytokines into systemic circulation, selective chemotaxis and preferential recruitment of specific defense pathways locally (eg, neutrophilic inflammation), upper respiratory secretions containing proinflammatory mediators, mechanical vibration (snoring) leading to local airway injury, and inflammation, etc.

Exacerbated or untreated asthma also leads to frequent arousals (sleep fragmentation) and sleep deprivation, which have been shown to be independent risk factors of upper airway collapsibility, hence (possibly) contributing to the development of sleep-disordered breathing (SDB). Patients with asthma tend to have greater reductions in lung volumes (functional residual capacity or end-expiratory lung volume) during sleep, especially during REM (R) stage, which could reduce the stiffening effect on the upper airway, similarly to the effect of recumbent position or abdominal obesity. This leads to more collapsible upper airway ("tracheal tug theory"). Additionally, the nose is the preferred breathing route during sleep,

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EDITOR'S COMMENT

Dr. Jeremy Weingarten, FCCP comments: Obstructive sleep apnea is primarily a respiratory disorder that just happens to occur during sleep. Much has been written on the association of OSA with other pulmonary diseases. The overlap syndrome (concomitant OSA and COPD) is a well-characterized disorder in which the mechanical disadvantage resulting from COPD results in OSA with greater gas exchange and ventilatory abnormalities. However, the association of OSA with asthma is less well established. The recent findings of the Wisconsin Sleep Cohort that asthma is associated with incident OSA is a novel finding that bears further investigation. In this edition of Sleep Strategies, Dr. Octavian Ioachimescu nicely summarizes the current findings, as well as potential mechanisms that may play a role in this association.

Continued from previous page

and nasal obstruction definitely contributes to SDB in predisposed individuals. Chronic or seasonal allergic diatheses (eg, rhinosinusitis, nasal polyposis) are very common among asthmatics (up to 95% of them), while nasal congestion is a well-known risk factor for snoring in both the general population and in subjects with asthma. Patients with allergic rhinitis have more often associated allergic asthma, whereas patients with nonallergic or perennial rhinitis tend to have associated nonallergic asthma. By using different technologies, several investigators found significantly smaller nasal airways (both cross-sectional areas and volumes) in individuals with asthma vs control subjects, irrespective of the allergy status. In support of the "unified airway" theory is also the fact that nasal and oral pharyngeal lymphoid tissues

Evidence suggests a bidirectional relationship between asthma and OSA, each condition influencing the other.

are frequently hypertrophied in both asthma and OSA (especially in children, where adenoidal or tonsillar hypertrophy is often seen). It has been shown that, at least in children, adenoidectomy/tonsillectomy is a procedure frequently curative for OSA and ameliorative for asthma.

Furthermore, smoking is an independent risk factor for OSA and gastroesophageal reflux disease, while tobacco or marijuana smoke may trigger symptoms of wheezing, cough, and sputum production, all suggestive of asthma or chronic bronchitis. Additionally, maternal smoking during the prenatal period has been consistently associated with early-life wheezing, and this effect seems to be augmented by continued exposure postnatally. A dose-response relationship has also been found between maternal smoking intensity prenatally and the decrease in airways' calibers during infancy and early life. Similarly, air pollution also adversely affects adult asthma, likely by worsening preexistent disease rather than causing new-onset asthma.

Where are we today?

A few final points:

- As the article in *JAMA* by Teodorescu and colleagues showed, asthma is a risk factor for new-onset, incident OSA (although a bidirectional connection likely exists).
- While we have a better understanding of the pathogenic connections between OSA and asthma, our knowledge gaps in this area are shrinking significantly.
- Nowadays, we know that OSA of childhood, although 'cured' by tonsillectomy and adenoidectomy, may herald the risk of developing OSA again during adulthood.
- Tracheostomy is no more the first line therapy for OSA – what a relief!
- Better nosologic classifications using risk factors, phenotypes, endotypes, etc, are on the way.
- Personalized medicine is continuing its journey from big promise to a more palpable reality.

Dr. Ioachimescu is an Associate Professor of Medicine at Emory University, in Atlanta, Georgia; staff physician, Medical Director of the Sleep Medicine Center and Sleep Medicine Section Chief at the Atlanta Veterans Affairs Medical Center; and the site director of the Emory University Sleep Medicine Fellowship.

Untreated OSA upped risk of repeat revascularization

BY AMY KARON
Frontline Medical News

FROM CHEST

Patients who had untreated, moderate-to-severe obstructive sleep apnea and underwent percutaneous coronary interventions were more than twice as likely to undergo repeat revascularization within the next 5 years as compared with patients on continuous positive airway pressure (CPAP), researchers reported in *CHEST*.

The first-in-kind finding "provides new evidence that untreated moderate-to-severe OSA [obstructive sleep apnea] is an independent risk factor for repeat revascularization after PCI [percutaneous coronary intervention] and that CPAP can reduce this risk," said Dr. Xiaofan Wu at the Beijing Anzhen Hospital at Capital Medical University in Beijing and

her associates. "Interestingly, the data show that untreated mild OSA was not associated with an increased risk of repeat revascularization, suggesting a dose-effect relationship between OSA severity and risk of complications after PCI."

Patients with untreated OSA have high levels of sympathetic excitation, oxidative stress, inflammatory mediators, endothelial dysfunction, and attenuated endothelial repair. All of these factors can promote atherogenesis, hypertension, arrhythmogenesis, and cardiac death, the researchers noted. But the effect of untreated OSA on PCI outcomes was not well understood, they said (CHEST 2015;147:708-18).

The finding provides new evidence that untreated OSA is an independent risk factor for repeat revascularization after PCI and that CPAP can reduce this risk.

Their study retrospectively evaluated 390 patients with OSA who had undergone PCI. The cohorts included 128 patients who had moderate-to-severe OSA and were successfully treated with

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CPAP, 167 patients with untreated, moderate-to-severe OSA, and 95 patients with untreated mild OSA. The investigators used subjective patient reports to assess adherence to CPAP. In all, 84% of treated patients had used CPAP for at least 6 months, and the rest had used CPAP for 3-6 months, they said.

Over a median follow-up of nearly 5 years, 25% of patients with untreated, moderate to severe OSA underwent repeat revascularization, compared with 14% of patients on CPAP for similarly severe OSA ($P = .019$), the investigators reported. In the adjusted analysis, untreated patients had more than double the likelihood of repeat revascularization during the follow-up period (hazard ratio, 2.13; 95% confidence interval, 1.19-3.81; $P = .011$).

Mortality and rates of major adverse cardiac and cerebrovascular events were similar among the groups, said the researchers. "Although untreated moderate-to-severe OSA was not associated with an increased risk of death in this cohort, we believe that timely diagnosis and treatment in patients undergoing PCI can serve as a clinically relevant method of secondary prevention to decrease the risk of repeat revascularization," they said.

VIEW ON THE NEWS

Dr. David Schulman, FCCP, comments: While prior studies have shown a reduction in cardiovascular morbidity with successful treatment of moderate-to-severe obstructive sleep apnea, this paper adds to the armamentarium of data by demonstrating an increased need for repeat revascularization among those not using continuous positive airway pressure. While purists may lament the limits of nonrandomized cohort data, the referenced association between untreated moderate-to-severe sleep apnea and the need for revascularization persisted after adjustment for potential confounders. Though these adverse outcomes may further our desire to treat our patients with sleep-disordered breathing, it remains unclear as to whether or not patients knowing these data will be more likely to adhere to therapy longitudinally.

Send kids home 2 hours after food challenge tests

BY BRUCE JANCIN
Frontline Medical News

HOUSTON – Food-allergic children undergoing a double-blind, placebo-controlled food challenge test can safely be discharged home after 2 hours provided they haven't experienced a severe immediate reaction in the interim, according to a large retrospective Dutch study.

Late reactions are unpredictable and very seldom severe, Jacquelien Saleh-Langenberg reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

She presented a study of 1,142 children who underwent double-blind, placebo-controlled food challenge testing at a tertiary clinic at the University of Groningen in the Netherlands, where she is a combined medical student and Ph.D. candidate. The food-allergic children were challenged with cow's milk, peanut, cashew, hazelnut, and egg.

A total of 400 children developed late reactions: 20.8% of children reported late reactions only on an active challenge day, 9.6% only on a placebo challenge day, and 4.6% reported reactions on both active and placebo challenge days.

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Of particular interest was the finding that 89 subjects developed isolated reactions on an active challenge day, and 92 did so on a placebo challenge day.

"Isolated late reactions occurred with comparable frequency after active and placebo challenge and are thus unlikely to be a real phenomenon," Ms. Saleh-Langenberg concluded.

Late reactions were manifest as gastrointestinal symptoms in 45% of cases and cutaneous symptoms in about one-third, with respiratory symptoms accounting for most of the remainder. Ninety-eight percent of late reactions were rated as mild to moderate, having a score of 1-6 on a 12-point severity scale.

The investigators developed a predictive model for late reactions occurring on an active challenge day. It proved to have little practical value, though.

The model, which included age, allergic rhinitis, severity of any immediate reaction, and hazelnut allergy, explained a mere 8% of the variance in the incidence of late reactions.

When late reactions occurred on an active challenge day, they did so a mean of 3.5 hours after testing. When they occurred on a placebo challenge day, they happened a mean of 4 hours after the challenge.

The reactions took an average of 2 hours and 1 hour, respectively, to disappear.

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‘Favorable’ NNT for sublingual grass allergy tablets

BY BRUCE JANCIN
Frontline Medical News

HOUSTON – The number needed to treat with Timothy grass sublingual immunotherapy tablets for allergic rhinitis to achieve a clinically meaningful response is 7.9, Dr. Stephen R. Durham reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

What the low number needed to treat (NNT) means in this instance is that, on average, 7.9 children or adults with Timothy grass–induced allergic rhinitis with or without conjunctivitis would need to be treated with Merck’s sublingual immunotherapy tablet (SLIT) rather than placebo daily for 3 years in order for 1 additional patient to obtain sustained benefit. Sustained benefit was defined as at least 50% well days for the entire grass pollen season during each of the 3 treatment years plus the subsequent 2 years of no treatment, explained Dr. Durham of Royal Brompton and Harefield Hospitals and Imperial College, London.

The risk-benefit ratio of SLIT was favorable as reflected in a NNH (treatment-related systemic allergic reaction) of 303. NNH was 305 when recalculated using epinephrine usage as the harmful endpoint.

A “well day” was considered as a day with no use of open-label rescue medication and in which the worst score recorded was “none” or “mild” for each of the four nasal and two ocular symptoms measured.

This NNT analysis was based upon pooled data from six pivotal randomized, double-blind, phase III, placebo-controlled clinical trials totaling 3,094 patients, according to Dr. Durham. A separate analysis of the same pooled data using a different definition of favorable response – that is, a total combined daily symptom and daily medication score of 3 or less during the entire grass pollen season during the 3 treatment years, plus the following 2 no-treatment years – yielded an NNT of 9.4.

The maximum total daily symptom score during any given year was 18, while the maximum daily medication score per year was 30-36, depending upon whether the participant was a child or adult, and whether the study was conducted in Europe or the United States. The risk-benefit ratio of SLIT for allergic rhinitis in the pooled analysis was favorable as reflected in a number needed to harm of 303, with harm defined as a treatment-related systemic allergic reaction. When the NNH was recalculated using epinephrine usage as the harmful endpoint, the NNH was closely similar at 305.

Merck’s Timothy grass SLIT, marketed as Grastek, is FDA-approved for treatment of allergic rhinitis in adults and children as young as 5 years of age. Dr. Durham reported receiving research grants and serving as a consultant to Merck, ALK, and Stallergenes. The NNT analysis was funded by Merck, and the phase III clinical trials on which the analysis was based were supported by ALK and Merck.

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FRONTLINE MEDICAL NEWS

Dr. Amber M. Patterson discusses an investigational three-shot immunotherapy regimen for grass pollen-induced rhinoconjunctivitis in adolescents. To view, scan the QR code or visit www.chestphysician.org.

Early pneumonia linked with asthma, wheeze

BY BIANCA NOGRADY
Frontline Medical News

Lower respiratory illness in childhood is associated with later development of asthma and wheeze that can persist into adulthood, and that are considered risk factors for adult chronic obstructive pulmonary disease, a prospective study has found.

Researchers assessed the lung function of 646 children – 338 of whom had experienced lower respiratory illness (LRI) before age 2 and 308 controls – and found those who had early pneumonia had a nearly twofold increase in the risk of asthma and wheeze up to age 26.

They also had the most severe subsequent deficits in lung function, while those with early nonpneumonia LRI had smaller but still significant impairments in lung function and an increased risk of wheeze, according to a report published online March 2 in Pediatrics (2015;135 [doi:10.1542/peds.2014-3060]).

The children who were included in this study were part of a birth cohort of 1,246 healthy infants enrolled between 1980 and 1984 in the Tucson Children’s Respiratory Study.

Participants included in the current study were required to have complete follow-up for LRIs during the first 3 years of life and to have at least one pulmonary function test completed at ages 11, 16, 22, or 26 years.

Physician-diagnosed asthma with active symptoms and active wheeze during the previous year were assessed prospectively by questionnaires completed by the participant’s parents at ages 11, 13, and 16 years and by the participant at ages 18, 22, 24, 26, and 29 years, according to the researchers.

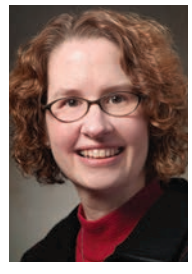
After the investigators adjusted for covariates, participants with early pneumonia had a significantly higher risk of active physician-diagnosed asthma (odds ratio: 1.95; 95% confidence interval: 1.11-3.44) during the previous year up to age 29 years, compared with those with no LRI during early life.

Early pneumonia was also associated with a significantly increased risk of active wheeze during the previous year up to age 29 years (OR: 1.94; 95% CI: 1.28-2.95) as were other LRIs, although the association with the latter was much weaker than that for pneumonia (OR: 1.37; 95% CI: 1.09-1.72), according to the authors.

Participants with early pneumonia had a significantly higher risk of active physician-diagnosed asthma during the previous year up to age 29 years.

“Because there is considerable evidence that asthma associated with airflow limitation is a strong risk factor for subsequent chronic obstructive pulmonary disease, the prevention of early-life pneumonia and of the factors that determine low lung function in infancy may contribute significantly to decrease the public health burden of chronic obstructive pulmonary disease,” wrote Dr. Johnny Y.C. Chan of Kwong Wah Hospital, Kowloon, Hong Kong, and the University of Arizona, Tucson, and his coauthors.

VIEW ON THE NEWS



Dr. Susan L. Millard, FCCP, comments: The researchers in the Tucson Children’s Respiratory Study have contributed greatly to our fund of knowledge regarding risk factors for childhood asthma. This study is no exception, showing that an acute pneumonia at a young age can have long-term sequelae.

No harm from restrictive transfusion threshold

BY MARY ANN MOON
Frontline Medical News

After cardiac surgery, using a restrictive transfusion threshold – forgoing transfusion until hemoglobin level drops to 7.5 g/dL – does not decrease morbidity or costs of care, compared with using a liberal transfusion threshold of 9 g/dL.

Several blood management guidelines and health policy statements recommend the restrictive approach in the hope that it will reduce the increasing demand on blood services and the high costs of storing, handling, and administering red-cell units, and also because transfusions following cardiac surgery have been linked to infection, low cardiac output, acute kidney injury, and increased mortality.

Clinicians remain uncertain about a safe threshold for transfusions in this setting, which is evidenced by the striking variation in transfusion rates among cardiac centers in the United States (8%-93%) and the United Kingdom (25%-75%), said Dr. Gavin J. Murphy of the British Heart Foundation and department of cardiovascular sciences, University of Leicester (England), and his associates.

They performed the Transfusion Indication Threshold Reduction (TITRe2) study to test the hypothesis that the restrictive approach is superior to the liberal approach regarding both postoperative morbidity and health care costs. Adults undergoing nonemergency cardiac surgery at 17 specialty centers in the United Kingdom were randomly assigned to a restricted (1,000 patients) or a liberal (1,003 patients) transfusion threshold. The median patient age was 70 years, and 68% were men. Most of the procedures were CABG or valve surgeries.

Contrary to expectations, the primary outcome – a composite of serious infection or an ischemic event such as stroke, MI, gut infarction, or acute kidney injury within 3 months – occurred in 35.1% of patients in the restrictive-threshold group and 33.0% in the liberal-threshold group. Secondary outcomes, including length of ICU stay and rates of clinically significant pulmonary complications, also were similar between the two study groups. Rates of other serious postoperative complications were similar, at 35.7% and 34.2%, as was general health status as assessed via the EuroQol Group 5-Dimension Self-Report Questionnaire, further contradicting the study hypothesis.

Mean health care costs were similar between the two study groups: the equivalent of $17,762 U.S. dollars with restrictive-threshhold transfusions and $18,059 with liberal-threshold transfusions, Dr. Murphy and his associates noted (N. Engl. J. Med. 2015 March 12 [doi:10.1056/NEJMoa1403612]).

Unexpectedly, 3-month mortality was significantly higher with restrictive- than with liberal-threshold transfusions (4.2% vs 2.6%). This association persisted in sensitivity analyses and "is a cause for concern," but it may be due to chance alone, they said.

The National Institute for Health Research's Health Technology Assessment Program, the NIHR Bristol Biomedical Research Unit in Cardiovascular Disease, and the British Heart Foundation supported the study.

VIEW ON THE NEWS

Dr. John Spertus comments: Transfusion rates need debate. Findings like those of Murphy et al. provide a great opportunity for discussion and debate, which could lead to development of a consensus on the best postoperative care for these patients. Cardiac surgery departments should review the TITRe2 trial results and decide which threshold they deem to be the most appropriate for transfusion.

The extreme range in hospitals' rates of transfusion in cardiac surgery – from less than 5% to more than 90% – is extraordinary. Having clinicians actively debate the evidence presented in TITRe2, create transparent interpretations, develop protocols, and hold themselves accountable for following those protocols would represent important steps for improving patient care.

Dr. John Spertus is at the University of Missouri-Kansas City and Saint Luke's Mid America Heart Institute, Kansas City. Dr. Spertus made these remarks in an editorial accompanying Dr. Murphy's report (N. Engl. J. Med. 2015 March 12 [doi:10.1056/NEJMe1415394]).

Biopsy bests HRCT for lung fibrosis, has risks

BY RICHARD M. KIRKNER
Frontline Medical News

Surgical lung biopsy performs well and is relatively safe for evaluating suspected interstitial lung diseases, but may be especially helpful in confirming the diagnosis and directing the treatment of patients with idiopathic pulmonary fibrosis with atypical signs and symptoms.

In patients with immune disorders or severe respiratory dysfunction, or on mechanical ventilation, clinicians should weigh the diagnostic benefits of surgical lung biopsy (SLB) against its potential risks, according to a systematic review and meta-analysis of 23 studies published between 2000 and 2014, comprising 2,148 patients. Dr. Qian Han of the Guangzhou Institute of Respiratory Disease in China led the investigative team.

The meta-analysis focused on diagnostic yield of biopsy samples and postbiopsy mortality within 90 days of surgery (J. Thorac. Cardiovasc. Surg. 2014 [doi:10.1016/j.jtcvs.2014.12.057). The mean age of patients across the studies ranged from 36 to 62 years. The population included 1,632 (76%) who had undergone video-assisted thoracic surgery (VATS) and 268 (12.5%) who had open-lung biopsy.

Slightly more than one third (33.5%) of diagnoses involved idiopathic pulmonary fibrosis, followed by nonspecific interstitial pneumonia (12%), hypersensitivity pneumonitis (9.6%), cryptogenic organizing pneumonia (7.5%), sarcoidosis (6.8%), and connective tissue disease related to interstitial lung disease (4%).

The median diagnostic yield across all studies was 95%, ranging from 42% to 100% depending on the study. One study showed a diagnostic yield below 70%. Eight studies showed that the biopsy influenced a change in the treatment plan 42%-90% of the time. In the entire meta-analysis, treatment plans were altered for 59.5% of patients who received a specific diagnosis and in 55.2% of those without a definitive diagnosis.

"These results suggested that an alteration in treatment may not be directed by a definitive histological diagnosis, and nonspecific histological results could also be useful in clinical practice," Dr. Han said.

Eleven of the studies used CT guidance to obtain biopsies without a preference to lobe, but two studies predisposed to the right lobes had diagnostic yields of 84% and 94%. One study avoided the lingual or middle lobe, with a diagnostic yield of 97%, and another focused on the lingular lobe only, with a 100% yield. Two studies showed that biopsy samples from lingual or middle lobes had the same diagnostic yield as did those from other lobes.

With regard to diagnostic performance based on biopsy numbers, one study showed that multiple biopsies may increase the diagnostic yield. Twelve studies obtained one to three samples, and among them eight studies suggested one sample containing both lesion and normal tissue was sufficient to represent pathological changes. One study showed that multiple biopsies may increase diagnostic yield.

Of the 16 studies that provided sufficient data on mortality rates, the pooled 30- and 90-day mortality rates were 2.2% (95% CI 1.0-4.0%) and 3.4% (95% CI 1.8-5.5%), respectively. The composite postoperative mortality rate was 3.6% (95% CI 2.1%-5.5%).

In their discussion, Dr. Han and colleagues addressed the controversy surrounding lingual vs. middle lobe biopsy by noting that high-resolution CT (HRCT) can be valuable in identifying the appropriate biopsy location. While multiple studies supported the effectiveness of only one biopsy as long as it contained both normal and abnormal tissue, the researchers pointed out that future studies evaluating biopsy samples would do well to evaluate biopsy number combined with sample size.

HRCT, while highly specific, may be less sensitive than SLB in the diagnosis of idiopathic pulmonary fibrosis, they found. Two studies the meta-analysis looked at compared the diagnostic yield between SLB and HRCT; SLB finally diagnosed idiopathic pulmonary fibrosis in 75%-91% of suspected cases and in 19%-74% of cases when HRCT did not raise suspicion of the disease. "These findings suggested that HRCT, albeit highly specific, is less sensitive in the diagnosis of IPF, therefore necessitating the utility of SLB in the diagnosis of these HRCT-omitted cases," Dr. Han said.

On the safety issue, while studies that excluded patients on mechanical ventilation reported lower mortality rates and two studies identified ventilator dependence as an independent risk factor for mortality, the investigators reported that the higher mortality rates were probably the result of a sicker patient population rather than the SLB procedure itself. They wrote that to "indiscreetly refuse" to perform SLB in these patients is "overcautious and inappropriate" given the benefits of SLB in validating diagnoses and influencing treatment plans.

These findings suggested that HRCT, albeit highly specific, is less sensitive in the diagnosis of IPF, therefore necessitating the utility of SLB in the diagnosis of these HRCT-omitted cases.

Dr. Han and his colleagues reported having no relevant disclosures.

VIEW ON THE NEWS

Dr. Katie S. Nason comments: The role of surgical biopsy in the high-risk population with interstitial lung disease is well suited for surgical review because thoracic surgeons must weigh the risks, including potential mortality, and benefits when discussion options with patients and families.

Current guidelines suggest that SLB is no longer essential for diagnosis of idiopathic pulmonary fibrosis, and they now consider an HRCT scan showing unusual interstitial pneumonia (UIP) sufficient for diagnosis. However, in the absence of diagnostic imaging criteria for UIP, specifically honeycombing, surgical lung biopsy with interpretation by an expert pathologist is necessary and should be performed to further define patients with possible UIP. Comprehensive application of this approach will delineate circumstances in which a surgical biopsy will be more informative than an HRCT scan as well as when a surgical biopsy is not necessary.

A multi-institutional, international registry is needed to collect and better understand data on the diagnostic yield and mortality after SLB for interstitial lung disease.

Dr. Nason is an assistant professor of cardiothoracic surgery at the University of Pittsburgh. She made her remarks in an invited editorial commentary that accompanied the article.

VITALS

Key clinical point: Surgical lung biopsy is helpful to confirm interstitial lung disease in patients with unique signs and symptoms, but the benefit of SLB should be balanced against the risks in patients with more severe disease.

Major finding: In two studies that compared the diagnostic yield between SLB and HRCT; SLB diagnosed idiopathic pulmonary fibrosis in 75%-91% of suspected cases and in 19%-74% of cases when HRCT did not raise suspicion of the disease.

Data source: Meta-analysis of 23 studies published between 2000 and 2014 and involving 2,148 patients.

Disclosures: The National Natural Science Foundation of China Young Investigator Funding supported the work. The investigators reported having no conflicts of interest.

For your patients with chronic obstructive pulmonary disease (COPD) who require maintenance bronchodilator treatment

Help Your Patients Breathe Better With ANORO ELLIPTA

Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist 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.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

ANORO ELLIPTA significantly improved trough (predose) FEV_1 by 167 mL vs placebo (*P*<0.001) at Day 169[1]

A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared the efficacy and safety of ANORO ELLIPTA (n=413) and placebo (n=280), each administered once daily by the ELLIPTA inhaler. The primary endpoint was trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).[1]

Once-daily ANORO ELLIPTA

The first and only FDA-approved product for patients with COPD combining 2 long-acting bronchodilators in 1 inhaler

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

Reference: 1. Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546.

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

ANORO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

ANORO™ ELLIPTA™
(umeclidinium and vilanterol inhalation powder)
FOR ORAL INHALATION USE

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) 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 LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting $beta_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

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

5.2 Deterioration of Disease and Acute Episodes

ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.

ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting $Beta_2$-Agonists

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

5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.

5.5 Paradoxical Bronchospasm

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

5.6 Hypersensitivity Reactions

Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.

5.7 Cardiovascular Effects

Vilanterol, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

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

5.8 Coexisting Conditions

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.9 Worsening of Narrow-Angle Glaucoma

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

5.10 Worsening of Urinary Retention

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

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

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

- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

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

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

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.

12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when

considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

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

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

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

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

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

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

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. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

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

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

ANORO ELLIPTA was developed in collaboration with Theravance.

GSK
Research Triangle Park, NC 27709

Revised 12/2013 ANR:1BRS

NETWORKS: Bronchopleural fistula therapy, low-dose CT scans for lung cancer screening

Interventional Chest/ Diagnostic Procedures

The use of bronchoscopically deployed valves for the treatment of bronchopleural fistula has been reported broadly. Currently, the Spiration IBV™ is approved as a Humanitarian Device by FDA for use in "prolonged air leaks of the lung or significant air leaks that are likely to become prolonged air leaks, following lobectomy, segmentectomy, or lung volume reduction surgery" (Spiration IBV Instructions For Use URL www.spiration.com/IFU). In the absence of extensive study, this technique has been granted several CPT codes for placement (**31647** and **31651**) and removal (**31649**) and the accompanying balloon occlusion to identify the leak (**31634**) (Kovitz et al. *CHEST*. 2013;144[2]:661). Interestingly, the most widely reported use of these devices is for nonapproved indications. Valves have been used in patients in the ICU on ventilators and ECMO (Mahajan et al. *J Thorac Cardiovasc Surg*. 2013;145[3]:626); in patients with CF bronchiectasis as a bridge to transplant, for complications of TB and various other disease-specific spontaneous as well as iatrogenic complications (Fischer et al. *J Heart Lung Transplant*. 2012;31:334) (El-Sameed et al. *Lung*. 2012;190[3]:347).


DR. GILDEA

In most cases, precise balloon localization is performed but also total lobar treatment reported. In the largest series by Travaline et al. (*CHEST*. 2009;136[2]:355), with 40 patients, only 8 of 40 had postsurgical indications; 1-9 Emphasys EBV valves were used; and there was a median air leak of 119 days prior to valve implantation with 93% of patients improving. Therefore, the largest study available is not the approved device, not the approved indication, and not the typical patient for which the cost-saving indication of early postoperative air leaks could be made. This reflects the clinical challenges that these complex patients present, leaving us with an untenable clinical problem.

Reimbursement data are lacking. Medicare claims data will not be available until 2016, and coverage decisions are spotty because of the "experimental" designation. Since these devices exceed $2,000 each and one to four valves are used in each case with higher numbers reported, this technique presents a high risk to institutions. While there may be cost savings for treating patients confined to the hospital for prolonged air leak to expedite discharge of approved and unapproved indications under the DRG; outpatient management makes these devices cost prohibitive in the absence of positive coverage decisions. Further investigation of actual utility in possible off-label indications, complications, and cost effectiveness is desperately needed before institutions take on the financial risks of offering valve treatment. Standard thoracic surgery management and/or other potentially less expensive techniques must be explored first until valve therapy is further defined.

Dr. Thomas Gildea, FCCP
Steering Committee Member

Thoracic Oncology

In a landmark decision, the Centers for Medicare & Medicaid Services announced in February a final national coverage determination providing for Medicare coverage of lung cancer screening with low-dose CT scanning (LDCT) (http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274; http://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2015-Press-releases-items/2015-02-05.html). CMS said that coverage would be effective immediately, though codes for the various services associated with the screening process are still forthcoming.


DR. TANOUE

Several members of the CHEST Thoracic Oncology NetWork contributed to the recent joint ACCP/ATS Policy Statement on lung cancer screening, which helped inform the CMS decision (Mazzone et al. *CHEST*. 2015;147[2]:295). The policy statement defines nine components necessary for high-quality lung cancer screening programs:

1. *Who is offered screening?* Adults aged 55-77 years with at least a 30 pack-year history of smoking, currently smoking, or having quit within the past 15 years. Screening may not be appropriate for patients with substantial comorbid conditions.
2. *How often and for how long to screen?* Screening is performed annually until age 77 and discontinued if smoking has ceased for 15 years or if health problems limit life expectancy or the ability to undergo curative treatment.
3. *How the CT is performed.* LDCT should be performed according to ACR-STR specifications, including compliance with recommended mean radiation dose.
4. *Lung nodule identification.* Establish a standard approach defining a "positive" finding, based on nodule size and characteristics.
5. *Structured reporting.* Establish a structured reporting system for description of nodules.
6. *Lung nodule management algorithms.* Develop standardized approaches to lung nodule management, including access to technology and technical expertise for nodule evaluation (PET imaging, minimally invasive thoracic surgery, nonsurgical approaches, etc), and incorporate a tracking system for nodule management and patient/provider communication.
7. *Smoking cessation.* Screening programs must have an integrated smoking cessation program.
8. *Patient and provider education.* Providers and patients should be educated in the benefits and harms of screening to inform decision support discussions, with development of educational materials and tools.
9. *Data collection.* Screening programs should collect data relating to program quality, as outlined above. Data should be collected about screening outcomes (complications, cancer diagnoses, survival, etc). An annual summary should be reported to an oversight body with the authority to credential screening programs.

For the full policy statement: Mazzone et al. Components necessary for high-quality lung caner screening: American College of Chest Physicians and American Thoracic Society Policy Statement. *CHEST*. 2015;147[2]:295.

Dr. Lynn Tanoue, FCCP
Chair

Pediatric Chest Medicine

Optimizing Health-care Quality and Preventing Child Health Disparities

As the health-care environment continues its trend toward increasing complexity, patients and families are likely to benefit from a progressive focus on multispecialty, multidisciplinary, and collaborative approaches to care in order to optimize clinical outcomes and prevent health-care disparities.

The Institute of Medicine's pillars of quality health care include equity, effectiveness, efficiency, patient centeredness, safety, and timeliness. Pediatrics offers unique opportunities with regard to quality improvement interventions and prevention of child health disparities. Health maintenance, when successfully applied in the pediatric population, may have profound and lifelong impact. Furthermore, early identification and optimal management of medical conditions may prevent disease-associated morbidity and mortality. Particular attention in pediatrics must be paid to the impact of development (emotional, physical, and cognitive), socioeconomic status, access to care, and education. While the disease focus and identified goals of clinical quality improvement (CQI) interventions may vary, factors that are likely to support favorable health outcomes include the utilization of multidisciplinary teams and the integration of invested non–health-care partners (community health workers, schools, etc); family involvement, and cultural sensitivity in intervention planning and implementation are also crucially important (Chin et al. *Pediatrics* 2009;124[suppl 3]: S224).

A number of CQI efforts in pediatric asthma have supported the assertion that the utilization of multidisciplinary and interprofessional teams can enhance clinical outcomes. The wider perspective of evolving care complexity and increased survival of previously fatal childhood disease requiring care transitions suggests that the traditional confines of medical specialty and subspecialty training will be continually challenged (Bridges et al. *Medical Education Online*. 2011;16:6035); a model of shared expertise and collaborative care is expected to support health outcomes while effectively managing resource utilization in an economically challenging environment. Approaches to medical education and training that provide experience in interprofessional teamwork are advocated.

Dr. Mary A. Nevin, FCCP, FAAP
Steering Committee Member

Continued on page 43

New CHEST membership model now in effect

To keep pace with the rapidly changing health-care environment and remain relevant to your practice, we have updated the CHEST membership to allow our members to do more.

Collaborate More

In response to emerging, team-based health-care models, CHEST opened up membership to the entire chest medicine team, including clinicians-in-training. Collaborative care is a priority focus as we move forward. These changes make our members more successful at delivering high quality, collaborative patient care.

Engage More

The new membership model lets you choose the benefits and the degree to which you want to engage with CHEST. Instead of membership levels based on your title, age, and stage of career, you can select the level you want based on the resources and benefits you want to access. This gives you the power to decide what CHEST membership means for you.

Achieve More

We've streamlined our online systems to make it easier for you to access the resources we offer.

The simplified structure provides a rich array of benefits and value in three member categories. See the table below for details, and learn more at chestnet.org/join. Effective this month, members have been placed into a new member category that aligns with their current level of engagement. If you have questions or want to upgrade to a higher category, contact CHEST Customer Support at chestcustomersupport@chestnet.org.

BASIC Annual Dues: $295*	ENHANCED Annual Dues: $395*	PREMIUM Annual Dues: $495*
Benefits: › Online access to the journal *CHEST* › Discounts for courses and products › Free online access to clinical practice guidelines › CHEST Career Connection access › Opportunity to join CHEST NetWorks › Access to the e-Community portal	Benefits: **All the benefits of BASIC membership, PLUS:** › Print access to the journal *CHEST* › Opportunity to become/remain an FCCP › Leadership opportunities › Invitation to networking events	Benefits: **All the benefits of ENHANCED membership, PLUS:** › Enhanced discounts › Advance access to course registration › Advance access to hotel reservations › Invitation to VIP events

*Discounts will be available for clinicians in training, nonphysician/nondoctoral clinicians, retired clinicians, and physicians outside the United States or Canada.

Find the best science at CHEST 2015, in Montréal

When CHEST travels to Montréal, Oct. 24-28, 2015, there will be no shortage of science to explore. The CHEST Annual Meeting 2015 will offer up the best in chest medicine and opportunities to improve patient care. You'll find state-of-the-art simulation education, late-breaking abstracts, postgraduate courses, and countless educational tools.

If that's not enough science for you, Montréal provides many opportunities to further explore medical and natural sciences.

COURTESY WIKIMEDIA COMMONS

Musée des Hospitalières de l'Hotel-Dieu de Montréal

Medical Science

Are you interested in medical history? Montréal is home to the Musée des Hospitalières and the Osler Library of the History of Medicine. Both of these museums require preappointments.

Visit the Musée des Hospitalières. This museum relates the history of the Hospitallers of Saint Joseph of Hôtel-Dieu, a history forever entwined with that of Montréal. You'll learn about history, medicine, and religious art.

Or, visit the Osler Library of the History of Medicine. This library opened in 1929 to house the collection of rare medical books donated by Sir William Osler, the renowned physician and McGill graduate and professor. This library is a major resource for historical research in the health sciences.

Natural Sciences

Visit the Spaces for Life museums, including the Biodome, Botanical Garden, Insectarium, and Rio Tinto Alcan Planetarium.

These museums make up the largest natural sciences museum complex in Canada, and they aim to raise awareness about protecting the environment.

The Biodome allows you to explore a re-creation of American ecosystems: tropical rain forest, Laurentian maple forest, Gulf of St. Lawrence, and the Labrador coast and sub-Antarctic islands.

You'll learn about the natural environment and the interactions between animal and plant species.

The Montréal Botanical Garden is known as one of the world's greatest botanical gardens, with 22,000 plant species and cultivars, 10 exhibition greenhouses, Frédéric Back Tree Pavilion, and more than 20 thematic gardens. Get out and enjoy natural beauty and fresh air.

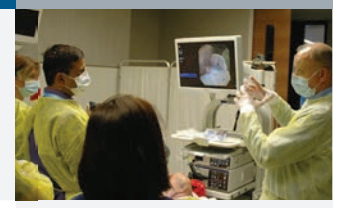
One of the largest insect museums in North America, the Insectarium is home to 250,000 specimens of living and naturalized insects. You'll be delighted by the incomparable adaptations and surprising behavior of insects.

The Rio Tinto Alcan Planetarium uses cutting-edge technology to create a unique experience of the universe through two complementary shows – one focused on science, the other more whimsical. Explore the sky and the stars with a fresh look at astronomy.

Montréal will captivate you with its unique collection of science museums, and CHEST 2015 will keep you current with the latest developments in chest medicine.

Don't miss out on the opportunity to inspire and energize your patient care. Learn more and register today at chestmeeting.chestnet.org.

2015 Education Calendar



Live Learning Courses

Advanced Critical Care Echocardiography
May 28-30

Celebration of Pediatric Pulmonology
June 12-13

Comprehensive Pleural Procedures
June 19-20

Difficult Airway Management
July 16-18

Mechanical Ventilation: Advanced Critical Care Management
July 30-August 1

Procedures for the Intensivist
August 7-8

Ultrasonography: Essentials in Critical Care
September 10-12

Comprehensive Bronchoscopy With Endobronchial Ultrasound
September 24-26

Focused Thoracic and Vascular Ultrasound
November 12-13

Critical Care Echocardiography
November 14-15

Ultrasonography: Essentials in Critical Care
December 3-5

> Learn More **chestnet.org/live-learning**

CHEST Board Review
Gaylord National Resort & Convention Center
Washington, DC

Critical Care Medicine
August 21-24

Sleep Medicine
August 22-24

Pulmonary Medicine
August 26-30

CHEST Annual Meeting 2015
October 24-28
Montréal, Québec, Canada

Montréal CANADA
October 24 - 28

Innovation, Simulation, and Training Center
Glenview, Illinois

Calendar subject to change. For most current course list and more information, visit chestnet.org/live-learning.

CHEST Annual Meeting 2015

Team Up at CHEST 2015

Connecting a Global Community in Clinical Chest Medicine

Montréal CANADA
October 24 - 28

Join us in Montréal, October 24-28, for CHEST 2015, your connection to education opportunities that will help optimize the clinical decisions you make.

Don't miss:

- More than 300 general sessions
- Postgraduate courses
- Simulation program
- Original investigation presentations
- New diagnostic and treatment solutions in the exhibit hall
- More

> Learn More and Register **chestmeeting.chestnet.org**

New This Year

Interdisciplinary program topics will address issues across the disciplines. Session speakers representing each role of the chest care team will present from their perspective, so your group can attend together for practical updates relevant to everyone.

Team up to advance patient care.

XV CHEST Central America Congress in Managua

BY DR. MARK J. ROSEN, MASTER FCCP
Medical Director, CHEST

On March 12-14, 2015, a delegation of CHEST members successfully conducted the XV CHEST Central America Pulmonary and Thoracic Surgery Congress in Managua, Nicaragua. Organized by Dr. Hector Cajigas, FCCP, and Dr. Jorge Cuadra, FCCP, this educational activity has been a yearly tradition since the year 2000 when Dr. Udaya Prakash, Master FCCP, organized the first pro bono group to attend this congress in Tegucigalpa, Honduras. Since then, many members of the College have collaborated with the Central America Federation of Pulmonary and Thoracic Surgery to conduct this program, seen as one of the highlights in the region's educational events in chest medicine.

This year's CHEST delegation included Dr. Luisa Bazan, Section Head of Sleep Medicine, Dr. Hector R. Cajigas, FCCP, Director Pulmonary Hypertension Program, and Dr. Javier Diaz-Mendoza, FCCP, Adult Interventional Pulmonary Medicine, Henry Ford Hospital, Detroit, Michigan; Dr. Paul R. Boesch, Pediatric Interventional Pulmonary Medicine, Dr. Udaya Prakash, Master FCCP, and Dr. Mark Wylam, Adult and Pediatric Pulmonary Medicine, Mayo Clinic, Rochester, Minnesota; and Dr. Angel Coz Yataco, FCCP, Associate Program Director Pulmonary and Critical Care Fellowship Program, University of Kentucky in Lexington, Kentucky.

Faculty at the XV CHEST Central America Pulmonary and Thoracic Surgery Congress, from left to right: Dr. Wylam, Dr. Prakash, Dr. Cajigas, Dr. Cuadra, Dr. Bazan, Dr. Diaz-Mendoza, Dr. Coz Yataco, and Dr. Boesch.

The organizers look forward to the next Congress to be held in San Jose, Costa Rica, in the spring of 2017, and to inviting CHEST members to participate on the faculty.

Pioneering an oncology clinical immersion program

BY LISA STANICK, MBA
Director, PREP Operations

The American College of Chest Physicians (CHEST) recently launched the inaugural Oncology PREP (Professional Representative Education Program) clinical immersion program. This PREP was developed by CHEST Enterprises under an exclusive licensing arrangement with the American Society of Clinical Oncology (ASCO), the world's leading professional organization representing physicians who care for people with cancer. The first Oncology PREP curriculum is focused on metastatic castration-resistant prostate cancer and is being conducted for sales representatives from a leading pharmaceutical company.

ONCOLOGY | PREP
An American Society of Clinical Oncology Educational Program

Oncology PREP is designed for pharmaceutical sales representatives to bolster their knowledge of best practices and innovative advances in oncology care in an effort to equip them to make informed contributions to discussions of disease management and patient care. Multidisciplinary teams at leading cancer centers, selected by CHEST, teach the patient-focused curriculum. Industry customers have no input into the content of the curriculum to ensure a completely unbiased educational experience for representatives.

General topics in each Oncology PREP course include risk factors, screening techniques, the latest procedures used in diagnosis and staging, treatment options and care management, and the evolving use of biomarkers. Participants also engage in patient simulation cases and panel discussions.

"CHEST has been offering this program for over 10 years in the pulmonary disease area, and we are proud to apply the success of that program to launch the first Oncology PREP clinical immersion program," said Dr. John C. Alexander Jr., FCCP, President, CHEST Enterprises Board of Directors. "Our team is honored to work with ASCO to launch this program to address the needs of prostate cancer clinicians, sales representatives, and, ultimately, patients."

In January 2015, a select group of sales leaders from the pharmaceutical company participated in a pilot program taught by a team of oncologists and urologists.

Courses for field representatives are currently being conducted at prominent cancer centers. Participants who successfully complete the program will receive an assessment-based certification of completion valid for 3 years.

In addition to CHEST PREP and Oncology PREP programs, CHEST has agreements with the American Congress of Obstetricians and Gynecologists (ACOG) and the Society of Interventional Radiology (SIR) to develop and conduct PREP clinical immersion programs in the areas of women's health and interventional radiology.

If you would like more information about these exciting PREP programs and the opportunity to develop curriculum content or participate as faculty, or if you would like to find out how your hospital or medical center can become a course site, please contact Lisa Stanick, Director – PREP Operations, at lstanick@chestnet.org or 224/521-9518.

CHEST voices input on Maintenance of Certification

BY DR. KEVIN M. CHAN, FCCP
ABIM Pulmonary Disease Board Member

NICKI AUGUSTYN
Senior Vice President, Education

On March 23, 2015, CHEST joined 26 other medical specialty societies at the American Board of Internal Medicine's (ABIM's) biannual Liaison Committee on Certification and Recertification (LCCR) meeting.

Originally established in 2002 to facilitate communication between ABIM and its medical society partners, this year's LCCR meeting took on special importance. It was the first gathering since ABIM President Richard J. Baron issued the admission, "We got it wrong," and announced changes to the Maintenance of Certification (MOC) program developed in response to requirements put in place by the American Board of Medical Specialties. This communication also unveiled the main short-term changes to the program:

- Introducing more flexible ways to meet the self-assessment requirement, including recognizing more CME activities for MOC points.
- Suspension of the practice assessment, patient voice, and patient safety requirements for 2 years.
- Altering the language used in public reporting of diplomate's status to "participating in MOC" (vs "meeting/not meeting").
- Updating the MOC exam.
- Holding fees at current or lesser levels through 2017.

The March meeting marked the initiation of efforts to engage more broadly physicians and the medical community in shaping the future of MOC.

Medical society representatives conveyed the sentiments of their respective memberships regarding the recent changes to the MOC program. Feedback ranged from messages of support for ABIM's willingness to listen to the community and the steps taken in recent months to frustrations and questions around the specifics of how the existing program will be operationalized and what shape the practice assessment might take in the future.

On the latter, while agreement around the principles of practice assessment was expressed, ABIM is not yet prepared to define what shape may be taken but remains committed to an open dialogue.

Participants, including CHEST, explored in a workshop setting the process of "community-centered design," a practice that invites the community to codesign the future of ABIM by helping articulate its core desires and motivations around shared values. Emphasis was placed on the roles that ABIM and the medical societies might play to advance this value. Physician and staff representatives from the societies were asked to consider the following two hypotheses posited by ABIM's Board of Directors:

It was clear to us that ABIM is committed to working with the medical community to transform its programs, and we encourage everyone to share their thoughts with us.

Shared Purpose Statement:
"Our community values the idea of doctors 'keeping up' throughout their medical careers."

ABIM's Role in the Community:
"In collaboration with the community, ABIM implements standards through which physicians, their patients, and the profession know they are keeping up."

Each group was tasked with testing these hypotheses by defining and then critiquing each other's definitions of what it means to be "keeping up" or, to put it another way, "staying current."

The exercise highlighted both the common themes and different viewpoints that existed across definitions, while also setting the stage for future conversations about how ABIM can:

- Work with the internal medicine community to develop a shared purpose and clarify ABIM's role in the community.
- Collaborate with medical societies and others in the community to define the areas in which the principles of co-creation could be applied in the context of MOC.
- Create future paths of engagement through which ABIM will seek input.

The meeting ended with LCCR participants sharing feedback on how ABIM could best partner with medical societies and other organizations to connect with the community.

Meeting participants identified the ABMS, ACGME, and ACCME, among others, as organizations with which ABIM should collaborate moving forward.

Formal discussions such as those described at the LCCR are integral as ABIM furthers the collective conversation with the medical community; however, ABIM is also receiving direct feedback from diplomates, and several in-person meetings and workshops are planned over the next few months.

The LCCR was an important opportunity for us to provide feedback to ABIM on behalf of CHEST and to work with them to improve the future.

It was clear to us that ABIM is committed to working with the medical community to transform its programs, and we encourage everyone to share their thoughts with us (kevichan@med.umich.edu or naugustyn@chestnet.org) or with ABIM directly. We are here to assure you that as a CHEST member, we will relay your concerns to ABIM. CHEST is committed to maintaining a voice in this ongoing dialogue and to providing you with the tools to achieve initial and maintenance of ABIM subspecialty certification.

This Month in *CHEST:* Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP
Editor in Chief

Predischarge Bundle for Patients With Acute Exacerbations of COPD to Reduce Readmissions and ED Visits: A Randomized Controlled Trial. By Dr. J. H. Jennings et al.

Understanding Why Patients With COPD Get Readmitted: A Large National Study to Delineate the Medicare Population for the Readmissions Penalty Expansion. By Dr. T. Shah et al.

Transbronchial vs Transesophageal Needle Aspiration Using an Ultrasound Bronchoscope for the Diagnosis of Mediastinal Lesions: A Randomized Study. By Dr. M. Oki et al.

Change of Junctions Between Stations 10 and 4 in the New International Association for the Study of Lung Cancer Lymph Node Map: A Validation Study from a Single, Tertiary Referral Hospital Experience. By Dr. S. Lee et al.

Health Literacy, Cognitive Function, Proper Use, and Adherence to Inhaled Asthma Controller Medications Among Older Adults With Asthma. By Dr. R. O'Conor et al.

CHEST Foundation supports chest medicine in Africa

When **Dr. Peter Moschovis** visited Sub-Saharan Africa in January 2013, he never imagined that 2 years later, he'd be helping design a pulmonary program in a hospital serving 8 million people. Although Massachusetts General Hospital (MGH) has been collaborating with Mbarara University of Science and Technology (MUST) for 15 years, Mbarara Regional Referral Hospital in Mbarara, Uganda, had only a single antiquated spirometer, no bronchoscopes, and no physicians with specialized training in respiratory diseases. Mbarara Hospital had a critical need for training in pulmonary medicine and basic equipment for diagnosis and treatment of lung diseases.

"Ugandan medical residencies are voluntary. Unfortunately, only those with time and personal resources or scholarship support are able to obtain the education needed for specialty training. Most Ugandan doctors are general practitioners practicing in low-resource settings and lack the tools to diagnose and treat many respiratory diseases," notes Dr. Moschovis.

Dr. Moschovis (front left) with staff from the Mbarara Regional Referral Hospital in Mbarara, Uganda.

In 2013, Dr. Moschovis won a CHEST Foundation Community Service Grant Honoring Dr. D. Robert McCaffree, Master FCCP. The original premise of Dr. Moschovis' project was aimed at developing a curriculum and purchasing a used spirometer and bronchoscope. After receiving the grant, Moschovis learned that even used bronchoscopes were cost prohibitive. However, with determination, Dr. Moschovis set out to acquire donated equipment from corporate sponsors in hopes of further developing the Mbarara Hospital's program and is now using the grant funds to help launch the region's first pulmonary clinic.

"The CHEST Foundation grant helped gain the credibility we needed to meet with others who had an interest in supporting our program. Being a CHEST Foundation grant winner opened doors for us."

Thanks to the CHEST Foundation grant, Dr. Moschovis and his colleagues at MGH were able to help Mbarara Hospital obtain a new bronchoscope, develop a curriculum in pulmonary medicine for medical residents and staff at MUST, and enable physicians from the United States to mentor Ugandan internists who have an interest in pulmonary medicine. The training and equipment has allowed Ugandan internists to improve the diagnosis and treatment of respiratory diseases, ultimately improving patients' lives and the care they receive.

"Through Dr. Moschovis' training program and the donated equipment, MUST has been better able to identify difficult diagnoses and deliver better patient care," says Dr. Dan Muyanja, the new director of the pulmonary program at MUST.

The CHEST Foundation provides millions of dollars to proudly support worldwide community service and research programs. Join us in making a global impact in chest medicine by supporting the CHEST Foundation (www.chestnet.org/foundation).

CLASSIFIEDS

Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

Central Maine Medical Center
The Central Maine Medical Family

Inpatient Pulmonary/Critical Care Position in Maine:

Join a vibrant Inpatient Pulmonary and Critical Care group of five in beautiful Maine! Central Maine Medical Center (CMMC) is seeking a BC/BE Pulmonary/Critical Care Physician to help provide pulmonary and critical care services to medical, surgical, trauma, and cardiac patients.

CMMC is a 250 bed, full service regional referral center with busy trauma, cardiothoracic, interventional radiology, vascular, and neurosurgical programs. We have a state-of-the art 19 bed ICU and a separate 16 bed cardiothoracic unit.

Competitive salary and benefits including CME, paid vacation, student loan repayment, 403b match, and relocation fees. Work schedule revolves around a 6 day on and 6 day off philosophy, with no longer than 12 hour shifts per day. There is no outpatient clinic work.

Residents and visitors enjoy an extraordinary lifestyle that revolves around top school systems, ski resorts, lake and ocean water sports, theatre, and world-class dining.

Interested applicants may submit CV to Julia Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauver@cmhc.org . Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

MOUNT NITTANY HEALTH

Mount Nittany Health Pulmonologist Opportunity

Position Highlights include:
Mount Nittany Physician Group currently provides a range of pulmonary medicine services including interventional procedures, allergy/immunology, and sleep medicine.

* Established practice with 6 physicians and growing patient demand within an expanding health system
* Mix of outpatient pulmonary medicine/procedures and inpatient pulmonary consults.
* Fully integrated EMR, electronic documentation and order entry
• Limited intensivist work available if desired, not required

Mount Nittany Medical Center, located in State College, PA, is a not-for-profit, 260 bed, acute care facility housing both inpatient and outpatient medical/surgical services. It is a growing and thriving facility offering unparalleled patient-focused care made all the more distinctive by excellent physicians, ease of access and facilities and systems engineered for the best in patient care.

State College, home to **Penn State University**, is a vibrant college town. It offers a diverse culture, a beautiful environment, excellent public and private schools, countless options for dining, theatre, sports and recreation, nightlife and more. This is all located within a safe, friendly community that makes the area perfect for raising a family. University Park Airport is located only five miles from town and State College offers easy access to Interstates 80 and 99.

Shelly Palumbo
Physician Recruiter
State College, PA
(814)231-6892 or (814)558-6223
michele.palumbo@mountnittany.org
www.mountnittany.org

UNIVERSITY of COLORADO HEALTH

Fort Collins, Colorado

Colorado Health Medical Group is seeking a Pulmonologist/Critical Care trained physician. Sleep Medicine training desirable but not required. Will rotate in two hospitals and our Loveland based clinic. Call is 1:11 nights and 1:5-6 weekends. Physician will be doing general Pulm/CC procedures and read sleep studies from outlying facilities.

If interested, email your CV to
Briann.Leone@uchealth.org

GUNDERSEN HEALTH SYSTEM®

PULMONARY/CRITICAL CARE PHYSICIAN

Gundersen Health System is seeking a BC/BE Pulmonary/Critical Care physician. Join a well-established group of board certified pulmonary and critical care physicians. Opportunity for critical care only is also available. Practice highlights:

- Your practice will include critical care, inpatient and outpatient pulmonary medicine
- Navigational, interventional bronchoscopies and other invasive procedures on a rotational basis
- Very minimal weekend call
- Part time sleep practice is optional
- Active participation in the teaching program
- Clinical research opportunities are available

Gundersen Health System, based in LaCrosse, WI, is a physician-led, integrated healthcare system employing over 450 physicians. Gundersen offers an excellent work environment, competitive salary and great benefits package. Most importantly, you will find a rewarding practice and an excellent quality of life.

Kalah Haug (608)775-1005, kjhaug@gundersenhealth.org
Gundersenhealth.org/MedCareers
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Pulmonary Vascular Disease

Updates in Lung Allocation Scoring System

Despite therapeutic advances, pulmonary arterial hypertension (PAH) remains a progressive illness with a high mortality. Lung transplantation is a therapeutic option for refractory cases (George et al. *Pulm Circ.* 2011;1[2]:182).

The previous lung allocation scoring system (LAS) did not include markers of disease severity specific to PAH, which led to underestimation of waitlist urgency (Benza et al. *Transplantation.* 2010;90[3]:298). The LAS is an adjusted scale from 0 to 100 that represents a weighted combination of predicted 1-year waitlist and post-transplant mortality.

DR. ELWING

The initial LAS was heavily influenced by diagnosis, FVC% predicted, oxygen requirement, need for mechanical ventilation and pulmonary artery pressure for non-PAH groups. It did not include hemodynamics or other indices of right ventricular function for PAH. Six-minute walk distance (6MWD) was only included as a bivariate factor of less than or greater than 150 feet (Egan. *Am J Transplant.* 2006;6[6]:1212).

Implementation of the LAS system in 2005 led to an increase in the proportion of transplants for IPF and improved the likelihood of transplantation for all diagnoses including PAH (Valapour et al. *Am J Transplant.* 2014;14[S1]:139). LAS decreased waitlist times, increased transplant volumes and reduced overall waitlist mortality without a change in post-transplant survival (Hachem and Trulock. *Semin Thorac Cardiovasc Surg.* 2008;20[2]:139). However, wait-list mortality for PAH transplant candidates has remained high compared to other groups (Chen et al. *Am J Respir Crit Care Med.* 2009;180[5]468) because of the failure to include key markers of PAH disease severity.

DR. GIRGIS

After further analyses of survival data, a comprehensive modification to the LAS was instituted in 2015 (OPTN. http://optn.transplant.hrsa.gov/media/1154/optn_lung_policy_update_02-2015.pdf. Accessed 04-10-15). This algorithm now includes right atrial pressure, cardiac index, serum bilirubin, serum creatinine and a continuous measure of 6MWD, all recognized important prognostic markers in PAH.

This optimization should allow better risk stratification for PAH patients, minimizing wait list-time for those with the most advanced disease and improve post-transplant outcomes. Clinicians should be aware of this change to the LAS and consider early referral to a transplant center for appropriate candidates.

Dr. Jean M. Elwing, FCCP
Steering Committee Member

Dr. Reda E. Girgis, FCCP
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Pulmonary Rehabilitation: An Often Overlooked Therapy

Recently, more COPD patients have been asking about new long-acting bronchodilators that are currently being advertised. While there is no doubt that long-acting bronchodilators play a role in the management of moderate to severe COPD, many patients have not been offered pulmonary rehabilitation, or they feel that it will not benefit them.

Pulmonary rehabilitation is defined as a comprehensive intervention that is patient-tailored to include exercise, education, and behavior change designed to improve the physical and psychological condition of people with chronic respiratory diseases (Spruit et al. *Am J Respir Crit Care Med.* 2013;180[8]:e13).

Much of the literature stems from COPD where pulmonary rehabilitation has been demonstrated to reduce dyspnea, improve quality of life, and increase exercise capacity. Even in those with severe disease (FEV_1 36% predicted), improvements in skeletal muscle function also have been demonstrated (Maltais et al. *Am J Respir Crit Care Med.* 1996;154:442).

Pulmonary rehabilitation has also been shown to be beneficial following admission for acute exacerbation of COPD and may reduce subsequent hospitalizations (Seymour et al. *Thorax.* 2014;69[2]:181; Puhan et al. *Cochrane Database Syst Rev.* 2011 Oct 5;(10):CD005305. doi: 10.1002/14651858.CD005305.pub3. *Review*).

Pulmonary rehabilitation is no longer just for those with COPD. Patients with interstitial lung disease, bronchiectasis, cystic fibrosis, asthma, pulmonary arterial hypertension, lung cancer, and those undergoing lung transplantation have benefited following pulmonary rehabilitation (Spruit et al. *Am J Respir Crit Care Med.* 2013;180[8]:e13).

Those with diffuse interstitial lung diseases, including usual interstitial pneumonia, experience improvements in dyspnea, quality of life, and 6-minute walk distance (Dowman et al. *Cochrane Database Syst Rev.* 2014 Oct 6;10:CD006322. doi:10.1002/14651858.CD006322.pub3. *Review*).

We need to encourage our patients to attend pulmonary rehabilitation stressing that this therapy is as important as pharmacologic interventions.

Furthermore, we need to insist that this efficacious intervention with minimal adverse effects is paid for by insurance providers and that our institutions ensure the availability of quality programs.

Dr. Nathaniel Marchetti, FCCP
Vice-Chair

CHEST Enterprises Welcomes New COO

Bob Musacchio, PhD, is the new Chief Operating Officer of CHEST Enterprises and Senior Vice President (SVP) of Business Development for CHEST.

DR. MUSACCHIO

Bob joins the organization following a 35-year career with the American Medical Association (AMA), most recently as Senior Vice President and Chief Development Officer for the association. His previous roles have included responsibility for global business development, business operations, information technology, membership, and publishing, contributing significantly to the overall operating performance of the AMA for all of its major products and customer markets. Welcome, Bob!

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Molecular blood test for non-invasive assessment of pulmonary nodules

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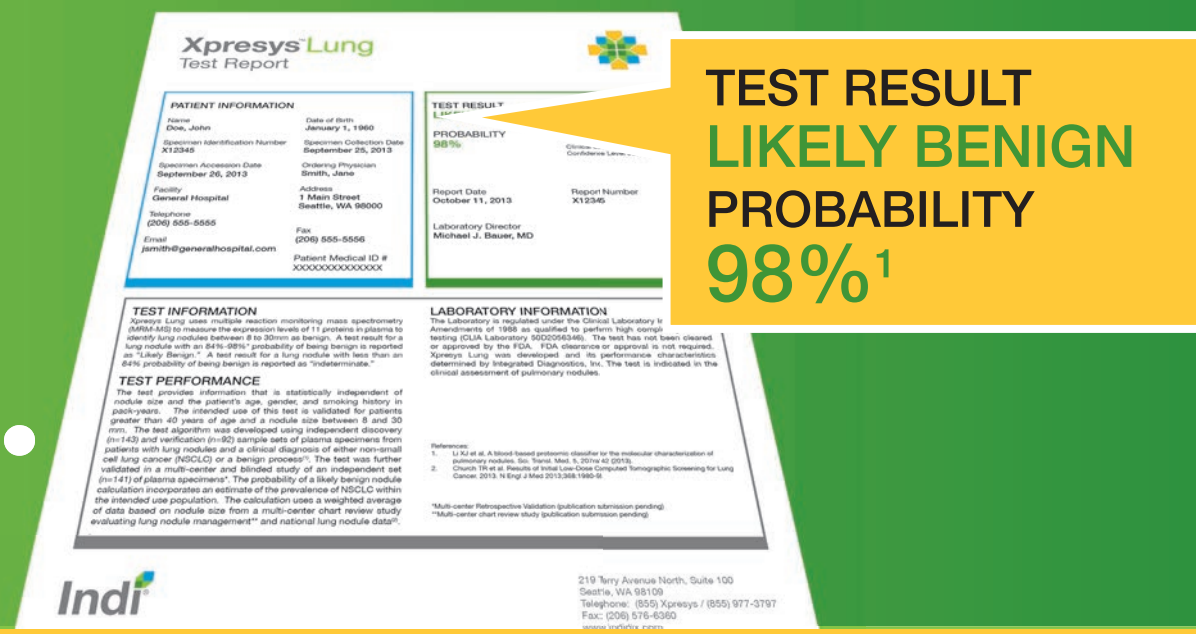

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LIKELY BENIGN
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98%[1]

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Why use Xpresys Lung?

- Vast majority of 8-30 mm nodules are benign
- Potential to reduce unnecessary invasive procedures
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What is Xpresys Lung?

- Non-invasive blood test for pulmonary nodules
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References:
1. Vachani, Anil, MD. "Validation of a Multi-Protein Plasma Classifier to Identify Benign Lung Nodules: Journal of Thoracic Oncology." LWW. Journal of Thoracic Oncology, 14 Jan. 2015. Web. 26 Jan. 2015 .