VOL. 9 • NO. 1 • JANUARY 2014

CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Looking back at CHEST 2013

Maimonides repeats its win at CHEST Challenge 2013. Each year, teams compete "Jeopardy!" game–show style for cash prizes and boasting privileges. More photos, page 30.

COURTESY ACCP

Quitting smoking cuts Ca patients' death risk

BY SHARON WORCESTER
Frontline Medical News

Men who continue smoking after a cancer diagnosis have significantly greater risk of death from any cause than did those who quit smoking at the time of diagnosis, according to findings from the prospective population-based Shanghai Cohort Study.

Of 1,632 men from that ongoing study who developed cancer after enrollment and who were eligible for the current analysis, 931 died during 25 years of follow-up, of whom 747 were smokers at the time of their cancer diagnosis. Of these smokers, 214 (29%) quit at the time of diagnosis, 197 (26%) smoked persistently after diagnosis, and 336 (45%) smoked intermittently after diagnosis.

After the researchers adjusted for age at diagnosis, education, cumulative number of pack-years of prediagnosis

See **Death risk** • *page 20*

'Meaningful use' reporting for Stage 2 extended until 2017

Revision offers time to improve Stage 3.

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Medicare officials have extended Stage 2 of the "meaningful use" Electronic Health Record Incentive Program through the end of 2016.

The change, announced in December, means that the earliest that physicians will progress to Stage 3 of the meaningful use requirements will be in January 2017. Officials at the Centers for Medicare and Medicaid Services are still developing the Stage 3 requirements and expect to issue a proposed rule sometime in the fall of 2014.

The extension primarily affects physicians who began attesting to meaningful EHR use in 2011 and 2012. Those physicians were scheduled to advance to Stage 3 in 2016, after 2 years of working on Stage 2. The change means they will have an additional year at Stage 2.

"The goal of this change is twofold: First, to allow CMS and [the Office of the National Coordinator for Health Information Technology] to focus efforts on the successful implementation of the enhanced patient engagement, interoperability, and health information exchange requirements in

See **'Meaningful use'** • *page 14*

INSIDE

News

Energy drinks hit at the heart
Taurine plus caffeine in beverages altered left ventricular contractility. • 2

Leg raise as sepsis tool
Increase in velocity time integral may predict fluid response in septic patients. • 6

Blood pressure goal
Elderly systolic goal is relaxed to below 150 mm Hg. • 7

Opinion

Does SCIP measure quality?
Effectiveness is questioned in efficacy debate. • 10

Practice Economics

SGR fix
Budget deal avoids 20% Medicare pay cut for now. • 14

SLEEP STRATEGIES: OSA syndrome takes toll on cognitive domain

BY DR. KENNETH CHET WALTERS AND DR. CHITRA LAL, FCCP

Obstructive sleep apnea syndrome (OSAS) is a very common, underrecognized disorder with significant implications for individual and global health. Over the past few decades, our understanding of OSAS has improved, leading to earlier diagnosis and treatment. In turn, increasing awareness of this disorder has yielded greater recognition of the sequelae associated with OSAS, including heart disease, stroke, and cognitive impairment.

See **Sleep Strategies** • *page 34*

CHEST Physician
151 Fairchild Ave.,
Suite 2,
Plainview, NY 11803-1709

CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY

Energy drinks amped up left ventricular contractility

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – Consumption of an energy drink containing caffeine and taurine slightly, but significantly, altered left ventricular contractility in healthy volunteers, while consuming the same amount of caffeine alone did not lead to an alteration in contractility in a prospective study.

"A possible explanation for this finding could be the presence of taurine, which has been shown to increase the release of calcium in muscles," Dr. Jonas Dörner reported at the annual meeting of the Radiological Society of North America.

He and his colleagues performed cardiac magnetic resonance imaging (MRI) in 31 volunteers before and 1 hour after consumption of an energy drink containing caffeine (32 mg/100 mL) and taurine (400 mg/100 mL). The average patient age was 27.7 years.

Postconsumption images revealed that mean peak strain increased 7% from baseline (–22.84 vs. –24.35; $P < .0001$) and peak systolic strain rate – a measure of deformation with respect to time – increased by 6% (–1.19 vs –1.26; $P = .0032$), reported Dr. Dörner, with the University of Bonn, Germany.

The investigators did not find any significant changes in heart rate, systolic blood pressure, or left ventricular (LV) ejection fraction. LV end-diastolic volume and LV stroke volume increased significantly by 2% and 4%, respectively.

The same imaging protocol was repeated on a different day in 10 patients after consumption of caffeine only. No significant differences were seen in mean peak strain (–22.99 vs. –23.20) or mean peak systolic strain rate (–1.15 vs. –1.16) with caffeine alone, although diastolic blood pressure was significantly elevated and LV end-diastolic volume significantly decreased, Dr. Dörner said.

The current study took advantage of an MRI technique called complementary spatial modulation of magnetization (CSPAMM) for LV myocardial tagging. The technique is more exact than traditional ultrasound or speckle tracking and is able to measure very small differences in strain, he explained in an interview.

Although the differences in strain in the study were "subtle," the findings need to be taken into perspective because younger patients often consume higher doses of caffeine and taurine via energy drinks. According to the Food and Drug Administration, caffeinated sodas cannot contain more than 71 mg of caffeine per 12 fluid ounces (approximately 20 mg/100 mL), but energy drinks often contain three times that amount, he noted.

More than 500 brands of energy drinks are available worldwide, and 30%-50% are consumed by children, teenagers, and young adults. A report by the European Food Safety Authority found no adverse effects for up to 1 g of taurine per kilogram of body weight per day.

Further studies are needed to evaluate the effect of long-term energy drink consumption and the effect of these drinks on patients with heart disease and in combination with alcohol, Dr. Dörner said.

Dr. Dörner reported having no financial disclosures; a coauthor reported consulting for Medtronic.

pwendling@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Marcos I. Restrepo, FCCP, comments: This series of observations calls into attention the possible risks of the multiple energy drinks (and its contents) available in the market. The worry that high levels of caffeine and taurine found in energy drinks affect contractility in healthy volunteers should raise concerns in patients with comorbid conditions or unidentified heart problems. In addition, regular consumers of energy drinks may worry about potential heart problems, if the consumption occurs repetitively and for longer periods. There is hope that regulatory agencies consider these findings and promote more studies to address the possible risks related to ingestion of energy drinks.

IN THIS ISSUE

News From CHEST • 21

NetWorks
Infections, e-cigarettes, lipid guidelines, and mechanical ventilation • 25

CHEST Physician Is Online
CHEST Physician is available on the Web at chestphysician.org.

Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of *CHEST Physician*.

CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

E-mail: chestphysiciannews@chestnet.org

CHEST Physician, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST Physician** is provided by Frontline Medical Communications Inc. Content for NEWS FROM CHEST is provided by the American College of Chest Physicians.

POSTMASTER: Send change of address (with old mailing label) to CHEST Physician, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.

CHEST Physician (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $230.00 per year. Phone 973-206-3434, fax 973-206-9378.

Editorial Offices 5635 Fishers Lane, Suite 6100, Rockville, MD 20852, 240-221-2400, fax 240-221-2548

Scan this QR Code to visit chestnet.org/chestphysician

Frontline Medical Communications Society Partners
Director, FMC Society Partners Mark Branca
Editor in Chief Mary Jo M. Dales
Executive Editors Denise Fulton, Kathy Scarbeck
Managing Editor Lori Buckner Farmer
Creative Director Louise A. Koenig
Print Production Manager Rebecca Slebodnik
Director of Recruitment Advertising Robert H. Zwick
Display Advertising Managers Derek Lundsten, 973-713-2650, dlundsten@americanmedicalcomm.com, Lauren Provenzano, 609-306-5776, lprovenzano@americanmedicalcomm.com
Advertising Offices 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378
Classified Sales Representative John Baltazar 917-488-1528, jbaltazar@americanmedicalcomm.com

FRONTLINE MEDICAL COMMUNICATIONS
Stephen Stoneburn, Chairman
Douglas E. Grose, EVP Digital Business Development/CFO
Marcy Holeton, President/CEO, Clinical Content Division
Alan J. Imhoff, President/CEO, Medical News Division
JoAnn Wahl, President, Custom Solutions

Jim Chicca, Executive Director, Operations
Carol Nathan, VP, Custom Programs
Lori Raskin, Corporate Director, Marketing & Research
Donna Sickles, Corporate Director, Audience Development

In affiliation with Global Academy for Medical Education, LLC.
Sylvia H. Reitman, MBA, Vice President, Medical Education & Conferences
David J. Small, MBA, Vice President, Events

Now approved

Opsumit®

macitentan tablets 10 mg

Please see Brief Summary of Prescribing Information, including ***BOXED WARNING*** *for embryo-fetal toxicity, on adjacent pages.*

ACTELION

Opsumit®
macitentan tablets 10 mg

Rx only

BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm *[see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), Use in Specific Populations (Pregnancy)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Use in Special Populations (Females and Males of Reproductive Potential)]*.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (OPSUMIT REMS Program)]*.**

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see *Warnings and Precautions (Embryo-fetal Toxicity)* and *Use in Specific Populations (Pregnancy)*].

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see *Dosage and Administration section 2.2 in full Prescribing Information* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see *Warnings and Precautions (OPSUMIT REMS Program)*].

OPSUMIT REMS Program

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see *Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity),* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

Notable requirements of the OPSUMIT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (Females and Males of Reproductive Potential)*].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	**Placebo (N=249)**
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see *Adverse Reactions (Clinical Trial Experience)*].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see *Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)*].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see *Warnings and Precautions (Embryo-fetal Toxicity)*]
- Hepatotoxicity [see *Warnings and Precautions (Hepatotoxicity)*]
- Decrease in Hemoglobin [see *Warnings and Precautions (Hemoglobin Decrease)*]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2: Adverse Reactions

Adverse Reaction	**OPSUMIT 10 mg (N=242)**	**Placebo (N=249)**
Anemia	13%	3%
Nasopharyngitis/pharyngitis	20%	13%
Bronchitis	12%	6%
Headache	14%	9%
Influenza	6%	2%
Urinary tract infection	9%	6%

DRUG INTERACTIONS

Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see *Clinical Pharmacology (Pharmacokinetics)*].

Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see *Clinical Pharmacology (Pharmacokinetics)*]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see *Clinical Pharmacology (Pharmacokinetics)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications (Pregnancy)*].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Nursing Mothers

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

Pediatric use

The safety and efficacy of OPSUMIT in children have not been established.

Geriatric use

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Females and Males of Reproductive Potential

Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see *Boxed Warning* and *Dosage and Administration section 2.2 in full Prescribing Information*].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Males

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see *Warnings and Precautions (Decreased Sperm Counts)* and *Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility*].

OVERDOSAGE

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal impairment: Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

OPSUMIT® (macitentan)

Drug Interactions

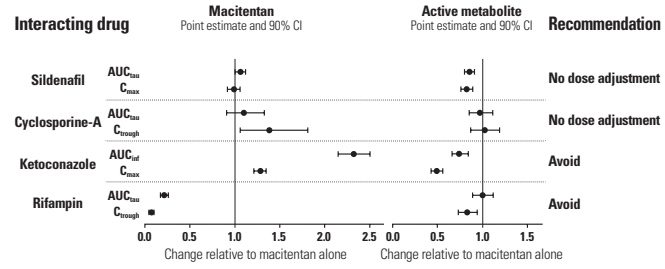
In vitro studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Effect of other drugs on macitentan: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1



Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see *Drug Interactions (Strong CYP3A4 Inhibitors)*].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

Mutagenesis: Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an *in vivo* micronucleus test in rats.

Impairment of Fertility: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Animal Toxicology

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

Manufactured for:
Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20131018

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013.

Passive leg raise may predict fluid response in sepsis

BY M. ALEXANDER OTTO
Frontline Medical News

SEATTLE – Septic patients are more likely to respond to fluid therapy if their velocity time integral – a Doppler ultrasound measurement of blood flow across the left ventricular outflow tract – increases by 15% or more with a passive single-leg raise, according to a preliminary, observational study of 32 patients at New York Methodist Hospital.

'People who don't respond with a VTI greater than 15% have higher repeat lactate levels.'

DR. BALK

A passive leg raise to 45 degrees simulates a 250- to 500-cc fluid bolus. "We have found that people who don't respond with a VTI greater than 15% have higher repeat lactate levels. Instead of giving them 2 L [of fluid] and then reassessing, maybe they're patients you want to start on pressors right away," Dr. Andrew Balk said at the annual meeting of the American College of Emergency Physicians.

Echocardiogram machines can automatically calculate VTI. The measurement, which Dr. Balk and his associates obtained from the apical five-chamber view, is a surrogate for, and can be used to calculate, cardiac output. Poor response to fluid challenge indicates that fluids are less likely to increase cardiac output and more likely to cause fluid overload, said Dr. Balk, associate director of the clinical ultrasound division at the hospital.

The patients' mean age was 68 years, and those with valvular pathology and atrial fibrillation were excluded from the study.

The group's mean baseline VTI was 22 cm (range, 15-29 cm), which leg raise elevated to a mean of 26 cm (18-34 cm), an increase of about 18% (4%-36%). A subsequent 2-L normal saline challenge increased VTI to a mean of 33 cm.

The mean baseline lactate level was 3.2 mmol/L (1.2-5.2 mmol/L), and 2 mmol/L (1-3 mmol/L) after the 2-L challenge. The percent change in VTI correlated significantly with the percent change in serum lactate levels. "Below-average responsiveness to the initial small fluid bolus was associated with a higher repeat lactate value … which suggests an inverse relationship between a patient's fluid responsiveness as observed by the change in VTI and the severity of sepsis," the researchers concluded.

The VTI/leg-raise approach looks promising as a possible quick bedside marker that identifies patients who need aggressive treatment, without the need for central line measurements, Dr. Balk said.

He reported having no disclosures.

aotto@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: The search for noninvasive measures of or predictors for volume responsiveness in patients with sepsis continues. VTI is the integral of velocity and time, that is, the distance a small blood bolus travels. When multiplied by the cross-sectional area of the aortic outflow tract, this would result in stroke volume.

Since one would not expect the cross-sectional area to change significantly after a fluid bolus, alterations in VTI should reflect alterations in stroke volume.

While promising, this technique is not as easy as the authors make it sound and is operator dependent, even though the machine does the calculating. The incident angle of the probe must remain constant during the leg raise (for a period of at least 90 seconds). The user must know whether valve pathology or left ventricular impairment is present and, if so, the degree.

In addition, massively volume-depleted patients may fail to respond adequately to a passive leg raise.

One would be remiss to rely on this small study, which does not report sensitivity or specificity, to establish a reliable percent increase for predicting lactate response or to guide fluid therapy.

However, this research by Dr. Balk and colleagues is certainly aimed in the right direction.

Meta-analysis: Statins beneficial, even after age 75

BY BRUCE JANCIN
Frontline Medical News

DALLAS – Reassurance regarding the cardiovascular benefits of statin therapy in the elderly, even in those above age 75, is provided by a new meta-analysis by the international Cholesterol Treatment Trialists' Collaboration.

The meta-analysis, which included 174,099 participants in 27 major, published, randomized controlled trials with a median follow-up of 4.9 years, should go a long way toward banishing physician and patient uncertainty about the appropriateness of statin therapy in the elderly. It's evident that such uncertainty is widespread from recent studies indicating only about half of patients over age 65 are on statin therapy post myocardial infarction (MI). Moreover, the controversial new prevention guidelines don't address the use of statins in patients over age 75, citing a lack of persuasive evidence because such patients were often excluded from participation in the major statin trials (J. Am. Coll. Cardiol. 2013 [doi: 10.1016/j.jacc.2013.11.002]).

Yet in the new meta-analysis by the University of Oxford–based Cholesterol Treatment Trialists' Collaboration, 7% of all participants – that's nearly 13,000 patients – were over age 75. That's a large enough number to be able to draw tentative conclusions. In addition, another 33% of subjects in the meta-analysis were aged 66-75 years, Dr. Jordan Fulcher observed in presenting the results at the American Heart Association scientific sessions.

Dividing the nearly 175,000 subjects into four age groups – 55 and younger, 56-65, 66-75, and over 75 – the investigators found that while statin therapy significantly reduced nonfatal MI, cardiovascular death, all-cause mortality, and major vascular events in each of the four age groups, there was also a significant trend for smaller relative risk reductions with advancing age. For example, the incidence of nonfatal MI or coronary heart disease (CHD) death in statin-treated patients aged 55 years or younger was 1.1%, compared with 1.5% in controls, for a 31% relative risk reduction per 39-mg/dL decrease in low-density lipoprotein (LDL) cholesterol, while in the over-75 group the rates were 2.8% versus 3.3%, for a less robust 24% relative risk reduction, reported Dr. Jordan Fulcher of the University of Sydney.

For major vascular events, which are a composite of nonfatal MI, CHD death, stroke, or coronary revascularization, patients aged 55 years or less who achieved a 39-mg/dL reduction in LDL had a 25% reduction compared with controls. This relative risk reduction was only 15% in the over-75 group after adjustment for baseline differences.

The Cholesterol Treatment Trialists' database includes virtually all the landmark statin trials whose acronyms are household names within medicine.

Funding for the trialists' work is provided by the U.K. Medical Research Council and other national health research organizations. Dr. Fulcher reported having no financial conflicts of interest.

bjancin@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Jun Chiong, FCCP, comments: Strategies to prevent future cardiovascular events in adults aged >75 years should be individualized, but this study showed that the benefit of long-term statin therapy extends to this age group. Physicians still must balance the benefits of secondary atherosclerotic cardiovascular disease prevention with the risk it may carry in older adults. It's still important to see future controlled studies that will clarify medication regimens, lifestyle modifications, and also revascularization strategies that will yield the greatest benefit/lowest risk in this rapidly expanding age group.

Elderly systolic target relaxed to below 150 mm Hg

BY MITCHEL L. ZOLER
Frontline Medical News

The group of experts who had constituted the JNC 8 panel, a team assembled in 2008 by the National Heart, Lung, and Blood Institute to update official U.S. hypertension management guidelines, set the target blood pressure for the general population aged 60 years or older to less than 150/90 mm Hg, a major break from longstanding practice to treat such patients to a target systolic pressure of less than 140 mm Hg.

This decision, which the panel contends was driven by lack of clear evidence for extra benefit from the below–140 mm Hg target, will surely prove controversial, along with the panel's relaxing of target blood pressures for patients with diabetes or chronic kidney disease to less than 140/90 mm Hg (increased from 130/80 mm Hg in the prior, JNC 7 guidelines). That controversy would be a fitting final curtain for the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8), a project that courted controversy by running years longer than anticipated and then generating several plot twists during the final months leading up to Dec. 18, when the former JNC 8 panel published its hypertension management guideline (JAMA 2013 Dec. 18 [doi: 10.1001/jama.2013.284427]).

The new target of a systolic pressure of less than 150 mm Hg for hypertensive patients aged 60 years or older without diabetes or chronic kidney disease "is definitely controversial," said Dr. Paul A. James, cochairman of the panel and professor of family medicine at the University of Iowa in Iowa City.

"There is A-level evidence that getting blood pressure below 150 mm Hg results in improved outcomes that really matter, but we have no evidence at this time to support going lower," to less than 140 mm Hg. "The good news is that the panel is comfortable that we don't do harm," by treating patients to less than 140 mm Hg. "But why put patients at increased risk for medication adverse events?" he said in an interview.

Dr. James stressed that his group released their conclusions and guideline on their own, identifying themselves as "the panel members appointed to the Eighth Joint National Committee (JNC 8)." Leaders from the NHLBI announced last June that the agency would not issue cardiovascular disease management guidelines, and would instead fund evidence reviews and partner with other organizations to issue guidelines.

The former JNC 8 panel applied "a very narrow interpretation" of the clinical evidence where the evidence is very incomplete," said Dr. Michael A. Weber, professor of medicine at State University of New York, Brooklyn.

Dr. James had no disclosures. Dr. Weber said that he has been a consultant to Novartis, Takeda, and Forest.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

ACP urges changes to curb prescription drug abuse

BY JANE ANDERSON
Frontline Medical News

A new national Prescription Drug Monitoring Program is one of several clinical and policy recommendations from the American College of Physicians aimed at reducing patient abuse and street sales of drugs prescribed for pain, sleep disorders, and weight loss.

The proposed national Prescription Drug Monitoring Program potentially could help physicians avoid drug interactions and identify drug-seeking and "doctor shopping" behaviors, according to the policy paper published online in Annals of Internal Medicine (2013 Dec. 10 [doi: 10.7326/M13-2209]).

The paper also calls for the establishment of evidence-based, nonbinding guidelines regarding recommended maximum dosage and duration of therapy for patients taking controlled substance medications.

A 2010 survey found that 16 million Americans age12 and older had taken a prescription pain reliever, tranquilizer, stimulant, or sedative for nonmedical purposes in the previous year.

Additional efforts are urged to reduce substance abuse and to increase medical research on addiction and its causes and treatments.

"Prescription drug abuse is found throughout all aspects of our population," the ACP paper says.

Physicians have an ethical obligation to manage and relieve pain, the position paper said, yet they must do so responsibly and in accordance with scientific evidence. In the paper, ACP said it supports a comprehensive national policy on prescription drug abuse that covers education, monitoring, proper disposal, and enforcement.

According to a 2010 survey from the Substance Abuse and Mental Health Services Administration, 16 million Americans aged 12 years and up had taken a prescription pain reliever, tranquilizer, stimulant, or sedative for nonmedical purposes at least once in the previous year.

VIEW ON THE NEWS

Dr. Eleanor Summerhill, FCCP, comments: This ACP position paper provides recommendations to assist physicians and policymakers in addressing the difficult challenge of appropriately managing pain while deterring prescription drug abuse.

One of the most important proposals calls for the establishment of a national Prescription Drug Monitoring Program to more readily identify "doctor shopping" and other signs of abusive behaviors.

The recommendations are an important first step in providing a framework upon which a more comprehensive public health policy and supporting infrastructure may be built.

USPSTF gives final grades on lung cancer screening

BY WHITNEY McKNIGHT
Frontline Medical News

Low-dose computed tomography screening of those at high risk for lung cancer has received a grade B recommendation from the U.S. Preventive Services Task Force. Initially available for public comment in July 2013, the Task Force's recommendations are now final and published.

The action allows the Centers for Medicare and Medicaid to mandate this service be provided without charging a copay or deductible. Widespread availability of screening

Screening protocols for patients in the low-risk group should receive a grade C from the USPSTF.

DR. BACH

raises concerns about inappropriate use of low-dose computed tomography (LDCT) and the associated costs of the procedure, physician experts noted in editorials and interviews.

The USPSTF defines high-risk patients as heavy smokers who are aged 55-80 years and have a 30-pack-year or more habit, and former heavy smokers who have quit in the past 15 years. Screening should be discontinued once a person has not smoked for 15 years.

Patients also can be selected for screening based on risk factors other than tobacco use, including occupational exposures, radon exposure, family history, and incidence of pulmonary fibrosis or chronic obstructive lung disease.

Because of the potential for patients to experience "net harm, no net benefit, or at least substantially less benefit" from screening, the USPSTF stated it may be inappropriate to screen patients who have comorbidities that limit life expectancy, or who would be either unwilling or unable to have curative lung surgery.

Other forms of screening, including chest x-rays and sputum cytology, are not recommended because of their "inadequate sensitivity or specificity."

The USPSTF's recommendations are based largely on a systematic review of several randomized, controlled trials published between 2000 and 2013, including the National Lung Screening Trial. That study of more than 50,000 asymptomatic adults, aged 55-74 years, showed a 16% reduction in lung cancer mortality and a 6.7% reduction in all-cause mortality when patients were screened using LDCT. One cancer death was averted for every 320 patients screened, and one death from all causes was prevented in every 219 patients screened.

"Lung cancer causes as many deaths in the United States as the next three leading types of cancers combined, all of which already have screening interventions," wrote Dr. Frank C. Detterbeck, FCCP, of Yale University in New Haven, Conn., and Dr. Michael Unger, FCCP, of the Fox Chase Cancer Center in Philadel-

Continued on page 15

POINT/COUNTERPOINT

Does SCIP measure quality of care?

Excerpts from a debate at the annual meeting of the American Society of Anesthesiologists

Yes: SCIP is both efficacious and effective.

BY ROBERT S. LAGASSE, M.D.

The Surgical Care Improvement Project (SCIP) was a national campaign that set out to reduce surgical mortality and morbidity by 25% by 2010 through recommendations in targeted areas: wound infections, perioperative MIs, and venous thromboembolism. The recommendations have become pay-for-performance measures. There are seven in the area of infectious disease to reduce surgical site infections. There is one measure for reducing perioperative MI: Continue beta-blockers (for patients who are on them) in the perioperative period. For venous thromboembolism prevention, give prophylaxis within 24 hours before to 24 hours after surgery.

DR. LAGASSE

It's key to understand the difference between efficacy and effectiveness. I think we would all agree that the SCIP measures have efficacy. Efficacy trials determine whether an intervention produces the expected result under ideal circumstances. Effectiveness trials measure the degree of beneficial effect under "real-world" clinical conditions. The problem with effectiveness trials is that those real-world conditions may change the effect, or they might just change the ability to measure the effect.

I believe that the SCIP measures have proven efficacy because they all are based upon randomized controlled trials that were identified by systematic reviews amenable to meta-analysis. All of these measures are Level 1 recommendations, based on the highest forms of evidence. The studies that Dr. Barash uses to criticize SCIP measures are cohort studies. They do not randomize. There may be unknown confounding variables.

There have been effectiveness trials that show that the SCIP measures do work. One showed a 27% decrease in surgical site infections, another showed a 62% decrease in surgical site infections, and a third showed a 39% decrease in surgical site infections.

Perhaps the strongest endorsement of efficacy of the SCIP measures comes from Dr. Kaveh G. Shojania, who has written several reviews of the efficacy of medical interventions. He said there were 11 patient safety practices rated most highly in terms of strength of the evidence, and 3 are SCIP measures: appropriate use of prophylaxis to prevent venous thromboembolism in patients at risk, use of perioperative beta-blockers in appropriate patients, and appropriate use of antibiotic prophylaxis in surgical patients (AHRQ Publication No. 01-E058).

Several trials published by pretty good researchers in reputable journals show a lack of effectiveness of SCIP measures. Even those researchers admit to the efficacy of SCIP measures. The lead investigator of the best effectiveness trial, a retrospective cohort study, wrote, "There are several explanations as to why we did not observe an association between timely antibiotic administration and surgical site infection (SSI). The first is that timely antibiotic administration does not diminish SSI risk. This is an unlikely interpretation. There are numerous randomized controlled trials and observational studies that demonstrate the efficacy of prophylactic antibiotics in reducing SSI for various surgical procedures" (Ann. Surg. 2011;254:494-9).

The SCIP measures are based on best evidence. They are measurable and effectible, as demonstrated in multiple randomized controlled trials. Studies of effectiveness have had variable results due to methodological flaws.

A separate retrospective cohort study showed a decrease in SSI only if two or more SCIP recommendations were followed (JAMA 2010;303:2479-85). Shocking – if you give the wrong antibiotic at the

Yes *continued on following page*

No: Studies have not shown effectiveness.

BY PAUL BARASH, M.D.

When it was created, SCIP did not reflect reality. SCIP started at the U.S. Department of Veterans Affairs, which conducted a 10-year study. They found a 25% relative risk reduction, but that was only a 0.8% absolute risk reduction for the incidence of complications, a drop from about 3.1% to about 2.3% (Arch. Surg. 2002;137:20-7).

It would be great to have randomized controlled trials on the effectiveness of SCIP, but it's not happening. We're going to have to go by high-fidelity observational trials, which according to a number of researchers in the field, have the same impact as randomized controlled trials.

DR. BARASH

One study of 35,543 patients in 44 hospitals found a whopping 27% reduction in surgical site infections, but that was only a 0.6% absolute reduction, from about 2.5% to about 1.9% (Am. J. Surg. 2005;190:9-15). There was no significant difference between groups.

Another study showed improved compliance with SCIP measures, but no change in surgical site infection rate (Dis. Colon Rectum 2010;53:24-30). This is the theme in study after study after study.

A 2008 study enrolled 9,195 patients undergoing colorectal, orthopedic, or vascular surgery and looked at SCIP compliance vs. surgical site infection. The SCIP rate correlated with the hospital case mix. If you look at the SCIP rate in terms of antibiotic timing, SCIP is not significant. The study basically showed that variables other than timely antibiotic administration are affecting surgical site infection rates (J. Am. Coll. Surg. 2008;206:814-9).

Hospital performance on process measures may not be a good marker of surgical site infection or the outcome we're looking at, according to study findings that unmeasured effects may have a larger impact than measured effects.

Hospital performance on process measures may not be a good marker of surgical site infection or the outcome we're looking at, according to another study, which reported that unmeasured effects may have a larger impact than the measured effects (Health Serv. Res. 2008;43:1464-84).

There is a randomized controlled trial that randomized patients to strict control with the SCIP measures or routine treatment at the hospital. The SCIP-treated patients had nearly twice the incidence of surgical site infections as the patients receiving standard treatment. The authors concluded that combining each of the SCIP factors into one big category doesn't necessarily work (Arch. Surg. 2011;146:263-9).

Should we be evaluating outcome measures with performance measures (e.g., percent timely antibiotic administration) to determine whether they work or not? One editorial evaluated eight articles with data on 31,448 patients, looking just at antibiotic administration within 1 hour of surgery, a SCIP measure. It found a higher infection rate if antibiotics were administered within 30 minutes of incision (JAMA 2010;303:2527-8). There was no significant difference in another study between standard of care and SCIP for venous thromboembolism (Am. J. Surg. 2012;204:591-7).

When people find that SCIP is not working, they turn to other measures to reduce surgical site infection. The Comprehensive Unit-based Safety Program (CUSP) is targeted at a specific problem that a specific hospital is having in managing infections. It's not coming from Washington; it's based at the hospital. One study showed that following CUSP, there was a significant reduction in surgical site infections despite the fact that previous to that there was 95% compliance with SCIP standards (J. Am. Coll. Surg. 2012;215:193-200). SCIP was work-

No *continued on following page*

Yes *continued from previous page*

right time, it might not work.

Another retrospective cohort study found no association with adjusted complications and SCIP compliance. Hospitals in the lowest compliance group had patients in lower-income ZIP codes and lower unadjusted complication rates. So, poor people go home and don't come back, perhaps because of payment considerations. The study didn't have enough patients; it also used measures that don't apply to SCIP (Arch. Surg. 2010;145:999-1004).

SCIP did not design these measures for pay-for-performance programs. The intent was to decrease perioperative complications by 25% by 2010. When you start changing the baseline with pay-for-performance, it doesn't work. In a study by Hawkins et al., the authors tested the hypothesis that documented compliance with antibiotic prophylaxis guidelines on a pediatric surgery service does not reflect adherence to guidelines as intended.

In a 7-week observational study of elective pediatric surgical cases, adherence was evaluated for appropriate administration, type, timing, weight-based dosing, and redosing of antibiotics. Prophylactic antibiotics were administered appropriately in 141 of 143 cases (99%). Of 100 cases in which antibiotic prophylaxis was indicated, compliance was documented in 100% of cases in the electronic medical record; but only 48% of cases adhered to all five guidelines. Lack of adherence was due primarily to dosing or timing errors.

The SCIP measures, however, are based on best evidence. They are tightly linked with the desired outcomes. They are measurable and effectible, as demonstrated in multiple randomized controlled trials. Studies of effectiveness have had variable results due to methodological flaws.

Dr. Lagasse is a professor of anesthesiology and director of quality management at the Yale School of Medicine, New Haven, Conn. He is on the SCIP steering committee. He reported having no financial disclosures.

No *continued from previous page*

ing, but it wasn't affecting outcome.

Dr. Lagasse and I interpret one key study very differently. He abstracts a sentence from a Limitations section of the study and makes a sweeping generalization out of context. But the study showed no relationship between facility adherence to SCIP and the surgical site infection rate. The authors concluded, "Policies regarding continued SCIP measurement and reporting should be reassessed" (Ann. Surg. 2011;254:494-9).

The largest SCIP study from a single entity involved 32,459 patients in the Veterans Affairs medical system. Overall, antibiotics were administered within 28 minutes of surgical incision. Once they adjusted for confounders, they found no significant relationship between surgical site infection and the SCIP measures (JAMA 2013;148:649-57). No one has proven that giving antibiotics within 60 minutes of surgical incision yields a lower infection rate.

SCIP measures divert resources and divert clinical care. They obscure the nuances of care. They may harm the hospital and the provider, and they raise unnecessary legal risk if an antibiotic is not given within 60 minutes of incision.

Dr. Barash is a professor of anesthesiology at Yale University, New Haven, Conn. He reported having no financial disclosures.

Platelet inhibition test helps predict surgical bleeding

BY SHERRY BOSCHERT
IMNG Medical News

SAN FRANCISCO – Preoperative light transmission aggregometry assessments of platelet aggregation may help identify which patients on dual antiplatelet therapy are at greater risk of sustained bleeding from noncardiac surgery, a prospective study of 147 consecutive patients suggests.

The light transmission aggregometry (LTA) assessments of blood drawn immediately before noncardiac surgery were significantly lower in the 32% of patients with sustained bleeding than in the other patients.

All patients were on dual antiplatelet therapy, 95% of them on maintenance therapy with aspirin plus clopidogrel. Timing of the surgery was at the discretion of the surgeons. Treating physicians were blinded to LTA results. The mean preoperative

washout period for dual antiplatelet therapy was 1.5 days. Patients had vascular (76%), orthopedic (10%), abdominal (7%), or other (7%) surgery.

The ongoing study might help define a "bleeding cutoff" measure by LTA to better individualize the timing of surgery, Dr. Wolfgang Toller and his colleagues said in a poster session at the annual meeting of the American Society of Anesthesiologists.

In general, approximately 5% of patients in their first year of dual antiplatelet therapy undergo noncardiac surgery, which creates a conundrum for management. Discontinuing dual antiplatelet therapy before noncardiac surgery has been associated with a 20% risk of major adverse cardiac events, but there's a 20%-40% risk of moderate to severe bleeding if dual antiplatelet therapy is continued during noncardiac surgery, said Dr. Toller of the Medical University of Graz, Austria.

The 147 patients in the study underwent vascular surgery (76%), orthopedic surgery (10%), abdominal surgery (7%), or other surgical procedures (7%). All had been on P2Y12 receptor inhibitors within 7 days before surgery.

Investigators used the Chronolog 700 Lumi-Aggregometer to assess platelet aggregation in preoperative blood, using 5 mcm of adenosine diphosphate as the specific inductor for platelet aggregation.

Overall, they found an average 40% maximum change in light transmission from baseline after adding the adenosine diphosphate to blood samples. In patients with increased bleeding, however, the mean maximum change in light transmission was approximately 30% (suggesting less platelet aggregation), compared with a more than 40% change in patients who bled less from the surgery.

Dr. Toller reported having no financial disclosures.

sboschert@frontlinemedcom.com
On Twitter @sherryboschert

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: The vast majority of patients on dual platelet therapy (aspirin plus another agent such as clopidogrel) have had implantation of a drug-eluting coronary stent, who need to remain on this regimen for 1 year, after which it may be safely reduced to aspirin alone in most cases. In this first year, urgent surgery, such as that needed for cancer, as well as vascular surgery for ischemia or trauma, comes with the added risk of significant perioperative bleeding. Anesthesiologists Wolfgang Toller and associates describe using the in vitro platelet function test, called light transmission aggregometry, in 147 patients.When used just prior to surgery, the test was somewhat predictive of which patients were at elevated bleeding risk. They propose that this test may better define and individualize the timing of surgery. However, the differences in test results are small and recommendations are not yet definite. Nevertheless, refinements in testing may lead to more specific recommendations about which patients should have surgery postponed due to a much greater bleeding risk.

Budget deal avoids 20% Medicare pay cut for now

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Physicians won't have to contend with a 20% cut to their Medicare fees in early 2014, thanks to a bipartisan budget agreement signed into law on Dec. 26.

The agreement, which sets out limits on federal spending for 2014, delays the scheduled Sustainable Growth Rate (SGR) formula cut through March 31. Instead, physicians began receiving a 0.5% increase to Medicare fees on Jan. 1.

The temporary move was praised by physician groups, who are pushing lawmakers to move swiftly to complete a permanent repeal of the SGR formula early this year.

"There is overwhelming, bipartisan support for ending SGR in a fiscally responsible manner and closing the book on the annual cycle of draconian Medicare physician payment cuts and short-term patches," Dr. Ardis Dee Hoven, president of the American Medical Association, said in a statement.

A permanent SGR fix looks more likely after both the House Ways and Means Committee and the Senate Finance Committee approved similar bills in December.

Each of the bills would repeal the SGR formula and begin to gradually tie physician payment to measures of cost and quality, consolidate the existing Medicare quality programs into a single pay-for-performance program, and provide incentive payments for physicians who move to alternative payment models.

Physicians are closer than ever to finally putting an end to the unpopular formula, according to Dr. Charles Cutler, chair of the board of regents of the American College of Physicians.

The committees "will work to stabilize payments, provide multiple pathways for physicians to qualify for positive updates and to participate in alternative payment models, create positive incentives for Patient-Centered Medical Homes, provide assistance to small practices and needed funding for development of quality measures," Dr. Cutler said in a statement.

Slight differences in the Senate and House bills must be worked out. For instance, the House Ways and Means Committee bill would provide a 0.5% pay bump for physicians through 2016, while the Senate Finance Committee's bill would freeze physician payments for a decade. Both bills call for a 2% Medicare pay increase for physicians who participate in alternative payment models after 2024, and a 1% increase for all others.

The Ways and Means Committee bill also includes extra protections for physicians in malpractice cases. It states that national quality guidelines that are tied to federal incentive programs should not be automatically considered a "standard of care" when it comes to potential medical liability lawsuits. And the House committee version includes a provision that requires electronic health records to be interoperable by the end of 2017.

Physicians are closer than ever to putting an end to the unpopular Sustainable Growth Rate formula, according to the chair of the ACP board of regents.

As the debate moves forward on a permanent SGR repeal, lawmakers may also consider extending the increase to Medicaid payments for primary care services and either sun-setting or repealing the Affordable Care Act–mandated Independent Payment Advisory Board. Both issues came up during the Finance Committee's deliberations in December.

Cost of permanent repeal remains the chief stumbling block. Lawmakers have yet to agree on how to offset the $116 billion 10-year cost of a full repeal of the payment formula.

The budget agreement, brokered by Rep. Paul Ryan (R-Wisc.) and Sen. Patty Murray (D-Wash.), also rolls back many of the across-the-board spending cuts to federal health programs mandated by sequestration. But exactly how much funding public health agencies like the Centers for Disease Control and Prevention and the National Institutes of Health will receive in 2014 is unclear. That will depend on what lawmakers agree on when they complete work on the agencies' budgets in early January.

However, the law isn't all good news for physicians. It also extends the 2% sequestration cut to Medicare payments by 2 years, to 2023.

mschneider@frontlinemedcom.com

More time to meet Stage 2 deadline

'Meaningful use' *from page 1*

Stage 2; and second, to utilize data from Stage 2 participation to inform policy decisions for Stage 3," Robert Tagalicod, director of the office of e-Health Standards and Services at the CMS, and Dr. Jacob Reider, acting National Coordinator for Health Information Technology, wrote in a blog post announcing the change.

A growing number of physician organizations and some lawmakers have called on the government to give physicians more time to meet Stage 2 requirements, saying that pushing forward with the aggressive timetable would leave many rural physicians behind.

"This new proposed timeline tracks ongoing conversations we at CMS and [the Office of the National Coordinator] have had with providers, consumers, health care associations, EHR developers, and other stakeholders," Mr. Tagalicod and Dr. Reider wrote. "This timeline allows for enhanced program analysis of Stage 2 data to inform the improvements in care delivery outcomes in Stage 3."

But Thomas A. Leary, vice president for government relations at HIMSS, said that while the extension of Stage 2 meaningful use is a positive step, his organization still wants to see Medicare officials give physicians a few more months to report on their first year of Stage 2 implementation.

mschneider@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Burt Lesnick, FCCP, comments: Physicians who have not yet started meaningful use will soon be subjected to escalating annual penalties. If your practice has not yet gone to an electronic health record, and intends to continue to serve Medicare patients, strong consideration should be given to implementing an EHR now.

Continued from page 9

phia in an editorial accompanying the report.

And while the use of LDCT is part of a structured screening process, not just a scan, the USPSTF report does not address many of the practical aspects of implementing lung cancer screening, they said.

Many patients who are not necessarily high risk will present to their physicians with anxiety about developing lung cancer. "These people have reasons for their concerns; turning them away because they do not meet the criteria does not provide them the reassurance they seek," the editorialists wrote. An educated discussion usually eases the patient's fear, but "this requires specialized knowledge and time. It is easier to give in and screen an anxious patient who does not meet the criteria."

As noted by the USPSTF, the potential harms of LDCT screening include false-negative and false-positive results, such as the potential for incidental findings, overdiagnosis, and radiation exposure. "In a high-quality screening program, further imaging can resolve most false-positive results; however, some patients may require invasive procedures," the recommendations state.

Dr. Peter B. Bach, director of the Center for Health Policy and Outcomes at Sloan-Kettering Cancer Center in New York, authored a second editorial that accompanied the recommendations. What is needed, he said, is more granular level of recommendations with more clinical utility.

"The expected degree of net benefit or level of certainty about the evidence is rarely uniform, even for selected populations," he wrote. There are subgroups in which we have a lot of insight that screening is quite a bit more likely to help than harm, and the findings from the NLST should drive the approach.

Across the quintiles of lung cancer risk studied in the NLST, those considered to have experienced a probable benefit from screening varied from 5,276 in the lowest-risk group to 161 in the highest-risk group. Similarly, when considering the NLST's benefit-to-harm ratio across the quintiles from lowest to highest, the number of false-positive results per lung cancer–related death prevented varied from 1,648 false-positive results per prevented death to 65, respectively, he said.

Screening protocols for patients in the low-risk group should receive a grade C from the USPSTF, which means the service should be offered selectively only, according to Dr. Bach. "Screening should not be mandated for insurance coverage in the low-risk population. Neither should doctors and patients be told that it is definitely a good idea for everyone, nor should it become a quality standard for doctors, hospitals, and insurance plans, which are all things that could happen with this "B" recommendation," Dr. Bach said in an interview.

Dr. Bach was the lead author of practice guidelines issued jointly in 2013 by the American College of Chest Physicians and the American Society of Clinical Oncology. Those guidelines, which are based mostly on the NLST, state that individuals aged 55-74 years who have at least a 30 pack-year smoking history should be screened with LDCT.

"I support the task force's role in the crafting of essential health benefits absolutely," Dr. Bach said. "But I think their power now to create mandates means they should up their game."

wmcknight@frontlinemedcom.com

FDA grants full approval to crizotinib for NSCLC

BY ELIZABETH MECHCATIE

The kinase inhibitor crizotinib has received full approval for the treatment of metastatic non–small cell lung cancer, based on a study that found treatment with the drug was associated with superior progression-free survival and overall response rates compared with chemotherapy.

The approval was announced by the Food and Drug Administration on Nov. 21 in a written statement.

In August 2011, crizotinib received accelerated approval for the treatment of metastatic non–small cell lung cancer (NSCLC) in patients whose tumors are anaplastic lymphoma kinase (ALK) positive, as detected by a test approved by the FDA at the same time. The drug approval was based on objective response rates of 50% and 61% in two single-arm

open-label trials; full approval was contingent on providing evidence that confirmed the clinical benefits.

This evidence was provided by an open-label, multinational randomized study of 347 patients with ALK-positive metastatic NSCLC, who had progressed after treatment with platinum-based chemotherapy. The patients were randomly assigned to treatment with crizotinib or chemotherapy, according to the statement. Those who received chemotherapy received pemetrexed or docetaxel if they previously had been treated with pemetrexed.

Median progression-free survival was 7.7 months among patients on crizotinib, compared with 3.0 months among patients on chemotherapy, a statistically significant difference.

The median progression-free survival was 7.7 months among those on crizotinib, compared with 3.0 months among those on chemotherapy, a statistically significant difference that represented a reduced risk of 51% (hazard ratio, 0.49). The objective response rate was 65% among those on crizotinib, compared with

Continued on following page

Continued from previous page

20% of those on chemotherapy, also a significant difference. The median response durations were 7.4 months and 5.6 months, respectively. In a planned interim analysis, however, overall survival was the same in both groups, according to the FDA.

Common adverse events associated with crizotinib, affecting at least 25% of treated patients, included nausea, diarrhea, vomiting, visual disorders, constipation, edema, elevated transaminase levels, and fatigue.

In a safety evaluation of 172 patients treated with crizotinib in the study, 37% had serious adverse

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, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see **DRUG INTERACTIONS** and **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.3)].

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see **OVERDOSAGE**]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

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, post menopausal 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 SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see **DOSAGE AND ADMINISTRATION** and **USE IN SPECIFIC POPULATIONS**].

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **WARNINGS AND PRECAUTIONS**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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.

Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV$_1$ at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment*	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 mcg N = 277 %**	**160/4.5 mcg N =124 %**	**80 mcg N =121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

* All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV$_1$ at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
	160/4.5 mcg N = 771	**160 mcg N = 275**	**4.5 mcg N = 779**	**N = 781**
Adverse Event	**%**	**%**	**%**	**%**
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. 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. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

events, the FDA said. Pneumonia, pulmonary embolism, dyspnea, and interstitial lung disease were the most common. Adverse events, which included acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, interstitial lung disease, respiratory failure, and sepsis, were fatal in nine patients.

Crizotinib is marketed as Xalkori, by Pfizer. It comes in a capsule formulation and is administered at a dose of 250 mg, twice a day, with or without food.

The prescribing information is available at www.xalkori.com/documents/Xalkori_PI.pdf.

Serious adverse events associated with crizotinib should be reported to the FDA's MedWatch program at 800-332-1088 or www.fda.gov/medwatch.

emechcatie@frontlinemedcom.com

VIEW ON THE NEWS

Dr. W. Michael Alberts, FCCP, comments: It's uncommon, but if you have lung cancer with this abnormality, do we have a drug for you! Three percent to 4% of patients with non–small cell lung cancer have a chromosomal rearrangement that generates a fusion gene between ALK (anaplastic lymphoma kinase) and EML4 (echinoderm microtubule- associated protein-like 4). This results in constitutive kinase activity that contributes to carcinogenesis. Crizotinib inhibits the kinase activity of the fusion protein. As demonstrated in the study cited in the article, when used as second-line treatment, the progression-free survival advantage is meager but statistically significant, at 7.7 months versus 3.0 months.

Tobacco prevention gets short shrift

Fifteen years after states reached settlements with the tobacco industry worth more than $246 billion, most have broken their promises to spend a significant portion of the money on smoking cessation and prevention programs, according to a report from a coalition of public health organizations.

The report found states have received more than $390 billion from the settlement and from tobacco taxes but have spent less than 3% of that money on tobacco-prevention programs. Deep cuts have reduced tobacco-prevention funding by a third since 2008, the report said. Meanwhile, tobacco companies spend more than $18 to market tobacco products for every $1 the states spend to reduce tobacco use, the report said.

– Jane Anderson

Smoking after cancer diagnosis

Death risk *from page 1*

smoking, cancer site, and treatment modalities, the risk of death was 76% higher in those who smoked persistently or intermittently after diagnosis than in those who quit at diagnosis, reported Dr. Li Tao of the Cancer Prevention Institute of California, Fremont, and her colleagues.

Median survival was 2.1 years after diagnosis for those who continued smoking, compared with 4.4 years for those who quit, the investigators said (Cancer Epidemiol. Biomarkers Prev. 2013;22:2404-11). Using a time-dependent approach and including all patients with cancer, the investigators found that the overall risk of mortality was 59% greater for smokers vs. nonsmokers after cancer diagnosis.

"The multivariate-adjusted hazard ratios of death for smoking relative to nonsmoking after cancer diagnosis were 1.92 for patients with lung cancer, 1.76 for patients with stomach cancer, 1.65 for patients with colorectal cancer, and 3.66 for patients with bladder cancer," they wrote.

In a similar analysis that included only current smokers at cancer diagnosis, smoking after cancer diagnosis was associated with a 79% increased risk of death relative to nonsmoking after diagnosis for all patients.

"The [hazard ratios] of death for smoking vs. nonsmoking after cancer diagnosis were 2.36 in patients with lung cancer, 1.63 in patients with stomach cancer, 2.31 in patients with colorectal cancer, 2.95 in patients with bladder cancer, 2.27 in patients with prostate cancer, and 1.34 in all other patients with cancer," they said.

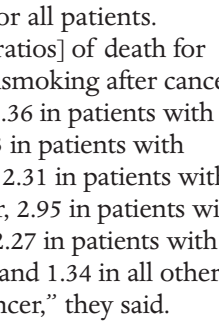
The Shanghai Cohort Study is investigating the association between lifestyle and cancer development in more than 18,000 middle-aged or older men who were enrolled during 1986-1989. Smoking status is ascertained via annual in-person interviews. Patients in the current analysis had a mean age of 68.8 years and were followed for a mean of 5.3 years after cancer diagnosis. They had a median survival time of 5.4 years after diagnosis.

This study has considerable strengths – such as knowledge of baseline smoking status and the prospective design. It also has limitations, including limited treatment data and inclusion of only patients who survived 1 or more years after cancer diagnosis.

This study was supported by grants from the U.S. Public Health Service. The authors reported having no disclosures.

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: A new diagnosis of cancer is devastating news to patients, but may represent an important opportunity for physicians to intervene to change their patients' smoking behavior and subsequently improve health outcomes. Physicians can empower their patients to take control of their own health destinies by changing their personal behavior when facing a cancer diagnosis.



PRESIDENT'S REPORT: A new leader, a new year, but advancing in the same great direction!

BY DR. MICHAEL H. BAUMANN, FCCP

First, thank you very much – I am honored to be the 76th President of the American College of Chest Physicians. Next, thank you to Dr. Darcy D. Marciniuk, FCCP, our 75th ACCP President, who worked very hard for the College this past year and did a stellar job. His accomplishments will no doubt stand the test of time. And, the ACCP team will continue to tap into Darcy's skills in his role as our Immediate Past President.


DR. BAUMANN

Let me briefly introduce myself. My wife Barb, my two sons, Tyler and Jackson, and I live in Jackson, Mississippi. My daily Mississippi work life revolves around the University of Mississippi Medical Center, where I have been on faculty for nearly 20 years. We have over 9,000 employees and students on our campus daily. I have the privilege of working with a great group of colleagues who make my day-to-day life quite rewarding. Their considerable support is the reason I'm able to commit the time and energy to the ACCP Presidency this year.

Plan for the year

What does the ACCP team have planned for next year? Note, the word "team." This is not my plan, but a plan developed with you—our members' input. The team consists of our ACCP staff, leadership, *and*, most importantly, members like you. Your guidance and requests have been heard. In fact, I do not have a presidential "theme" for the year, unless "focus as a team" can be called a theme. As a team, let's finish all of the important core projects we have started! Not exactly a sexy banner-grabbing "theme," but pretty darn important!

I can't say this any better than Darcy did last year, so I will simply quote him:

"Our core strength is providing what clinicians around the world want most: education which enables them to deliver the best possible clinical care. The ACCP does not purport to be everything to everyone. We've adopted a disciplined approach that allows us to excel at exactly what we do – provide the very best and essential learning opportunities for the practicing clinician. Our journal *CHEST*, the annual CHEST conference, board review courses, simulation offerings, leadership development, and other innovative programs are all planned with that focus and important goal in mind."

This upcoming year, we will continue to focus on our core strength that aligns with the interests we have heard from our members yet again—in three words—more clinical education.

New technology-driven headquarters

To do this, we will harness our new headquarters' state-of-the-art Innovation, Simulation, and Training Center by offering more simulation and education opportunities that will be even more innovative. The ACCP recently achieved accreditation from the Society of Simulation in Healthcare. The ACCP is the only professional medical society to be accredited. But first, we need to finish building our new LEED-certified headquarters. We still have a bit more to do to finish up. And finish – we will. Our projected move in date is in February 2014.

Our new headquarters will be complemented by our ongoing investment in an all new information technology infrastructure, our new ACCP "central nervous system" - our brain. These technology systems will coordinate our many College projects, including our all-important member-focused activities. This "brain" will provide state-of-the-art connectivity for our members to seamlessly access our educational offerings and other College products. Members will be able to quickly acquire the essential new knowledge they need to care for their patients, for maintenance of certification requirements, and for personalized data to report their quality performance measures to meet future regulatory requirements.

All of these products and services will feature a new look and feel—our new visual brand identity, introduced during CHEST 2013 in Chicago and then launched online later that week

Guidelines, global, and more

More clinical practice guidelines are on the way. Already a trusted voice in guideline development, the ACCP team is developing new guidelines (and, updating prior guidelines) in a more nimble fashion (translate, faster) with a more user-friendly product (translate, more practical for the frontline provider). Work will be accelerating this year to bring you the latest guideline-based information that you need to provide the best and most up-to-date care for your patients.

More than 5,000 attendees experienced CHEST 2013 (a new record!), one of our yearly premier educational programs. The many innovative offerings reflected the hard work of the scientific program chair, Dr. Jack Buckley, and the entire ACCP team. Dr. Mark Metersky, from the University of Connecticut, is our program chair for CHEST 2014 to be held in Austin, Texas. Mark, the program committee, and the ACCP staff are already hard at work designing this meeting. Austin offers a unique venue that I'm sure you will enjoy.

ACCP's commitment to providing exceptional global education for our international members remains very strong. And we plan to strategically expand this important commitment. Excitement continues to grow around CHEST World Congress 2014 to be held in Madrid, March 21-24. If you haven't registered yet, do so soon. You won't be disappointed. Drs. Richard Irwin and Joan Soriano, our co-chairs, and their program committee, have put together an exceptional program in collaboration with our sister society, SEPAR, the Spanish Society of Pneumology and Thoracic Surgery.

Health-care reform

What's glaringly missing from this focus list? I purposely left to last the area creating the greatest anxiety for health-care providers today – health-care reform. Notice, I didn't say "doctors," but instead "health-care providers." We cannot, and must not, forget that the entire medical team is impacted by these changes. Most importantly, our patients and their families are impacted. And, this is not an issue isolated to the United States. Globally, health-care systems, – including regulators, payers, and governments – want excellent, quality patient care for less cost, or, at least for no increased cost. But, through all of these health care reform efforts, we must keep in mind that we can't lose the patient's voice.

My dad is 92 and my mom is 89. Both are patients in this evolving, complex, health-care system. I have

Continued on page 23

New President-Designate to serve CHEST in 2015-2016

Dr. Barbara A. Phillips, FCCP, is a Professor of Pulmonary, Critical Care, and Sleep Medicine in the Department of Internal Medicine and Medical Director, Sleep Laboratory at the University of Kentucky College of Medicine. She is board-certified in internal medicine, pulmonary medicine, critical care medicine, and sleep medicine.

After joining the American College of Chest Physicians as an affiliate member in 1982, Dr. Phillips advanced to Fellow of the College in 1983. She became a member of the Sleep Medicine NetWork and ACCP Governor for Kentucky. She has chaired the Sleep Institute and is Deputy Editor, SEEK Editorial Board Sleep Medicine Second and Third Editions. Dr. Phillips chaired the National Sleep Foundation and has served on the boards of the American Lung Association, the American Academy of Sleep Medicine, and the American Board of Sleep Medicine.


DR. PHILLIPS

Dr. Phillips received a Sleep Academic Award from the National Institutes of Health and was presented with the ACCP College Medalist Award at CHEST 2013. Dr. Phillips' research interests are effects of sleep apnea on performance and outcomes in commercial drivers, nonpharmacologic treatment of sleep apnea, and sleep in the aging. She will take the reins as President of the ACCP at CHEST 2015 in Montreal, Canada.

CHEST Foundation thanks its generous donors

The CHEST Foundation was pleased to honor some of the top contributors to the *Beyond Our Walls* Capital Campaign during CHEST 2013. Donors who generously supported the new CHEST global headquarters and Innovation, Simulation, and Training Center enjoyed a lovely reception held on the 99th floor of Chicago's Willis Tower. Special recognition was given to **Boston Scientific** and **Olympus** for contributing **$1,000,000** each to the campaign. Also honored were **$100,000** donors from **Jackson Pulmonary Associates, PA,** and **Maggie Sharma**.

(L-R) Paul A. Markowski, CAE and EVP/CEO of the ACCP; with representatives from Jackson Pulmonary Associates, PA: Dr. Timothy Cannon; Brian Hudson, and Dr. Benedict Ewaleifoh, FCCP; and Dr. John C. Alexander Jr., FCCP, Co-Chair Capital Campaign.

Representatives from Olympus honored for the company's generosity.

The new CHEST Global Headquarters in Glenview, Illinois.

Maggie Sharma (center) representing the family of the late Dr. Om P. Sharma, Master FCCP, with Paul A. Markowski, CAE and EVP/CEO of the ACCP (L), and Dr. John C. Alexander Jr., FCCP, Co-Chair Capital Campaign (R).

Boston Scientific's Beran Rose (center) with Paul A. Markowski, CAE and EVP/CEO of the American College of Chest Physicians (L), and Dr. John C. Alexander Jr., FCCP, Co-Chair Capital Campaign (R).

(L-R) Kelly M. Shriner of Boston Scientific with Dr. Stephanie M. Levine, FCCP, Chair of The CHEST Foundation, and Karen Passafaro of Boston Scientific.

PHOTOS COURTEST ACCP

Continued from page 21

heard from my parents, and my patients, the same concerns: With these many health-care changes has come the loss of patient-focus. Compassion and caring seems, from the all-important patient's perspective, to have been lost in the relentless drive to generate yet another RVU.

The health-care team must continue to provide the best patient-focused care possible in the face of this storm of health-care reform. This storm will not end anytime soon. But, the good news is, the ACCP team is here to help our nearly 19,000 members, and their teams, successfully navigate this storm. Let us be your trusted partner and provide the best focused educational opportunities, not only for pulmonary, critical care, and sleep medicine clinical content, but also education about these many health-care system changes. Our new CHEST Regulations and Reimbursement Committee will be focusing on crafting the best education possible to guide our members through these often confusing health-care waters. This all-encompassing education will enable all the members of the health-care team provide the best patient care possible.

I will be relying on all of you, our members, along with Paul A. Markowski, our Executive Vice President and CEO, Curt Sessler, FCCP, our President-Elect, Dr. Barbara A. Phillips, FCCP, our President-Designate, and all of our great ACCP staff to be sure we, as an ACCP TEAM, make the upcoming year the best it can be! I look forward to hearing from you about any questions you may have about these plans.

Thank you again for this opportunity to serve you, the ACCP, and our patients.

CHEST Global Headquarters Wins Green Development Award

Our new CHEST Global Headquarters in Glenview, Illinois, won the prestigious "Green Development of the Year Award" from the NAIOP Chicago, on December 2, at their 2013 Awards for Excellence program. NAIOP is the premier organization for commercial real estate professionals in metropolitan Chicago.

This month in *CHEST:* Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

EDITORIAL

Spread the Word About the Journal in 2014: Measuring Impact, Improving Search Capability, Saying Goodbye and Hello to Section Editors, Honoring Giants, and Looking Forward to a New Visual Identity. *By Dr. Richard S. Irwin; Nicki Augustyn; Cynthia T. French; Victoria Tedeschi; Jean Rice; Stephen J. Welch; on behalf of the Editorial Leadership Team.*

ORIGINAL RESEARCH

No Association of 25-Hydroxyvitamin D With Exacerbations in Primary Care Patients With COPD. *By Dr. M. A. Puhan et al.*

Albuterol Administration Is Commonly Associated With Increases in Serum Lactate in Patients With Asthma Treated for Acute Exacerbation of Asthma. *By Dr. L. M. Lewis et al.*

The Role of the Pulmonologist in Rapid On-site Cytologic Evaluation of Transbronchial Needle Aspiration: A Prospective Study. *By Dr. M. Bonifazi et al.*

Appropriate Sublobar Resection Choice for Ground Glass Opacity-Dominant Clinical Stage IA Lung Adenocarcinoma: Wedge Resection or Segmentectomy? *By Dr. Y. Tsutani et al.*

COMMENTARY

Establishing Pulmonary and Critical Care Medicine as a Subspecialty in China: Joint Statement of the Chinese Thoracic Society and the American College of Chest Physicians. *By Drs. Renli Qiao; Mark J. Rosen; Rongchang Chen; Sinan Wu; Darcy Marciniuk; Chen Wang; on behalf of the CTS-ACCP Pulmonary and Critical Care Medicine Workgroup.*

It's all about the guidelines (part 2 of 3)

BY BRENDA EDWARDS, CPC, CPMA, CPC-I, CEMC

In the first article of this series, we touched on the importance of the guidelines for proper coding, whether it is in ICD-9-CM or ICD-10-CM (chestphysician.org [in News From CHEST]). This article will dive into the conventions (1.A) for ICD-10-CM. The first important notation is at the start of the section. Sometimes a coder may be confused when the guidelines at the front of the manual state one thing, and the chapter instructions seem to state something else.

At the beginning of Section 1 it states, "The conventions and instructions of the classification take precedence over guidelines." So, if the Tabular Index gives an instruction that is different than the guidelines in the front of the manual, follow the Tabular Index guidelines.

Section 1.A contains the conventions describing the general rules. Some of the highlights include:

1.A.2: Characters for categories, subcategories, and codes may be either a letter or a number. Categories are three characters, but if there is no further breakdown, it may also be a code. For example, **I10 Essential (primary) hypertension** is a three-character code with no further breakdown. I11 **Hypertensive heart disease** is a category that needs additional characters to denote a valid code (I11.0 or I11.9).

1.A.3: For reporting purposes, only codes are permissible, not categories or subcategories, and any applicable seventh character is required. In other words, you have to continue until there are no more characters in the subcategory. As in the previous example, it would be invalid to just stop at I11, as there is a fourth character breakdown.

1.A.4 and 1.A.5: These guidelines refer to the seventh character extenders and placeholders. ICD-10-CM utilizes a placeholder "X" for future expansion and to fill in the empty characters for codes that requires a seventh character extender, when they are not six characters in length. For example, S09.21- is traumatic rupture of right eardrum, but this is not a complete code as it requires a seventh character. The partial code is five characters in length. In order to append the seventh character in the seventh character position, a placeholder "X" must be used. If this were an initial encounter, the appropriate seventh character would be "A." In this circumstance, the complete code would be S09.21XA Traumatic rupture of right eardrum, initial encounter.

1.A.6 to 1.A.9 are familiar guidelines explaining abbreviations used in the code book (for example, not elsewhere classified [NEC], not otherwise specified [NOS], etc).

1.A.12.a and 1.A.12.b: These guidelines explain the new exclusions for ICD-10-CM: "Excludes1" and "Excludes2." Excludes1 is a true exclusion and indicates that the code(s) listed under the Excludes1 should never be coded with the code above the Excludes1 note. For example, type 1 diabetes has an Excludes1 list that includes type 2 diabetes, gestational diabetes, and secondary diabetes. None of these diagnoses would be reported with type 1 diabetes on the same patient encounter.

Excludes2 indicates that the conditions excluded are not part of the condition listed above them. If the documentation states both conditions exist together, both should be reported. This will be seen with some acute on chronic conditions for which ICD-10-CM does not have a combination code. For example, category J01, acute sinusitis, has an Excludes2 note for chronic sinusitis. If a patient has documented acute on chronic maxillary sinusitis, J01.00 (acute maxillary sinusitis) would be reported along with J32.0 (chronic maxillary sinusitis).

The remaining conventions cover sequencing of codes, other verbiage (the use of "and," "with" "see," and so on), and default codes.

It is important to take the time to become familiar with the guidelines now in order to ensure proper, efficient code assignment when we go live.

Brenda Edwards entered the coding and billing profession 25 years ago and has been involved in many aspects of the field. Her current responsibilities include chart auditing, coding and compliance education, and contributing articles to AAPC and industry publications. Brenda is an AAPC ICD-10-CM trainer and has presented for AAPC workshops, regional conferences, and local chapter meetings. She has also served on the AAPCCA local chapter board of directors.

NETWORKS: Infections, e-cigarettes, lipid guidelines, and MV

Chest Infections

Antibiotics that "mist the target"

The increase in multi-drug resistance (MDR) and the dearth of new antibiotics in the "pipeline" has prompted interest in aerosolized antibiotics (AA) for treating ventilator-associated pneumonia (VAP). Toxic antibiotics like colistin may be aerosolized, reaching high concentrations in distal airways with minimal systemic absorption.

Aerosolized antibiotics have mostly gained traction in the "adjunctive" role (added to systemic antibiotics). Advances in nebulizer technology, and adjustments in ventilator settings and the breathing circuit to optimize drug delivery, have paved the way for clinical application.

Rattanaumpawan and colleagues randomized 100 patients with VAP due to MDR gram-negative bacilli (GNB) to aerosolized colistin *vs* placebo in addition to IV antibiotics, without benefit in clinical outcomes (*J Antimicrob Chemother.* 2010;65[12]:2645).

Three recent studies used advanced vibrating plate aerosolization: Lu and colleagues compared aerosolized colistin +/- IV aminoglycoside in 43 patients with VAP with MDR GNB vs IV antibiotics alone in 122 others with sensitive GNB (*Anesthesiology.* 2012;117[6]:1335); outcomes were similar.

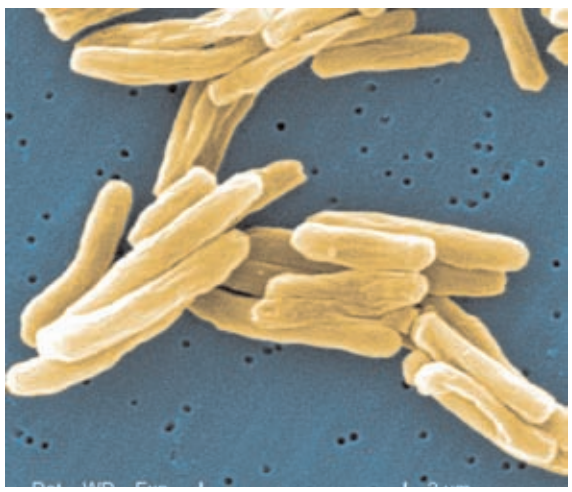
In another study, 40 patients with drug-susceptible GNB received inhaled-only ceftazidime plus amikacin, vs systemic antibiotics. Treatment success was nonsignificantly higher in the aerosol-only group; antibiotic resistance developed only in the IV group (*Am J Respir Crit Care Med.* 2011;184[1]:106). Niederman and colleagues, in a randomized VAP trial (n=69), found adjunctive inhaled amikacin reduced overall exposure to antibiotics with less clinical failure compared with control (*Intensive Care Med.* 2012;38[2]:263).

The advantage of AA may be in avoiding systemic antibiotic overexposure. Further studies will investigate adjunctive vs stand-alone AA, optimal dosing strategies, and agents for gram-positives.

Dr. Paul Richman, FCCP
Steering Committee Member
Dr. Michael Niederman, FCCP
Chair

BCG vaccination for TB: Time for a reexamination?

Bacillus Calmette-Guerin (BCG) is the single most widely used human vaccine in history, with over 3 billion individuals vaccinated in total and 100 million annually (Liu et al. *Hum Vaccine.* 2009;5[2]:70).



JANICE CARR/CENTERS FOR DISEASE CONTROL AND PREVENTION

Tuberculosis: Human trials and decades of clinical experience with bacillus Calmette-Guerin have shown that it is useful for prevention of TB, and particularly for interdiction of major complications of TB (dissemination, meningitis, and mortality) in children.

The vaccine was developed in the early 20th century from a strain of *Mycobacterium bovis*. The original virulent strain had become attenuated by numerous subcultures in vitro over 13 years by Calmette and Guerin (McShane et al. *Tuberculosis [Edinb].* 2012;92[3]:283).

Over the past 100 years, BCG has been disseminated to many laboratories and countries for use and has required frequent subculturing. As a result, the strains have diverged and do not have the same virulence properties as the original, and BCG should not be viewed as a single organism (Liu et al. *Hum Vaccine.* 2009;5[2]:70). Strain divergence has been reduced due to lyophilization of cultures over the past 47 years. Naturally occurring mutants of BCG have deletions of major virulence factors that affect the ESX-1 protein secretion system, one of several secretion systems found in the TB genome. Absence of these proteins results in impaired growth of TB in macrophages, modulates phagolysosomal fusion, and reduces bacterial virulence. The ESX-1 secretion system plays a major role in virulence of TB, and loss of the system accounts for much of the loss of virulence of BCG (Liu et al. *Hum Vaccine.* 2009;5[2]:70). These mutations may contribute to differences in side effects and efficacy of the vaccine utilized in different locales.

Other virulence factors of TB and BCG relate to the lipid content/composition of the cell wall of mycobacteria. These lipids are also integrally involved in pathogenicity (Liu et al. *Hum Vaccine.* 2009;5[2]:70). Absence or mutations in these lipids result in attenuation of infection in both mouse and guinea pig models.

Human trials and decades of clinical experience with BCG have shown that it is useful for prevention of TB and particularly for interdiction of major complications of TB (dissemination, meningitis, and mortality) in children (Checkley et al. *Trends Pharmacol Sciences.* 2011;32[10]:601; Trunz et al. *Lancet.* 2006;367[9517]:1173).

The responses for pulmonary TB in younger and older adults are not as robust (Colditz et al. *JAMA.* 1994;271[9]:698). For decades, the World Health Organization (WHO) has recommended BCG in high-risk endemic areas and for children. BCG is not recommended in general in developed countries where the endemic rate of TB is low; the utility of the skin test for diagnosis of latent TB would be compromised and the false-positivity rate of the test would be high.

Recognizing that BCG is not an ideal vaccine despite its widespread utility and experience over decades, further research has used the results of BCG attenuation to pursue avenues to improve BCG or to advance other vaccine candidates (Liu et al. *Hum Vaccine.* 2009;5[2]:70; McShane et al. *Tuberculosis [Edinb].* 2012;92[3]:283; Checkley et al. *Trends Pharmacol Sciences.* 2011;32[10]:601; Jeyanathan et al. *J Immunol.* 2008;181[8]:5618; Hokey et al. *Tuberculosis [Edinb].* 2011;91[1]:82; Morais et al. *Tuberculosis [Edinb].* 2010;90[2]:135; McShane et al. *Philos Trans R Soc Lond B Biol Sci.* 2011;366[1579]:2782; Rowland et al. *Expert Rev Vaccines.*2011;10[5]:645).

The newer vaccines in development against TB will have to be at least as good as the current BCG vaccine. Global challenges to the successful control of TB include the development of newer treatment drugs due to the presence of multidrug (MDR) and extensively drug resistant (XDR) strains, efforts to halt the progression of HIV, improvement of hygiene and environmental factors of developing countries, and continued research into refinements of BCG, as well as newer vaccines against TB. Only by these combined efforts will the burden of TB be reduced by 50% by 2015 and have ultimate eradication by 2050 (World Health Organization. 2011; http://www.stoptb.org/assets/documents/global/plan.TB).

Dr. Richard Winn, FCCP
Vice-Chair

Cardiovascular Medicine and Surgery

ACC/AHA lipid guidelines spark controversy

Years in the making, the new lipid guidelines[1,2] released by the American Heart Association (AHA) and the American College of Cardiology (ACC) to coincide with the AHA annual meeting in November ignited a firestorm of controversy.

The guidelines resulted from a complex process that stretched out 9 years from the publication of the consensus lipid guidelines in 2004. Convened and funded by the National Institutes of Health, the guidelines were eventually put out under the aegis of the AHA and ACC. The National Lipid Association, originally included in the process, ultimately declined to endorse them.

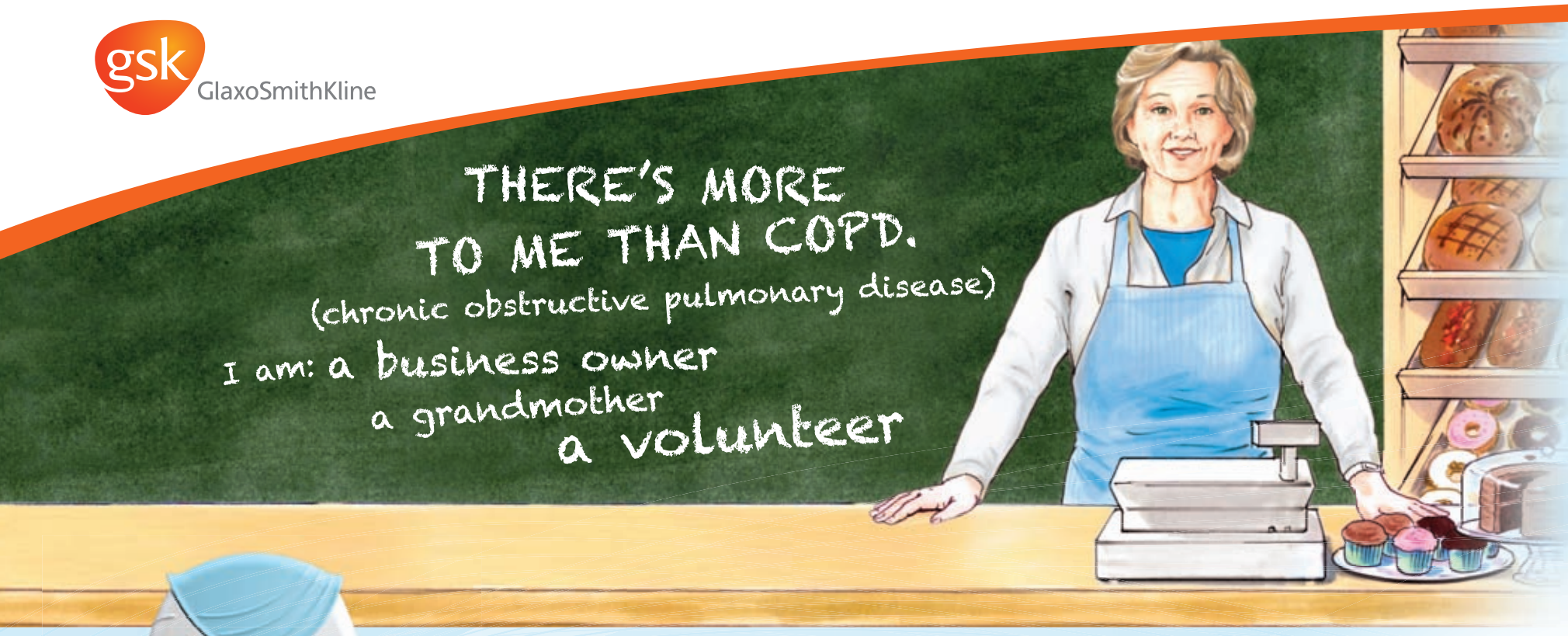
What was most controversial about the new guidelines was the move away from treating lipids to a specific target, instead focusing on which patients have been shown in randomized clinical trials to benefit from lipid-lowering therapy. These patients fall into 4 general categories:

1. Secondary prevention in patients with previous coronary or cerebrovascular events
2. with LDL cholesterol >190 mg/dL
3. Type II diabetics aged 40-75
4. Patients aged 40-75 with a 10-year risk of cardiovascular disease exceeding 7.5% according to a new algorithm

It was this last group that caused the most controversy. The classification has the potential to greatly increase the number of patients considered for lipid-lowering therapy, by as many as 45 million Americans.[3] Drs. Paul Ridker and Nancy Cook published data that challenged the accuracy of the proposed algorithm, showing that when calibrated against patients in large randomized trials, it may overestimate the risk by as much as 75%-150%.[3]

Defenders of the algorithm pointed out that patients in clinical trials may be at lower risk than those in the general population, and that the algorithm, despite its flaws, is most

Continued on page 32



BREO ELLIPTA

The only once-daily ICS/LABA (inhaled corticosteroid/long-acting beta$_2$-agonist) for the maintenance treatment of COPD.

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 for BREO ELLIPTA

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.

BREO ELLIPTA. One inhalation. Once daily.

THE ONLY ONCE-DAILY ICS/LABA FOR THE MAINTENANCE TREATMENT OF COPD

- Approved for long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD
- Approved to reduce COPD exacerbations in patients with a history of exacerbations
- Not approved for the relief of acute bronchospasm or for the treatment of asthma
- Delivered in the ELLIPTA inhaler

Important Safety Information for BREO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- 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.
- 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.

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

BREO ELLIPTA was developed in collaboration with Theravance

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

BREO™ ELLIPTA™
(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, and 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 Hypersensitivity reactions may occur after administration of BREO 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 take 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.

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

See 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.

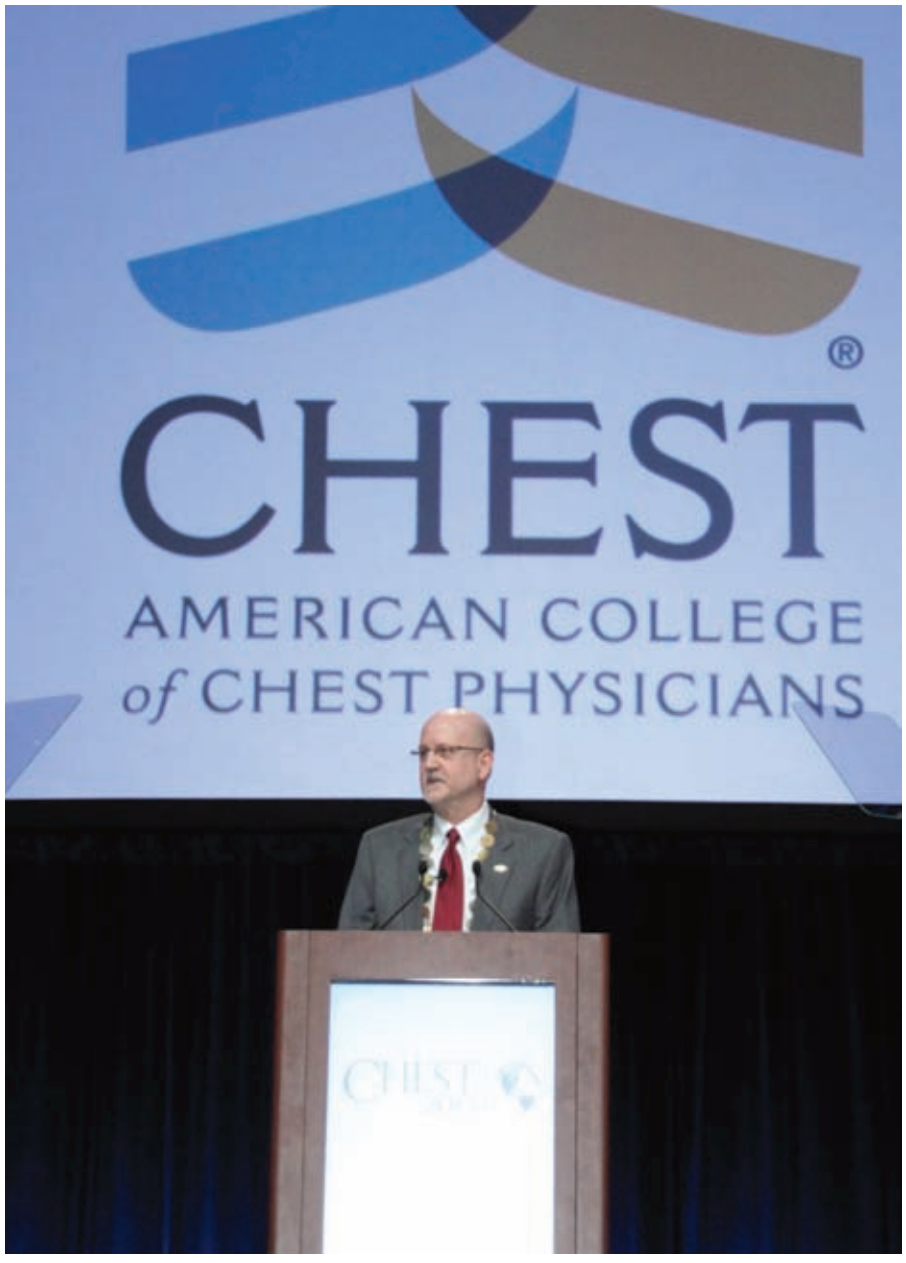
17.5 Risks Associated With Beta-Agonist Therapy Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

BREO ELLIPTA was developed in collaboration with Theravance

GlaxoSmithKline
Research Triangle Park, NC 27709

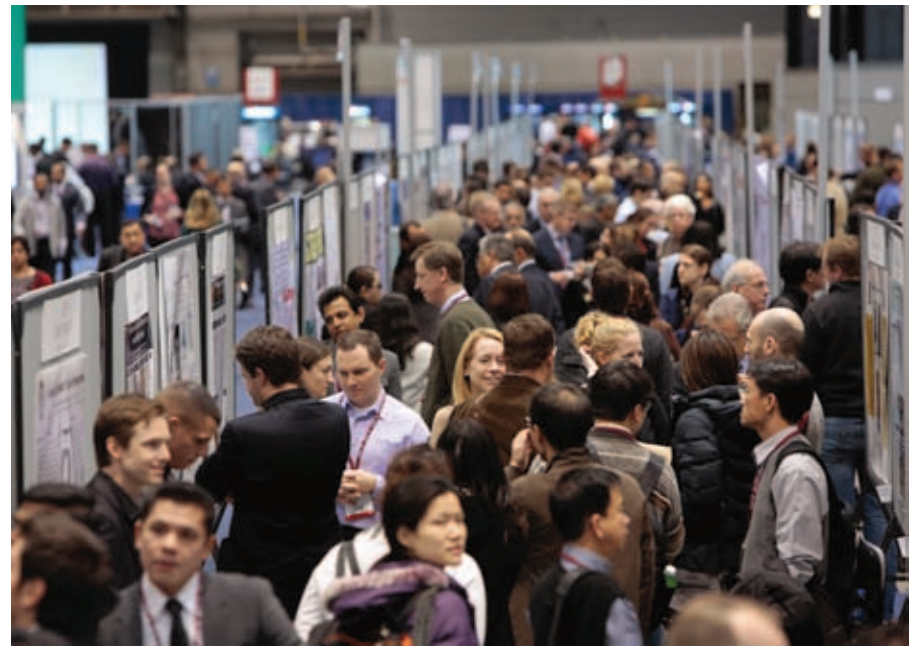
Revised 05/2013 BRE:1BRS

Recalling CHEST 2013



Photos courtesy ACCP

Dr. Michael H. Baumann, FCCP, as the new President, introduces the new branding for the organization during an opening session at CHEST 2013, held in October in Chicago.



Posters, posters, posters. The popular Poster Grand Rounds at CHEST enables presenters to discuss their research with experts from around the world.

Games Augmenting Medical Education (GAMEs): The 2013 Game Center was created to offer educational content on topics such as COPD and PAH, and pulmonary cases in a fun and innovative way.

This year's annual Outreach Event took place at Tonti Elementary School in Chicago. Dr. Mary Anne McCaffree was one of many volunteers who participated in teaching students about good lung health.

Our new FCCPs from around the globe were inaugurated into the organization during the annual Convocation ceremony. They took the traditional pledges of Fellowship, No Tobacco, and Patient-Focused Care.

Winners-All at CHEST 2013

CHEST 2013 attendees were all around winners, experiencing the most well-attended CHEST meeting ever. Plus, we had special winners who were acknowledged during the meeting. Those recipients of the ACCP Awards, CHEST Foundation Awards, and Honor and Memorial Lecturers are listed on the CHEST 2013 website at chestmeeting.chestnet.org/Program. Abstract and case report winner s and winners of CHEST Bingo are listed below.

Congratulations to everyone!

Alfred Soffer Research Award winners

This award is named in honor of Dr. Alfred Soffer, Master Fellow of the College, Editor in Chief of the *CHEST* journal from 1968 to 1993, and Executive Director for the ACCP from 1969 to 1992. The Alfred Soffer Research Award is granted to CHEST 2013 abstract presenters for their outstanding original research.

$1,250 award winners
Alexander Chen, MD
Damian Dupuy, MD
David Odell, MD, MMSc

$900 winners
Christopher L. Carroll, MD, FCCP
Francesca Gibellino, MD
Nichole T Tanner, MD, MS, FCCP

Young Investigator Award Winners

The Young Investigator Award is open to CHEST abstract presenters enrolled in a training or fellowship program or have completed a fellowship program within 5 years prior to CHEST 2013. Semifinalists were evaluated on the basis of their written abstract and their presentation at CHEST 2013.

$1,250 winners
Hiren J. Mehta, MD
James Ramsahai, MD and Kewan Aboulhosn, MD
Bilal Safadi, MD

$900 winners
Amit Banga, MD
Richard Hedelius, DO
David Rice, MD
Michael Silverberg, MD

Top Three Posters Award winners

Top Three Posters semifinalists were evaluated on their written abstract and quality of their poster presentation during CHEST 2013. The Top Three poster winners, based on the grade received during their presentation, will receive $750. All other semifinalists will receive $500. All categories were eligible.

$750 winners
Juan Fernandez Lahera, DMD
Vladimir Koblizek, MD
Andrea Loiselle, MD

$500 winners
Erin Murphy, MD
Capt. Andrew J. Skabelund, MC, USAF

Case Report Session Award winners

The following case report winners presented the "Best Case" in their respective CHEST 2013 session. Each winner will receive a $100 prize.

Airway Cases I: Douglas Closser
Airway Cases II: Rishi Mehta
Atypical Presentations in the ICU: Srikant Nannapaneni
Bronchology Cases I: Harry Nima-Zegarra
Bronchology Cases II: Christopher Erb
Cancer Cases I: David McNamara
Cancer Cases II: Rafid Fadul
Cardiovascular Cases I: Anup Singh
Cardiovascular Cases II: Kara Goss
Cardiovascular Critical Care: Satish Chandraprakasam
Critical Care Cases: Stacie Cook
ICU Cases: Stephen Baldassarri
ICU Complications:Frederick Clayton
Infectious Disease Cases I: Luke White (on behalf of Nalin Mallik)
Infectious Disease Cases II: Deirdre Kathman
Infectious Disease Cases III: Laura Hinkle
Infectious Disease Cases IV: Brooke Colbert
Interstitial Lung Disease Cases I: Ryan Kern
Interstitial Lung Disease Cases II: Natoushka Trenard
Miscellaneous Cases I: Maria Velez
Miscellaneous Cases II: Ian Lee
Miscellaneous Cases III: Aarti Mittal
Miscellaneous Cases IV: Justin Ardoin
Miscellaneous Cases V: Daniel Miller
Pleural Cases: Jason Bellardini
Pneumonia and Pneumonitis: Nadia Morgan
What's New in the ICU: Deepa Kuchelan

CHEST 2013 - BINGO WINNERS

Monday, October 28
Jeri Humphries, PA-C
Pattan Mahaboob Khan, MD, FCCP
Carole Lovering, ACNP
Jeffrey W. Hawkins, MD, FCCP
Vijay S. Baid, MD, FCCP

Tuesday, October 29
Charles Peng, MD
Laura Miske, MSN
Sue Galanes, APN
COL Zygmunt Orzechowski
Vipul Shah, MD

Wednesday, October 30
J. Michael Petway, MD, FCCP
Lianne Lin, MD
Parimal T. Bharucha, MBBS
Lester W. Blair, MD, FCCP
Karen I. Mella, RRT

ACA: The five Ws of the value-based payment modifiers

BY JEANNA STOVALL, MSA, RHIA
CHEST Regulations & Reimbursement Director

In efforts to assist our membership with navigating regulatory changes in our industry, this article with provide answers to who, what, when, where, and why on value-based payment modifiers.

Over the past few years, you may have seen plenty of communication from the Centers for Medicare and Medicaid Services (CMS) surrounding quality of care and payment incentive programs for treating Medicare beneficiaries. A recent addition to the other quality or incentive programs you may be aware of like PQRS (Physician Quality Reporting System) or EHR (electronic health record) incentive is the Value-Based Payment Modifier Program.

Requirements under the Affordable Care Act necessitate the creation of a value-based payment modifier. This program is a differential payment program to physicians or group of physicians operating under the Physician Fee Schedule (PFS). The Value-Based Payment Modifier Program (throughout the final rule referred to as "VM" or Value Modifier) is based upon a comparison of quality of care standards and the cost of that care provided to Medicare beneficiaries.

A key facts to remember about the VM program is namely the phase-in target date of January 2015. However, even more important than the phase-in date is the measurement criteria and source of funding for this program—performance outcomes will be measured through PQRS and the program is budget-neutral. This means that from the phase-in date of eligible professionals (EPs) on January 1, 2015, through not later than January 1, 2017, compliance of all physicians and groups of physicians is required.

Understanding the regulatory nuances of the health-care landscape may be difficult, and if there is a topic you would like hear more about, please don't hesitate to correspond.

CMS anticipates an inclusion of all group practices with 100 or more EPs on January 1, 2015, and practices with 10 or more EPs by 2016. Approximately 17,000 group practices and nearly 60% of all of practicing physicians have required participation by calendar year 2016. Lastly, the VM incentive funding source, top quality performing EPs will come from payment decrease of low quality performing EPs.

I know what you may be thinking; my last few comments seem strange, especially if the tool to measure performance is currently under voluntary participation. I am inclined to believe that CMS will use VM to further improve upon the level of quality care that Medicare beneficiaries receive and encourage full participation in PQRS.

Understanding the regulatory nuances of the health-care landscape may be difficult, and if there is a topic with which you would like assistance or would like to hear more about, please don't hesitate to correspond.

According to cms.gov, The following professionals are among eligible to participate in Physician Quality Reporting System (PQRS):

1. Medicare physicians
2. Practitioners
3. Therapists (including physician assistants, nurse practitioners, clinical nurse specialists and certified registered nurse anesthetists and anesthesiology assistants).

To learn more, see the CMS Media Fact Sheet (www.chestnet.org/Guide lines-and-Resources/Payment-Practice-and-Quality/Coding-and-Reimbursement).

Continued from page 25

likely more accurate than the previous algorithms that were derived from the Framingham population more than 30 years ago.

Other experts felt that the new guidelines overstressed randomized clinical trials to the exclusion of epidemiologic and population-based observational data, data they felt demonstrate convincingly that treatment to lower targets produces better outcomes even if clinical trials were not designed to not show statistically significant differences between patients who meet targets and those who have even more substantial lipid-lowering.

What remains unclear is whether the controversy about the guidelines will introduce unwanted uncertainty into the field, leading clinicians and patients to question the value of lipid-lowering as a preventive therapy, or whether disagreement will spur healthy discussions that will ultimately lead to more clarity and improved outcomes. Time will tell.

Dr. Steven M. Hollenberg, FCCP
Steering Committee Member

References

1. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Nov 7. doi:pii: S0735-1097(13)06028-2. 10.1016/j.jacc.2013.11.002. [Epub ahead of print].
2. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013 Nov 12. [Epub ahead of print].
3. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet*. 2013; 382:1762-1765.

Clinical Pulmonary Medicine

e-Cigarettes: Promise or peril?

e-Cigarettes are battery-powered devices that convert nicotine and other ingredients into vapor, simulating the visual, sensory, and behavioral aspects of smoking without the combustion products accountable for smoking's damaging effects. An ever-growing number of companies around the world manufacture a wide variety of e-cigarette brands, despite scant information on the safety of the ingredients for human inhalation. The electronic cigarette is an emerging phenomenon that is becoming increasingly popular with smokers worldwide. Users report buying them to help quit smoking, to reduce cigarette consumption, to relieve tobacco withdrawal symptoms due to workplace smoking restrictions, and to continue to have a "smoking" experience but with reduced health risks. Electronic cigarette sales increased from 50,000 in 2008 to 3.5 million in 2012.

As of 2011, in the United States, one in five adults who smoke has tried electronic cigarettes. Among grade 6 to 12 students in the United States, those who have ever used the product increased from 3.3% in 2011 to 6.8% in 2012.

Tobacco-industry scientists argue that e-cigarettes deliver lower amounts of nicotine than regular cigarettes, are less toxic, and don't expose others to second-hand smoke. One recent study showed that e-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches and few adverse events. A recent study from France's National Consumers Institute, however, concluded that e-cigarettes are "potentially carcinogenic" because some brands contain levels of formaldehyde that approach those of conventional cigarettes.

Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels. Until then, we should not assume they are safe simply because they appear to be less harmful than traditional cigarettes.

Wikimedia Commons/ Martevax/ Creative Commons License

Electronic cigarette sales increased from 50,000 in 2008 to 3.5 million in 2012.

FDA is refusing to let them into the country and may soon ban their sale, as major US medical associations have strongly urged against the e-tobacco products.

Dr. Sat Sharma, FCCP
Steering Committee Member

Allied Health

Implementing mechanical ventilation orders by "Doing the Math"

Many RCPs (myself included) prefer mechanical ventilation (MV) orders that specify a target arterial pH (pHa), in lieu of listing a respiratory rate (RR) and tidal volume (V_T). If a baseline arterial blood gas (ABG) report is in hand, it's easy to identify the target arterial carbon dioxide tension ($PaCO_2$), which will elicit a homeostatic pHa: target $PaCO_2$ = (5/3) • [HCO_3–].

For example, suppose that a patient exhibits the following ABGs following an overdose of barbiturates: pHa = 7.20; $PaCO_2$ = 68 mm Hg; and [HCO_3 -] = 26 mEq/L. If 7.40 is the pHa that we wish to impose: target $PaCO_2$ = (5/3) • 26 = 43 mm Hg.

Suppose further that our hypothetical patient initially displayed an RR of 10 breaths/min. We can reach the target $PaCO_2$ by applying the following expression: RRfinal = RRinitial • ($PaCO_2$initial / $PaCO_2$final).

For our hypothetical patient, this expression reverts to: RRfinal = 10 breaths/min • (68 mm Hg/43 mm Hg) = 16 breaths/min! On the other hand, if the attending physician or house officer indicates that s/he wishes to elicit a pHa that's near the lower limit of the homeostatic range, we can simply select a target $PaCO_2$ that's a few mm Hg higher than that shown above. This strategy is usually employed when the patient is known to be a CO_2-retainer.

Want to "drill down" on this material? A video, handout, script, and posttest are accessible at: ambulatorypractice.org/education-research/respiratorytherapy-education/ventilator-targets. Enjoy!

Bob Demers, RRT,
Chair

Moving beyond the impact factor to alternative metrics

BY DR. CHRISTOPHER CARROLL, FCCP; AND DR. DEEP RAMACHRANDRAN
CHEST Social Media Co-Editors

Over the past decade, those of us who practice in the medical field have had to adjust to a new system of health-care metrics which give us insights into our performance. The field of medical publishing is no different. For years, scientists have relied upon the impact factor (IF) to gauge the amount of discussion around a certain article. While the IF tracks journal citations, it doesn't track who is talking about a particular article. This is an especially important distinction in a world increasingly turning to social media platforms for information.

CHEST now offers a tool to measure the social impact of journal articles. Altmetric is a new tool that allows authors and readers to see what articles are being discussed and gaining traction in the larger and increasingly important realm beyond traditional media. Altmetric tracks sharing across social media channels such as blogs, Twitter mentions, and Facebook posts. Using this tracking, it assigns a score to measure the social influence of articles. On the *CHEST* website (journal.publications.chestnet.org), the Altmetric tool can be found on the right side of the article view on a single article page.

When clicking on the Altmetric button, a screen showing the score will appear. The Altmetric score measures the quantity and quality of attention that an article receives online. Articles that score higher than 20 are being talked about more frequently. Recent conversations about that particular article will also be visible. Demographics are also available that show the world region where those conversations are taking place. If interested, users can sign up for e-mail alerts to receive updates when new conversations occur around a particular article.

Using this tool provides direct insight into the importance of a scientific article within the broader context of the Internet. Authors and readers can immediately understand the value and reach of content, while also discovering new content.

Over the past few years, *CHEST* has focused on expanding its social reach, first by sharing content on social media platforms, second by engaging us to curate that content, and now by tracking the impact of the content. We look forward to forging new conversations around the science of chest medicine and taking these discussions "beyond our walls" to the broader social environment.

CLASSIFIEDS

Also available at www.MedJobNetwork.com

CALIFORNIA

Coastal suburban Southern CA - Seeking a BC/BE CCM physician to join a well-respected Intensivist Program for 7-on, 7-off shifts (14/month) in 20 bed unit of a 265 bed hospital.

For more information or to submit your CV please contact:

Samantha Farrell, RN -
Intensivist Program Manager -
pm.sjintensivist@gmail.com

ARIZONA

Outstanding opportunity in metro Phoenix area.

Practice includes all aspects of pulmonary medicine including sleep and critical care.

Excellent opportunity for a new graduate or physician looking to make a lateral move.

Please forward CV via fax to 480-655-1640
Attn: Cathy or via email to
cpatzke@azlungcenter.com

CHEST Physician
CLASSIFIEDS

For Deadlines and More Information, Contact:
John Baltazar
Tel: (917) 488-1528
jbaltazar@americanmedicalcomm.com

FRONTLINE MEDICAL COMMUNICATIONS

Hendersonville - Western North Carolina

BC/BE Pulmonary/Critical Care Medicine Physician inpatient/outpatient hospital-employed practice opportunity (Sleep Medicine optional) 1:3 call. Practice adjacent to 222-bed UNC Health Care-affiliated Pardee Hospital. Beautiful Hendersonville, WNC (near Asheville). No Visa Sponsorship. **No Placement Firm Inquiries**.
CV to: Lilly Bonetti (828) 694-8342
lilly.bonetti@pardeehospital.org
www.pardeehospital.org

Kentucky

7 person well established Pulmonology group in Louisville, KY seeking pulm/cc/sleep physician. Competitive salary, incentive bonus and partnership track. Opportunity to practice both inpatient/outpatient pulmonary medicine. Sleep medicine available but not a must.

Please send CV to:
kvanderpool@kpadocs.com

DALLAS

Established and well-respected 3 physician PUL/CC practice has opportunity for full-time/part-time BE/BC PUL/CC physician to join.

Practice includes diverse office, ICUs and rounding at near-by LTACs. Sleep Medicine a plus.

Startup volume is readily available.

Excellent patient demographics, EMR-EClinicalWorks, strong referral base.

Our strong team environment and mission allows us to focus on the highest quality and friendly patient care.

No cash buy in. Partnership Track.

Production bonus.

Competitive salary/benefits with CME and vacation, 401K /profit share.

No state income tax. Centrally located in Dallas w/ superb dining, fantastic shopping, access to major affiliates, cultural centers and first-rate schools with family oriented communities.

Serious applicants only.

Email your CV and letter to
pulmonarycare@hotmail.com

New York

St. Barnabas Hospital, a Level 1 Trauma Center in the Bronx, New York has great opportunities for Critical Care Physicians to practice in a multi-disciplinary ICU.

We are looking for a full time employee but have part-time and per-diem work available as well.

Please fax CV to: 718-960-6122.

Moving? Look to Classified Notices for practices available in your area.

OSAS and cognitive impairment

Sleep Strategies *from page 1*

OSAS can affect cognition across the lifespan from infants to geriatric patients. Habitual snoring during the first year of life has been associated with lower scores on the Bayley Scales of Infant and Toddler Development, comparable with those seen in infants with iron-deficiency anemia (Grigg-Damberger et al. *Curr Opin Pulm Med*. 2012;18[6]:580). Such scores can predict future intelligence quotient scores, educational achievements, and job performance (Dezoate et al. *Child*. 2003;29[5]:367). OSAS of any severity as well as habitual snoring has been shown to increase the risk of hyperactivity, inattention, and poor school performance in children (Bourke et al. *Sleep Med*. 2011; 12[3]:222), and some of these metrics have been shown to improve with therapy. Thus, even primary snoring in children should not be considered a wholly benign condition.

Mild cognitive impairment (MCI) is defined as a subtle but measurable cognitive dysfunction, greater than that which would be expected with normal aging; memory loss is typically the presenting symptom. The conversion rate of MCI to frank dementia is roughly 15% per year (Petersen et al. *Arch Neurol*. 1999;56[3]:303). OSAS has been shown to be associated with MCI in adults (Cosentino et al. *Sleep Med*. 2008;9[8]:831); studies have also shown OSAS to be associated with impaired vigilance (Findley et al. *Chest*. 1995;108[3]:619) and executive function (Naismith et al. *J Clin Exp Neuropsychol*. 2004;26[1]:43). Thus, the cognitive dysfunction associated with OSAS is a real and measurable problem. If these relationships are causal, as one might suspect, aggressive screening for OSAS in patients with MCI might be warranted in the hope of reversing the disorder.

There are likely to be multiple mechanisms underlying the association between cognitive impairment and OSAS. Excessive daytime sleepiness can induce an impairment of vigilance and memory, both of which are components of cognitive function. A vicious cycle may ensue, with patients forgetting to use their CPAP, leading to worsening cognition. Intermittent hypoxemia is associated with a pro-inflammatory state and endothelial dysfunction that may be the intermediate mechanism by which cognitive impairment occurs. Genetic factors may modulate the association between cognitive impairment and OSAS. The apolipoprotein E4 allele located on chromosome 19 is a strong risk factor for early-onset Alzheimer's disease and has been shown to increase the risk of developing both OSAS (Kadotani et al. *JAMA*. 2001;285[22]:2888) and neurocognitive decline among patients with OSAS (Gozal et al. *Neurology*. 2007;69[3]:243). A higher intelligence quotient, younger age, and higher education level may protect the brain from the detrimental effects of the intermittent hypoxia associated with OSAS (Grigg-Damberger et al. *Curr Opin Pulm Med*. 2012;18[6]:580). The situation becomes even more complex when considering other comorbidities often exist in the OSA population and can affect cognition, including tobacco and alcohol use, stroke, hypothyroidism, congestive heart failure, obesity, psychoactive medication use, and depression, among others.

©VIOLA83181/ISTOCKPHOTO.COM

Cognitive dysfunction associated with obstructive sleep apnea syndrome includes mild cognitive impairment and impaired vigilance and executive function.

Neuroimaging techniques have been used to identify brain abnormalities in patients with OSAS. Functional and structural changes, as well as altered levels of neurochemical mediators like N-acetyl aspartate and choline, have been reported. A common finding among MRI studies is decreased volume of the hippocampus; functional MRI has shown decreased brain activation in the cingulate cortex and other brain regions during sustained attention tasks, compared with control subjects (Ayalon et al. *Sleep*. 2009;32[3]:373). Both of these brain areas, which are involved with memory consolidation, are also affected by gray-matter loss in patients with OSAS (Macey et al. *Am J Respir Crit Care Med*. 2002;166[10]: 1382). These changes may explain symptoms of retrograde and anterograde amnesia in such patients.

DR. WALTERS

DR. LAL

If OSAS is associated with cognitive impairment, then treatment might reverse the brain changes causing this impairment. A small study evaluated cognitive performance and brain morphology before and after CPAP treatment in patients with OSAS (Canessa et al. *Am J Respir Crit Care Med*. 2011;183[100]: 1419). Testing before CPAP treatment showed impairment in several cognitive domains and focal reductions of gray-matter volume in the left hippocampus and several other brain areas when compared with healthy age- and education-matched control subjects. After CPAP treatment for 3 months, significant improvements in memory, attention, executive function, and gray-matter volume in hippocampal and frontal structures were seen, suggesting that even a short duration of CPAP treatment can partially reverse the brain abnormalities of OSAS.

The duration of disease prior to therapy in these patients is unknown, but it is notable that patients with frank cognitive deterioration were excluded; whether more severe cognitive impairment would improve with therapy for sleep-disordered breathing remains unknown. It is possible that if left untreated, these changes could progress and become irreversible. Thus, emphasis should be placed on early diagnosis and treatment of OSAS.

Newer stimulant medications like armodafinil have been shown to improve not only sleepiness but also long-term memory (Roth et al. Sleep Breath. 2008;12[1]:53). Although these medications are FDA-approved for the treatment of residual sleepiness in patients with treated sleep apnea, their role in improving cognitive function needs to be evaluated further.

It is important for sleep medicine physicians to be cognizant of the effects of OSAS on cognitive function and to screen for it in their clinics. One simple screening instrument is the MCFSI (Mail-In Cognitive Function Screening Instrument), which is a self-administered test designed to identify cognitive impairment (Walsh et al. Alzheimer Dis Assoc Disord. 2006;20(4 Suppl 3):S170). The authors have found this tool to be a quick and effective screening tool in their patients with OSAS, although large studies validating it in this population are lacking.

It is our practice to refer patients with significantly abnormal scores on preliminary tests to a neuropsychologist for complete evaluation, which could involve the administration of tasks specifically designed to test for vigilance and working memory like the psychomotor vigilance task and digit span, providing more objective evidence of cognitive impairment. It also serves as a baseline for the individual patient for long-term follow-up.

Continued on following page

EDITOR'S NOTE

Evidence continues to mount demonstrating the multiple systemic effects of sleep apnea; in this month's Sleep Strategies, Drs. Walters and Lal review the cognitive repercussions of untreated sleep-disordered breathing. Given what we know about the growing prevalence of sleep apnea, should we consider more aggressive screening for OSA in patients demonstrating cognitive decline in much the same way we screen those with refractory hypertension or atrial fibrillation? While the sheer volume of referrals that could stem from such a practice may be daunting, the opportunity to potentially impact the natural history of dementia seems too promising to ignore.

Dr. David Schulman, FCCP, Section Editor

New members join the CHEST Physician editorial board

Dr. Jennifer D. Cox, FCCP, is an Assistant Professor of Pulmonary and Critical Care Medicine and clerkship director for the fourth-year medical student Critical Care Selective, Morsani College of Medicine, University of South Florida, in Tampa, Florida. Her academic interests include medical student, resident, and fellow education and simulation training. Her clinical interests include mechanical ventilation, critical care, palliative care in the ICU and advanced bronchoscopic techniques in the diagnosis of pulmonary and mediastinal nodules and masses.

Dr. Eric J. Gartman, FCCP, is an Assistant Professor of Medicine,Warren Alpert Medical School,Brown University, in Providence, Rhode Island. He is the site director for the Brown Fellowship Training Program in Pulmonary and Critical Care Medicine. He is a staff physician at the Memorial Hospital of Rhode Island in the Division of Pulmonary, Critical Care, and Sleep Medicine. He serves several leadership roles locally, including President of the Rhode Island Thoracic Society and Assistant Director of the weekly statewide Brown chest conference. Dr. Gartman's clinical and research interests are in airway diseases, pulmonary physiology, and critical care medicine.

Dr. Ramesh M. Gowda, MBBS, is Director, Peripheral Interventions, Cardiac Catheterization Laboratory, Beth Israel Medical Center, Heart Institute, New York, New York. He practices both general and interventional cardiology. He is proficient in radial access and a variety of newer techniques that treat peripheral arterial diseases. His procedures include but are not limited to coronary, carotid, and peripheral angiography; interventions; and pericardiocentesis. Dr. Gowda has served on the Cardiovascular Medicine and Surgery NetWork.

Dr. James A. L. Mathers Jr., FCCP, recently retired from Pulmonary Associates of Richmond, in Richmond, Virginia, with 30 years of private practice experience in pulmonary, critical care, and sleep medicine. Dr. Mathers has served the American College of Chest Physicians in numerous leadership roles including President in 2008-2009; Regent-at-Large on the Board of Regents; two terms on the Executive Committee of the Board; Trustee of The CHEST Foundation; Chair of the Government Relations Committee; and Chair of the Critical Care Work Group. Dr. Mathers has worked with national societies, legislators, and regulatory agencies to remove barriers to appropriate care for patients with diseases of the chest. He is currently a member of the National Association for Medical Direction of Respiratory Care and is the author of its monthly *Washington Watchline*.

Dr. Daniel R. Ouellette, FCCP, is an Associate Professor of Medicine, Wayne State University School of Medicine, in Detroit, Michigan, and a senior staff physician at Henry Ford Hospital in Detroit, where he chairs the Credentials Committee for the Pulmonary and Critical Care Fellowship Program. Dr. Ouellette has over 20 years of military service and was the consultant to the US Army Surgeon General for Pulmonary Medicine during the last several years of his military career. He is the Chair of the Guideline Oversight Committee for the American College of Chest Physicians (CHEST). Dr. Ouellette has been active in the leadership of CHEST with previous positions, including Chair of the Clinical Pulmonary NetWork, Chair of the Council of Governors, and a member of the Board of Regents. Dr. Ouellette's clinical areas of interest include general pulmonary and critical care medicine and evidence-based practice.

Dr. Francis J. Podbielski, FCCP, is Visiting Clinical Associate Professor of Surgery at the University of Illinois at Chicago - College of Medicine and the Medical Director of the lung cancer program at Jordan Hospital in Plymouth, Massachusetts. He joined the American College of Chest Physicians in 1997 and has served as the Governor for Massachusetts and was the Vice-Chair and Chair of the US and Canadian Council of Governors, the Chair of the Membership Committee, a member of the Nominating Committee and the Chest Medicine Affairs Committee, a Vice-Chair of the Capital Campaign Committee, and a member of the Board of Regents of the College. Dr. Podbielski's interests are thoracic oncology and surgical management of chest infections.

Dr. Eleanor M. Summerhill, FCCP, is an Associate Professor, Division of Pulmonary and Critical Care Medicine, Warren Alpert School of Medicine, Brown University, in Providence, Rhode Island. She is the Director of the Internal Medicine Residency Program at Memorial Hospital of Rhode Island. Dr. Summerhill has served on the American College of Chest Physicians (CHEST) Critical Care and Disaster Medicine NetWork steering committees and is a past Governor for Rhode Island. She has also been very active in developing the simulation-based difficult airway course for CHEST. Dr. Summerhill's research interests include simulation in medical education, disaster preparedness, obstructive lung diseases, and respiratory muscle function.

Dr. Krishna Sundar, FCCP, is Medical Director of the Sleep-Wake Center and Associate Professor (Clinical) in the Division of Pulmonary and Critical Care Medicine, University of Utah, in Salt Lake City, Utah. He is board-certified in sleep medicine, pulmonary disease, critical care medicine, and internal medicine. Dr. Sundar's research interests are centered on understanding the impact of OSA therapy in chronic lung disease and delineating mechanistic pathways of disease from untreated OSA. His work has included herpes reactivation in the ICU, use of ventilator strategies in influenza-ARDS, and understanding role of nonphagocytic NADPH oxidase in acute lung injury.

Continued from previous page

The long-term implications of OSAS on cognitive function are just beginning to be realized. The importance of early diagnosis and treatment of OSAS is becoming more evident, as we may be able to stop or partially reverse some of the underlying neurologic abnormalities with treatment. Given the strong association between OSAS and cognitive impairment, we recommend that all patients with MCI or frank dementia be screened for OSAS as a potentially reversible cause of these conditions; polysomnography should subsequently be offered to those patients who are deemed to be high risk for having OSA. Discussions with cognitively impaired patients about the implications of nonadherence with CPAP should be reiterated at each visit, particularly given the significant barrier that such impairment may create to reliable use of therapy.

Drs. Walters and Lal are from the Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC.

Why is this patient short of breath?

A simple, six-minute in-office test can help you find out with no capital risk to your practice.

In just six minutes Shape® can help drill down to the root cause of exertional dyspnea – right in the clinic. Shape is simple, objective and intuitive. With our pay-per-procedure plan there's no cost for the device. Shape elevates cardiopulmonary exercise testing to a new level.

Learn more by calling 1-888-SHAPE98 (888-742-7398)

or by visiting www.shapemedsystems.com.

SHAPE™