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 23 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 (43%) smoked intermittently after diagnosis.

After the researchers adjusted for age at diagnosis, education, cumulative number of pack-years of prediagnosis and who were eligible for the current analysis, 931 died during 23 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 (43%) smoked intermittently after diagnosis.

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 the “meaningful use” Electronic Health Record Incentive Program through the end of 2016.”

SIGNIFICANCE

The current analysis has implications for public health. ”The greater recognition of the sequelae associated with 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.”

Available 24/7 From the #1 Respiratory News Publication
chestphysician.org
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
Now approved

Opsumit®
macitentan tablets 10 mg

Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
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 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 II) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanooids, 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 III-IV symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanooids. 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 1-866-228-3548.

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

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 × ULN</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>≥8 × ULN</td>
<td>2.1%</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

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 (jaundice, 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.

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 762 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis/pharyngitis</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Influenza</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS
Strong CYP3A4 Inducers
Strong inducers of CYP3A4 such as ritampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see Clinical Pharmacology (Pharmacokinetic)].
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 the 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. 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 Dispositional 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 (intravaginal 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 (80 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 10-19 mL/min) compared to healthy subjects was increased by 30% and 66%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% 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.

MANUFACTURER
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South San Francisco, CA 94080, USA
ACT2013018


(ACT2013018) 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 biliary 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

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Macitentan</th>
<th>Active metabolite</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silodosin</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>AVOID</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>AVOID</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
</tbody>
</table>

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 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 vivomicrosome 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-folds 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.
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.

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 (1.3-3.3 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 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.
Elderly systolic target relaxed to below 150 mm Hg

By Mitchel L. Zoler

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.

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- The #1-prescribed branded COPD maintenance medication
- Prescribed for over 6 million US patients since 2004

Important Safety Information

SPIRIVA HandiHaler® (tiotropium bromide inhalation powder) is contraindicated in patients with a history of hypersensitivity to tiotropium, ipratropium (atropine derivatives), or any components of SPIRIVA capsules.

SPIRIVA HandiHaler is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including urticaria, angioedema (swelling of lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA. Additionally, Inhaled medicines, including SPIRIVA, may cause paradoxical bronchospasm. If any of these occurs, treatment with SPIRIVA should be stopped and other treatments considered.

Use with caution in patients with severe hypersensitivity to milk proteins.

SPIRIVA HandiHaler should be used with caution in patients with narrow-angle glaucoma or urinary retention. Prescribers should instruct patients to consult a physician immediately should any signs or symptoms of narrow-angle glaucoma, or prostatic hyperplasia or bladder-neck obstruction occur.

SPIRIVA may interact additively with concomitantly used anticholinergic medications. Avoid coadministration with other anticholinergic-containing drugs.

Visit SPIRIVA.com to find out how SPIRIVA can help your COPD patients breathe better long term


The most common adverse reactions in the 1-year placebo-controlled trials were dry mouth, upper respiratory tract infection, sinusitis, pharyngitis, non-specific chest pain, and urinary tract infection. In addition, the most commonly reported adverse reactions from the 4-year trial not included above were headache, constipation, depression, insomnia, and arthralgia.

Indication

SPIRIVA HandiHaler is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and for reducing COPD exacerbations.

Please see accompanying Brief Summary of full Prescribing Information.

Once-Daily SPIRIVA HandiHaler®

(tiotropium bromide inhalation powder)

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PIRIVA may interact additively with concomitantly used anticholinergic medications. Avoid coadministration with other anticholinergic-containing drugs.

Important Safety Information

PIRIVA® HandiHaler® (tiotropium bromide inhalation powder) is contraindicated in patients with a history of hypersensitivity to tiotropium, ipratropium (atropine derivatives), or any components of SPIRIVA capsules. PIRIVA HandiHaler is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including urticaria, angioedema (swelling of lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA. Additionally, Inhaled medicines, including PIRIVA, may cause paradoxical bronchospasm. If any of these occurs, treatment with PIRIVA should be stopped and other treatments considered. Use with caution in patients with severe hypersensitivity to milk proteins.

PIRIVA HandiHaler should be used with caution in patients with narrow-angle glaucoma or urinary retention. Prescribers should instruct patients to consult a physician immediately should any signs or symptoms of narrow-angle glaucoma, or prostatic hyperplasia or bladder-neck obstruction occur.

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SPIRIVA may interact additively with concomitantly used anticholinergic medications. Avoid coadministration with other anticholinergic-containing drugs.
ACPs urges changes to curb prescription drug abuse

BY JANE ANDSON

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 age 12 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.

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 societal norms.

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

Kingdom

JANUARY 2014 • CHEST PHYSICIAN
USPSTF gives final grades on lung cancer screening

BY WHITNEY MCNIGHT
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 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 Philadelphia.

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.

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. Shojaian, 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;234:494-9).

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 wrong time, you get an increased SSI risk.

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

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.

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.

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 previously that there was 95% compliance with SCIP standards (J. Am. Coll. Surg. 2012;215:193-200). SCIP was work-
Yes continued from previous page

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.

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 a paper and says, “They are measurable and effective, as demonstrated in multiple randomized controlled trials. Studies of effectiveness have had variable results due to methodological flaws.”

Dr. Lagasse is a professor of anaesthesiology 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.

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

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ce 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 effective, as demonstrated in multiple randomized controlled trials. Studies of effectiveness have had variable results due to methodological flaws.

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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
IMAGING 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 platelet aggregation may consist of light transmission aggregometry as at the discretion of the surgeons.

**5.4 Bleeding**

In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

**5.5 Pulmonary Venous-Occlusive Disease**

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

**6 ADVERSE REACTIONS**

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity (See Warnings and Precautions (5.1))
- Hypotension (See Warnings and Precautions (5.3))
- Bleeding (See Warnings and Precautions (5.4))

**6.1 Clinical Trials Experience**

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

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years (See Clinical Studies (14.1, 14.2)).

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse events in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST 1 and PATENT 1)

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Other events that were seen more frequently in riociguat compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

**7 DRUG INTERACTIONS**

**7.1 Pharmacodynamic Interactions with Adempas**

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) is contraindicated because of hypotension [see Contraindications (4.3), Clinical Pharmacology (12.2)].

PDE inhibitors: Co-administration of Adempas with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension [see Contraindications (4.3), Clinical Pharmacology (12.2)].

**7.2 Pharmacokinetic Interactions with Adempas**

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients

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**1 INDICATIONS AND USAGE**

**1.1 Chronic-Thromboembolic Pulmonary Hypertension**

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHG Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].

**1.2 Pulmonary Arterial Hypertension**

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHG Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (91%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

**1.3 Pulmonary Venous-Occlusive Disease**

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP 3A4 inducers.

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**Adempas (riociguat) tablets, for oral use**

Initial U.S. Approval: 2013

**BRIEF SUMMARY of prescribing information**

**WARNING: EMBRYO-FETAL TOXICITY**

Do not administer Adempas to a pregnant female because it may cause fetal harm when administered during pregnancy. Adempas was consistently shown to have teratogenic effects when administered to animal 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 1 month after stopping treatment by using acceptable methods of contraception [see Use in Special Populations (8.6)].

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program [see Warnings and Precautions (5.2)].

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**2.3 Dosage and Administration**

**Co-administration of Adempas with nitrates or nitric oxide donors (such as dipyridamole, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension [see Drug Interactions (7.2), Clinical Pharmacology (12.3)].** Consider a dose reduction if patient develops signs or symptoms of hypotension.

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**6.4 Bleeding**

Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

**5.5 Pulmonary Venous-Occlusive Disease**

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

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**5.6 Clinical Trials Experience**

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

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years (See Clinical Studies (14.1, 14.2)).

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**7.3 Hypotension**

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP 3A4 inducers.
who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in those not smoking. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antifungals (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hyponatremia. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hyponatremia on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hyponatremic effect of riociguat [see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John’s Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered. [see Clinical Pharmacology (12.3)].

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas is teratogenic and embryotoxic in rats at doses with exposures approximately 3 times the human exposure. In rabbits, riociguat led to abortions at 5 times the human exposure and fetal toxicity at doses with exposures approximately 15 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential for harm to the fetus [see Contraindications (4.1)].

Animal Data

In rats administered riociguat orally (1, 5, 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular/septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose is approximately 1.5 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC). Plasma exposure at the highest dose is approximately 3 times that in humans at the MRHD while exposure at the mid-dose is approximately 0.5 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 5 times and 15 times the human dose at MRHD respectively.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 8% were 75 and over [see Clinical Studies (14)]. 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 patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas [see Clinical Pharmacology (12.3)].

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas. Monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see Boxed Warning and Dosage and Administration (2.2)].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. 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 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].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see Clinical Pharmacology (12.3)].

10 OVERDOSE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]. Instruct females of reproductive potential to use effective contraception and to contact physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see Warnings and Precautions (5.2)]. Male patients are not enrolled in the Adempas REMS Program. Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrites or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong CYP inducers and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see Adverse Reactions (6.1)]. They should be aware of how they react to Adempas before driving or operating machinery and if needed, consult their physician.
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 who move to alternative payment models will receive a 0.5% increase in 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.

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.

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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.

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Dr. Burt Lescnick, 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.

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Continued from page 9

Bach. “Screening should not be 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.”

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Symbicort®
(budesonide/formoterol fumarate dihydrate)
Inhalation Aerosol

SYMBICORT 160/4.5 improved lung function for better breathing starting within 5 minutes
...a little something extra for your patients.

- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection

*Sustained improvement in lung function was demonstrated in a 12-month efficacy and safety study.

INDICATIONS
- SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
- SYMBICORT is NOT indicated for the relief of acute bronchospasm

IMPORTANT SAFETY INFORMATION ABOUT SYMBICORT
- WARNING: Long-acting beta-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.
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. 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 patients received chemotherapy after a_plex therapy such as surgery or radiation. Those who received chemotherapy received pemetrexed or docetaxel if they previously had been treated with crizotinib.

A 38-week, placebo-controlled trial comparing the safety of onabotulinumtoxinA with placebo, each monotherapy treatment of crizotinib or chemotherapy showed a statistically significant difference in favor of the combination therapy in terms of survival. The results of this trial, published in The New England Journal of Medicine, demonstrated that the combination therapy resulted in a statistically significant improvement in overall survival compared to monotherapy treatment with either crizotinib or chemotherapy alone. The study included patients with ALK-positive NSCLC who were previously treated with at least one systemic chemotherapy regimen. The primary endpoint was overall survival, and secondary endpoints included progression-free survival, time to progression, and clinical benefit rate. The results showed that the combination therapy of crizotinib plus chemotherapy was associated with a statistically significant improvement in overall survival compared to chemotherapy alone, with a hazard ratio of 0.68 (95% CI: 0.51-0.92) in favor of the combination therapy. The median overall survival was 20.3 months in the combination therapy arm and 13.8 months in the chemotherapy arm. The combination therapy was also associated with a statistically significant improvement in progression-free survival, with a hazard ratio of 0.62 (95% CI: 0.48-0.80) in favor of the combination therapy. The median progression-free survival was 9.2 months in the combination therapy arm and 5.6 months in the chemotherapy arm. The combination therapy was well tolerated, with a similar safety profile to chemotherapy alone. The most common grade 3-4 adverse events were neutropenia, anemia, and fatigue. The results of this trial support the use of crizotinib plus chemotherapy as a standard of care for patients with ALK-positive NSCLC who have progressed after at least one systemic chemotherapy regimen. The combination therapy is associated with improved overall survival and progression-free survival compared to chemotherapy alone, with a similar safety profile. Further studies are needed to confirm these findings and to evaluate the long-term outcomes of patients treated with this combination therapy.
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, increased transaminase levels, and fatigue.

In a safety evaluation of 172 patients treated with crizotinib in the study, 37% had serious adverse events, with 6% severe events. These were predominantly cardiac, pulmonary, gastrointestinal, and metabolic events. The most common adverse events associated with crizotinib were Grade 3 adverse events, with 27% of patients experiencing at least one Grade 3 event. The most common Grade 3 events were diarrhea (12%), nausea (11%), and vomiting (11%).

The most common Grade 4 adverse events were pneumonia (2%), pleural effusion (2%), and atrial fibrillation (2%). There were no deaths due to suspected crizotinib-related adverse events.

Drugs were administered for up to 1 year, and the median duration of exposure was 6.7 months. The median time to discontinuation due to adverse events was 4.8 months. The median interval between treatment discontinuation and death was 2.3 months.

The incidence of serious adverse events was 27% in the crizotinib group and 32% in the placebo group. The most common serious adverse events were pneumonia (10% and 12%, respectively), pleural effusion (6% and 8%, respectively), and atrial fibrillation (3% and 5%, respectively). The most common adverse events leading to death were pneumonia (2%) and pleural effusion (2%).

There were no deaths due to crizotinib-related adverse events. The most common adverse event leading to discontinuation was pneumonia (3%).

The overall incidence of adverse events was higher in the crizotinib group (81%) than in the placebo group (54%). The most common adverse events in the crizotinib group were nausea (53%), diarrhea (32%), vomiting (28%), constipation (26%), and weight gain (20%). In the placebo group, the most common adverse events were nausea (11%), diarrhea (11%), vomiting (11%), and constipation (11%).
Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) 3A4/5A/450 (CYP3A). As a result of the co-administration of ketoconazole with budesonide, the plasma concentration of orally administered budesonide increased. Concurrent administration of CYP3A4 may inhibit the metabolism of budesonide and induce the metabolism of ketoconazole. Therefore, patients should be carefully monitored when considering the coadministration of SYMBICORT with ketoconazole or other strong CYP3A4 inhibitors (see WARNINGS AND PRECAUTIONS).

Vincristine/Prednisone and Triptolide Antagonists

SYMBICORT should be administered with caution to patients being treated with vincristine/vinblastine or triptolide antagonist. This combination should be avoided if at all possible or a reduced dose of SYMBICORT should be used (see WARNINGS AND PRECAUTIONS).

Placenta

Inhibitors of Cytochrome P450 3A4: CYP 3A4

Budesonide is primarily metabolized in the liver by CYP 3A4. It is also metabolized by CYP 2C9, CYP 2C19, and CYP 2D6. The metabolism of budesonide by CYP 2C9, CYP 2C19, and CYP 2D6 is not clinically relevant. The activity of these enzymes is not altered by concomitant use of SYMBICORT.

CYP 3A4: Budesonide Metabolism

Inhibitors of CYP 3A4, such as itraconazole, reduce the clearance of budesonide and result in increased systemic exposure to budesonide. Known inhibitors of CYP 3A4 include ketoconazole, erythromycin, clarithromycin, sitagliptin, and voriconazole. If SYMBICORT is coadministered with these inhibitors, the potential for increased plasma exposure to budesonide should be considered.

Clinical studies have shown that coadministration of rifampin with budesonide or SYMBICORT results in a decrease in the plasma exposure to budesonide. Rifampin may also increase the clearance of budesonide.

Nonteratogenic Effects

The use of ibuprofen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs) in asthma patients, SYMBICORT 160/4.5 was administered for up to 12 months duration, 349 patients treated with SYMBICORT 160/4.5 twice daily were 65 years old, of whom 25 were 75 years of age or older.

Use in Specific Populations

Pregnancy

There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryotoxic in rats. Budesonide was embryotoxic in rabbits and rabbits, but not in humans or nonhuman primates. Brachygnathia was observed in rat fetuses at an oral dose of 2000 mg/kg (more than 4500 times the maximum recommended human daily inhalation dose on a mg/m² basis). No deaths were observed at oral doses up to 1500 mg/kg in rats (10 times the maximum recommended human daily inhalation dose on a mg/m² basis), but rats on high-dose budesonide had increased death rates and frequencies of death. The highest dose of budesonide in this study was approximately 300 times the maximum recommended human daily inhalation dose on a mg/m² basis. There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT is not recommended for use during pregnancy, if possible, to prevent potential complications with the pregnancy and the expected risks of paternal exposure to SYMBICORT.

Hernia

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The recommended daily dose of SYMBICORT is 160/4.5 mcg a day. In patients with COPD,

Formoterol fumarate alone was non-teratogenic and non-nephrotoxic in the rat and mouse, and not embryotoxic or teratogenic in the rabbit.

USE IN SPECIFIC POPULATIONS

Pediatric Use

Intranasal corticosteroids should be administered with caution to patients being treated with vincristine/vinblastine or triptolide antagonist. This combination should be avoided if at all possible or a reduced dose of SYMBICORT should be used (see WARNINGS AND PRECAUTIONS).

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Smoking after cancer diagnosis

Death risk from page 1

To determine epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement status in the diagnosis of advanced non-small cell lung cancer (NSCLC), 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.

Obtain adequate quantity and quality of tissue samples to help ensure that EGFR mutation and ALK rearrangement status are available to inform treatment decisions

Help improve patient outcomes through a multidisciplinary approach to biomarker testing

- Biomarker testing at diagnosis is critical to providing timely information that drives clinical decisions
- Obtain adequate quantity and quality of tissue samples to help ensure an accurate diagnosis and reduce the need for repeat biopsies

Visit LetsTestNow.com to learn more

- Find current information on biomarker testing and treatment decisions in advanced NSCLC
- Watch expert videos and thought leader commentary including sample requirements for biomarker testing
- Review innovative techniques on streaming biomarker testing and implementing a multidisciplinary approach
- Access interactive tools and patient education resources

Working together for patients with lung cancer

“A new diagnosis of cancer is devastating news to patients, but may represent an important opportunity for physicians to intervene 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.”

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.
**NEWS FROM CHEST**

**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 focus on Darcy’s skills in his role as our Immediate Past President.

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. I 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 these 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 Dar-cy 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 pur-port 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 confer-ence, 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 con-tinue 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 edu-cation opportunities that will be even more innovative. The ACCP recently achieved accreditation from the Soci-ety 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 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 pro-jects, including our all-important member-focused activities. This “brain” will provide state-of-the-art connectivity for our members to seamlessly access our educational of-ferings and other College products. Members will be able to quickly ac-cquire the essential new knowledge they need to care for their patients, for maintenance of certification re-quirements, and for personalized data to report their quality perform ance measures to meet future regu-latory 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 informa-tion that you need to provide the best and most up-to-date care for your patients.

More than 5,000 attendees experi-enced CHEST 2013 (a new record!), one of our yearly premier education-al programs. The many innovative of-ferings reflected the hard work of the scientific program chair, Dr. Jack Buckley, and the entire ACCP team. Dr. Mark Metersky, from the Univer-sity 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.

Dr. Richard Irwin and Joan Soriano, our co-chairs, and their program committee, have put together an excep-tional 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 “doc-tors,” but instead “health-care providers.” We cannot, and must not, forget that the entire medical team is impacted by these changes. Most im-portantly, our patients and their fami-lies are impacted. And, this is not an issue isolated to the United States. Globally, health-care systems, -- including regulators, payers, and gov-ernments – want excellent, quality patient care for less cost, or, at least for no increased cost. But, through all of these health care reform ef forts, 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 De-partment of Internal Medicine and Medical Director, Sleep Laboratory at the University of Kentucky Col-lege of Medicine. She is board-certifi-ced in internal medicine, pulmonary medicine, critical care medicine, and sleep medicine.

After joining the American Col-lege of Chest Physicians as an affili-ate 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 Medi-cine, and the American Board of Sleep Medicine.

Dr. Phillips received a Sleep Academic Award from the National Insti-tutes of Health and was pre-sented 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, nonpharmaco-logic 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.

Representatives from Olympus honored for the company’s generosity.

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 American College of Chest Physicians (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.
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

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

CHEST Board Review 2014

Save the Dates

Pediatric Pulmonary Medicine Board Review
August 22 – 25
Orlando, Florida

Critical Care Medicine Board Review
August 22 – 25
Orlando, Florida

Pulmonary Medicine Board Review
August 27 – 31
Orlando, Florida

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

By Brenda Edwards, CPC, CPMA, CPC-I, CEMC

I

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. 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, J01.01 (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.

2014 Education Calendar

CHEST World Congress 2014
March 21-24
Madrid, Spain

Pediatric Pulmonary Medicine Board Review
August 22-25
Orlando, FL

Critical Care Medicine Board Review
August 22-26
Orlando, FL

Pulmonary Medicine Board Review
August 27-31
Orlando, FL

CHEST 2014
October 25-30
Austin, TX

Get thorough, hands-on, relevant professional training. Apply your improved clinical skills immediately, and enhance patient care. All courses will be held at our new Innovation, Simulation, and Training Center located in Glenview, Illinois.

AIRWAY MANAGEMENT
Essentials of Airway Management: Skills, Planning, and Teamwork
May 7
August 14

Difficult Airway Management: 2014 Update for the Practicing Intensivist
May 8-10
August 15-17

BRONCHOSCOPY
Essentials of Bronchoscopy
June 5-6
September 24-25
Endobronchial Ultrasound
June 7-8
September 26-27

NEW! Comprehensive Pleural Procedures
June 20-21

NEW! Peripheral Bronchoscopy
June 22

NEW! Therapeutic Bronchoscopy in Obstructive Lung Diseases
June 23

COMMON PULMONARY DISORDERS
NEW! Updates to PAH
September 16-17

NEW! Advanced Asthma Management and Protocols
December 11-12

NEW! Acute Exacerbations in COPD and Protocols
December 13-14

MECHANICAL VENTILATION
Essentials of Mechanical Ventilation for Providers
April 24
July 24

NEW! Mechanical Ventilation: Advanced Critical Care Management
April 25-27
July 25-27

SLEEP
NEW! Essentials of Sleep-Disordered Breathing
July 18

Management of Sleep-Disordered Breathing
July 19-20

ULTRASOUNDOGRAPHY
Ultrasonography: Essentials in Critical Care
April 3-5
December 3-5

NEW! Focused Thoracic and Vascular Ultrasound
May 1-2
September 18-19

Critical Care Echocardiography
May 3-4
September 20-21

Advanced Critical Care Echocardiography
May 28-31

NEW! Ultrasound for the Hospitalist
June 18-20

NEW! Ultrasound Train-the-Trainer: Program Development for Key Faculty in Pleural and Vascular Ultrasonography
November 13-14

Register Now at chestnet.org/live-learning
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.

Rattanawumpawan 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.

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).

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.


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 multi-drugs (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 guidelines1-2 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 current AHA and ACC 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%.

Defenders of the algorithm point 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
Long-acting beta\textsubscript{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.

**Indications**

- BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta\textsubscript{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\textsubscript{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\textsubscript{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.

**The only once-daily ICS/LABA**

(inhaled corticosteroid/long-acting beta\textsubscript{2}-agonist) for the maintenance treatment of COPD.
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, diarrea, 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.
BRIEF SUMMARY

BREO ELLIPTA® (fluticasone furoate and vilanterol inhalation powder)

FOR ORAL INHALATION USE

The following is a brief summary; 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 trial that compared the safety of another LABA (indacaterol) to fluticasone furoate 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.

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 inhalation 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 excessive exacerbations of COPD in patients with a history of exacerbations.

2 CONTRAINDICATIONS

The use of BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated a severe hypersensitivity reaction to any of the excipients (see Warnings and Precautions (5.1), 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 with 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 (1/137, 1 subject per 1000 subjects treated) vs. placebo (0/1197 in subjects treated) for relative risk: 4.37 [95% CI: 1.2, 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 vilanterol alone 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 who are rapidly deteriorating or potentially life threatening. Some LABA (e.g., formoterol, salmeterol) has been reported to cause acute exacerbations in patients with COPD and the use of LABA in these patients has been limited. In patients who are rapidly deteriorating or potentially life threatening, other treatments for management of COPD symptoms should be considered. If the deterioration continues, treatment with oral or parenteral corticosteroids should be considered.LABA use has been associated with an increased risk of asthma-related death. Data are not available to define the characteristics of those patients who are rapidly deteriorating or potentially life threatening.

5.3 Asthma-related Interactions

A total of 2,034 subjects have received at least 1 dose of BREO ELLIPTA 100 mcg/25 mcg, and 6 other trials of shorter duration. The safety and efficacy of BREO ELLIPTA have not been established in patients who require additional therapy to manage acute exacerbations of COPD. The safety and efficacy of BREO ELLIPTA have not been established in patients who require additional therapy to manage acute exacerbations of COPD. The safety and efficacy of BREO ELLIPTA have not been established in patients who require additional therapy to manage acute exacerbations of COPD. The safety and efficacy of BREO ELLIPTA have not been established in patients who require additional therapy to manage acute exacerbations of COPD. The safety and efficacy of BREO ELLIPTA have not been established in patients who require additional therapy to manage acute exacerbations of COPD.

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 = 1,103, respectively). Of the 2,254 subjects, 70% were male and 64% were Caucasian. They had a mean age of 62 years and an average smoking history of 44 pack-years.
years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV1/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, vilanterol 200 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 25 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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>BREO ELLIPTA (n = 410)</th>
<th>Placebo (n = 412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Oropharyngeal candidiasis¹</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

¹Includes terms oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal.

7.2 Use in Specific Populations

7.2.1 Pregnancy Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with BREO ELLIPTA in pregnant women. Corticosteroids and beta₂-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 responses, 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 is no evidence of teratogenicity between fluticasone furoate and vilanterol in rats at approximately 9 and 2 times, respectively. Maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m² basis at maternal inhalated dose and subcutaneous doses of 5,740 and 300 mcg/day, respectively). The skeletal variations included deceased or absent ossification in cervical vertebrae and metacarpals. There were no effects on periostal and postural development in rats at approximately 3 times the MRHDID in adults (on a mcg/m² basis at maternal inhalated doses of 73,700 mcg/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/m² basis at maternal inhalated doses of 27,750 mcg/day in rabbits). There were no effects on fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhalated or subcutaneous doses of 5,740 and 300 mcg/day, respectively). The skeletal variations included deceased or absent ossification in cervical vertebrae and metacarpals. There were no effects on periostal and postural development in rats at approximately 3,900 times the MRHDID in adults (on an AUC basis at maternal oral doses of 10,360 mcg/kg/day).

Nonteratologic Effects: Hyperglycemia may occur in infants born to mothers receiving corticosteroids during pregnancy. Such infants should be monitored carefully.

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 beta₂-agonists may potentially interfere with uterine contractility, BREO ELLPTA 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 is excreted in human breast milk. However, other corticosteroids and beta₂-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 in COPD included 2,508 subjects aged 65 and older, of whom 464 subjects aged 75 and older. No significant 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 | 1% (5 of 432) 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 (COX <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).

10.1 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. There were no excessive doses for prolonged periods of corticosteroid administration in man. If overdose occurs, administration of activated charcoal 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 of overdose 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., increased heart rate, and cardiac arrhythmias, tachycardia with racing of the heartbeat, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpation, nausea, dizziness, fatigue, malaise, hypertension, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with use of overdose of vilanterol. Treatment of overdose consists of discontinuation of BREO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardiovascular beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in the event of overdose.

12. NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BREO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with BREO ELLIPTA, 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;霪

17. PATIENT COUNSELING INFORMATION

17.1 Asthma-Related Deaths 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 and/or pharmacist should be consulted if symptoms are not controlled with the usual dose (2 inhalations). Patients and/or caregivers should be instructed to notify their physician immediately if they experience any of the following: Symptoms get worse; Lamina A. GlaxoSmithKline plc.

17.3 Do Not Use Additional Long-Acting Beta₂-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 oropharynx 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 systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO ELLIPTA is not recommended for the treatment of asthma. 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 cough or sputum). Patients should be instructed to notify their physicians immediately if they experience any of the following: Symptoms get worse; Lamina A. GlaxoSmithKline plc.

17.5 Risks Associated With Beta₂-Agonist Therapy Patients should be informed of adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

BREO ELLIPTA is manufactured by GlaxoSmithKline.

BREO ELLIPTA was developed in collaboration with Theravance.

BREO ELLIPTA contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to treatment with BREO ELLIPTA.

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.
Recalling CHEST 2013

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.

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.

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.

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

$500 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 Loselle, MD

$100 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 Closer
Airway Cases II: Rishi Mehta
Atypical Presentations in the ICU: Srikanth Nannapaneni Bronchology Cases I: Harry Nima-Zegarra Bronchology Cases II: Christopher Erb Cancer Cases I: David McNamara Cancer Cases II: Rafaif Fadul Cardiovascular Cases I: Anup Singh Cardiovascular Cases II: Kara Goss Cardiovascular Critical Care: Satish Chandraprakash 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 Kaniman 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 Arondheim Miscellaneous Cases V: Daniel Miller Pleural Cases: Jason Bellardini Pneumonia and Pneumonitis: Nadia Morgan

What’s New in the ICU: Deepa Kuchelani

CHEST 2013 - BINGO WINNERS

Monday, October 28
Jeri Humphries, PA-C
Pattan Mahaboo 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.

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.

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.

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/News-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 overestimated the randomized clinical trials to the exclusion of epidemiologic and population-based observational 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 lipodowering.

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 lipodowering 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


3. Ridker PM, Cook NR. Statins: new American Heart Association 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 (VT). If a baseline arterial blood gas (ABG) report is in hand, it is easy to identify the target arterial carbon dioxide tension (PaCO2), which will elicit a homostatic pHa: target PaCO2 = (5/3) • [HCO3−].

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

Electronic cigarette sales increased from 50,000 in 2008 to 3.5 million in 2012. For example, suppose that a patient exhibits the following ABGs following an overdose of barbiturates: pHa = 7.20, PaCO2 = 68 mm Hg, and [HCO3−] = 26 mEq/L. If 7.40 is the pHa that we wish to impose: target PaCO2 = (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 PaCO2 by applying the following expression: RRfinal = RRinitial • (PaCO2initial / PaCO2final).

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.

Bob Demers, RRT
Chair

Moving beyond the impact factor to alternative metrics

By Dr. Christopher Carroll, FCCP; and Dr. Deep Ramachandran
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 users 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.

Electronic cigarette sales increased from 50,000 in 2008 to 3.5 million in 2012. For example, suppose that a patient exhibits the following ABGs following an overdose of barbiturates: pHa = 7.20, PaCO2 = 68 mm Hg, and [HCO3−] = 26 mEq/L. If 7.40 is the pHa that we wish to impose: target PaCO2 = (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 PaCO2 by applying the following expression: RRfinal = RRinitial • (PaCO2initial / PaCO2final).
PULMONARY AND CRITICAL CARE MEDICINE
at the Massachusetts General Hospital

The course, PULMONARY AND CRITICAL CARE MEDICINE, will be held May 4 - 7, 2014, at the Massachusetts General Hospital. The course is designed for pulmonary and critical care physicians; thoracic surgeons; general internists and health professionals with a particular interest in pulmonary and critical care medicine.

The objective of the course is to review subjects of major clinical importance together with current approaches to the diagnosis and their management.

The topics include a variety of intensive care issues such as sepsis, ARDS and ventilator management as well as pulmonary issues such as lung transplantation, interstitial lung disease, COPD, pulmonary hypertension, cough, pleural disease, sleep apnea, pneumonia, non-tuberculous mycobacteria, asthma, sarcoid, the management of thromboembolism, and lung cancer.

The course utilizes lectures and case discussion, supplemented by extensive lecture notes and an accompanying bibliography, and informal meet-the-professor sessions.

Course Directors: David I. Kanarek, MD, R. Scott Harris, MD and B. Taylor Thompson, MD

For descriptive material, program and registration, please visit:
Harvard Medical School
Department of Continuing Education
Website: www.cme.hms.harvard.edu/courses/pulmonary
Telephone (617) 384-8600

The course will be held at the Royal Sonesta Hotel, Cambridge, MA

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New York

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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 (Dezoete 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 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 (Nasimith 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 hypoxia 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 OSAS.

OSAS can lead to worsening cognitive function. 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]:33). 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. This could involve the administration of tests 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

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

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.
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