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Older adults who have previously received only PPSV23 should receive a dose of PCV13 at least 12 months later.

ACIP advises PCV13 for all 65 and older

BY AMY KARON
Frontline Medical News

FROM MORBIDITY AND
MORTALITY WEEKLY REPORT

All adults who are 65 years or older should receive 13-valent pneumococcal conjugate vaccine (PCV13) routinely in series with 23-valent pneumococcal polysaccharide vaccine (PPSV23), according to a new recommendation from the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP). The recommendation appears in the Sept. 19 issue of *Morbidity and Mortality Weekly Report*.

The ACIP recommenda-

tion calls for pneumococcal vaccine-naïve adults aged 65 and older to receive one dose of PCV13 vaccine, followed by a dose of PPSV23 6-12 months later (MMWR 2014;63;822-5). Older adults who have previously received only PPSV23 should receive a dose of PCV13 at least 12 months later, wrote Sara Tomczyk of the CDC and her associates.

ACIP has recommended PPSV23 for older adults since 2010. In 2012, the committee made its first recommendation for PCV13, targeting patients 19 years and older who have immunocompromising conditions, functional or an-

See **PCV13** • page 7

Medicare proposes to cover LDCT screen for lung ca

Specialized centers may manage most.

BY GREGORY
TWACHTMAN
Frontline Medical News

Medicare has announced a proposal to cover low-dose computed tomography screens for patients at high risk for lung cancer.

"The evidence is sufficient to add a lung cancer screening counseling and shared decision making visit, and for appropriate beneficiaries, screening for lung cancer with low-dose computed tomography, once per year, as an additional preventive service benefit under the Medicare program," officials from

the Centers for Medicare & Medicaid Services wrote in the proposed national coverage decision, which was announced Nov. 10.

The proposed coverage decision was made despite the Medicare Evidence Development and Coverage Advisory Commission recommendation earlier this year that opposed covering LDCT screening. More recently, however, a study has found LDCT screening to be cost effective for patients at high risk for lung cancer (N. Engl. J Med. 2014;371:1793-802 [doi:10.1056/NEJMoa1312547]).

See **LDCT** • page 6

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Device use did not impair sexual quality of life. • 9

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Medicare inches toward pay for counseling patients. • 31

Rapid prophylaxis didn't cut PEs

BY SHERRY BOSCHERT
Frontline Medical News

AT THE ACS CLINICAL CONGRESS

SAN FRANCISCO – Delivering prophylactic therapies against venous thromboembolism sooner and to more patients admitted for trauma failed to reduce the risk of pulmonary embolism in a 6-year study of

data on 23,863 patients.

Dr. Matthew J. Pommerening and his associates at the University of Texas, Houston, retrospectively studied data on the management and outcomes of 11,292 adults admitted to their level 1 trauma center in 2006-2008 before implementation of a performance-improvement pro-

gram, and 12,571 patients admitted in 2009-2011, after the program was in place.

The performance-improvement program included sequential interventions such as audits for missed doses of thromboprophylactic medications, goals for earlier and more aggressive

See **PE in Trauma** • page 8

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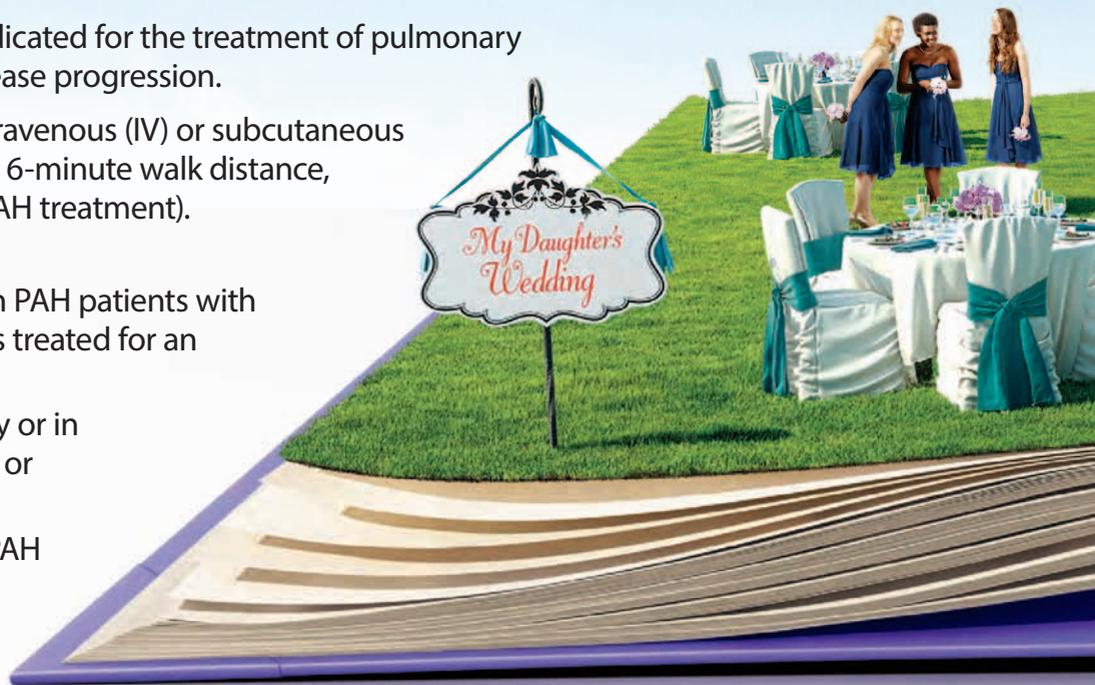
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HELP HER WRITE FUTURE CHAPTERS

Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
 - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
 - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).



IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

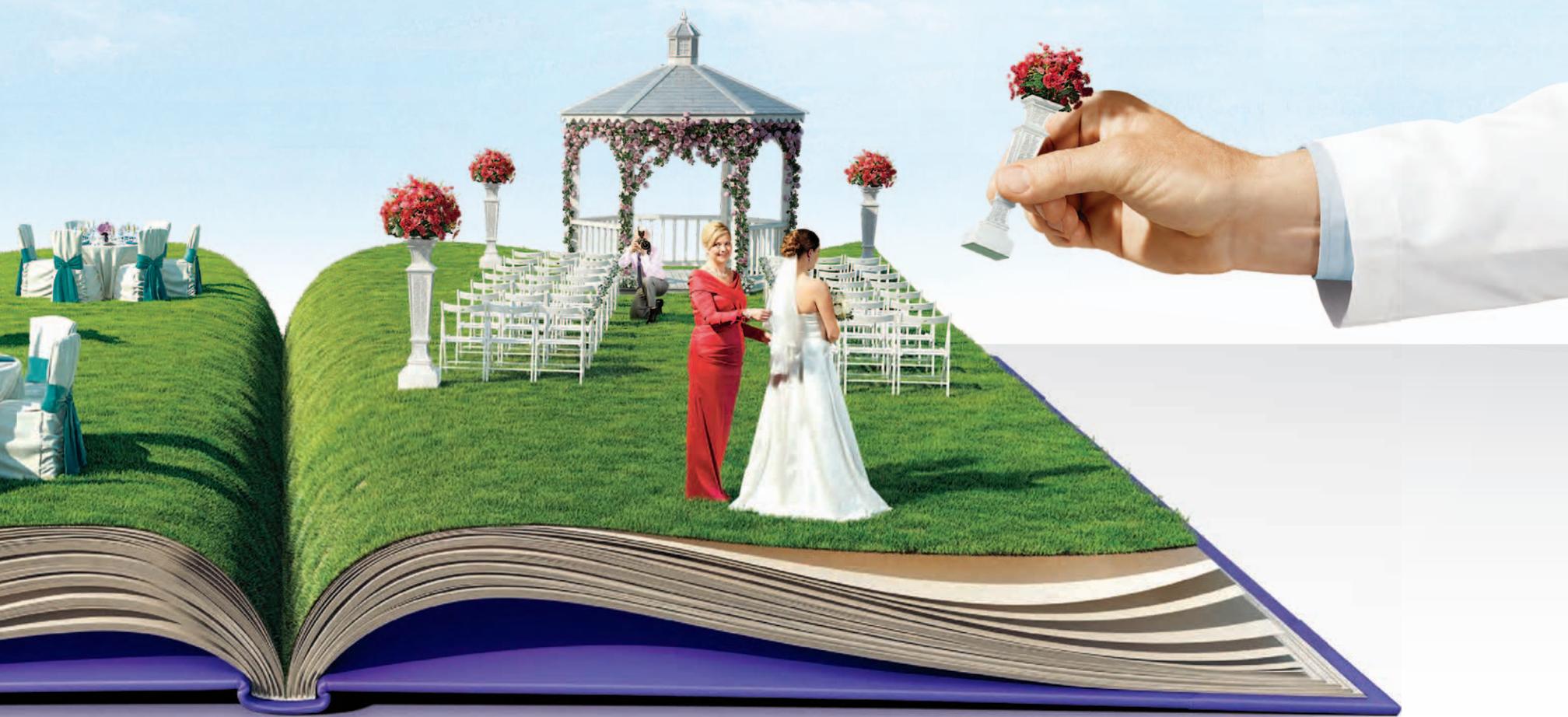
Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- 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.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study $>3 \times \text{ULN}$ were 3.4% for OPSUMIT vs 4.5% for placebo, and $>8 \times \text{ULN}$ were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin $>2 \times \text{ULN}$, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT



Patient dramatization

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 in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. 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.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by $\geq 3\%$) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 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. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

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

FUTURE.
FORWARD. |  **Opsumit**
macitentan tablets 10 mg



Rx only

BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

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

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

CONTRAINDICATIONS

Pregnancy

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

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

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

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

OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include the following:

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

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

OPSUMIT® (macitentan)

Hepatotoxicity

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

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

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

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

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

Hemoglobin Decrease

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

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

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

Table 2: Adverse Reactions

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

DRUG INTERACTIONS

Strong CYP3A4 Inducers

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

OPSUMIT® (macitentan)

Strong CYP3A4 Inhibitors

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

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

Animal Data

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

Nursing Mothers

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

Pediatric use

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

Geriatric use

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

Females and Males of Reproductive Potential

Females

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

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

Males

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

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

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

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

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

OPSUMIT® (macitentan)

Drug Interactions

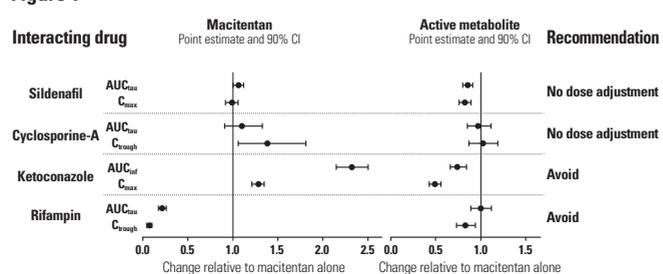
In vitro studies

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

In vivo studies

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

Figure 1



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

Effect of macitentan on other drugs

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

Animal Toxicology

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

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

Manufactured for:

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

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

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Lung cancer screen

LDCT from page 1

Based on the proposal, appropriate candidates for screening would be 55-74 years old, show no signs of lung disease, and have a smoking history of at least 30 pack-years. Further, appropriate patients would be either current smokers or would have quit within the past 15 years.

Another stipulation of the proposal is the requirement for a physician or qualified nonphysician practitioner to schedule a visit for counseling and shared decision making with patients before issuing a written order for LDCT screening.

The time requirement and questions about how this counseling would be covered makes the counseling visit “one of the most interesting things in the Medicare requirement,” said Steven Zeliadt, Ph.D., core

investigator at VA Health Services Research & Development Services and professor at the University of Washington in Seattle. “That’s very different than other cancer screening tests, and for Medicare to really be encouraging and requiring that is something providers and systems are going to [need to] figure out.”

As a result of the counseling requirement and standards of expectation for centers performing screening LDCT, specialized centers are likely to gain traction and manage the bulk of these patients, Dr. Zeliadt said.

These will be the places that integrate both parts of the screening by conducting the LDCT test as well as providing the counseling. This differs from the model used for colon cancer and prostate cancer screening, where

VIEW ON THE NEWS

Dr. Vera A. De Palo, FCCP, comments: Routine radiographic screening for lung cancer has long been debated. On Nov. 10, CMS announced a proposal to cover low-dose CT screening for asymptomatic patients with a high risk for lung cancer.

The proposal stresses the documentation of multiple elements including the requirement for

scheduling a counseling and shared decision-making session before issuing an order for the low-dose CT scanning.

While the required elements are many, the potential benefit to patients is great.

A CHEST press release welcoming the preliminary decision may be accessed at <http://www.chestnet.org/News/Press-Releases>.

test results are sent to the physician so that he or she can counsel the patient.

Such centers exist now, he noted. “They hire counselors and [conduct] an hour-long prescreening visit.”

That model doesn’t easily fit into an office-based setting and does not take advantage of the physician/patient relationship, he added. “There is an opportunity for a familiar provider to engage patients around counseling, so (moving the screening to a center) takes away from the long-term relationship,” including knowing more deeply each patient’s risks and history with smoking and attempts to quit.

It also may detract from opportunities to maintain conversations about smoking cessation, and the need to quit as patients may “feel protected by screening.”

CMS has solicited comments on the proposed national coverage decision with a deadline of Dec. 10.

The determination of eligibility for LDCT screening will depend on age; absence of signs or symptoms of

lung disease; a specific calculation of cigarette smoking pack-years; and if a former smoker, the number of years since quitting. Shared decision making, including the use of one or more decision aids, needs to include the benefits, harms, follow-up diagnostic testing, over-diagnosis, false-positive rate, and total radiation exposure.

Counseling must address the importance of adherence to annual LDCT lung cancer screening, the impact of comorbidities, and the ability or willingness to undergo diagnosis and treatment. Also, counseling needs to include the importance of maintaining cigarette smoking abstinence among former smokers and a plan for smoking cessation in current smokers and, if appropriate, offering additional Medicare-covered tobacco cessation counseling services.

Written orders for both initial and subsequent LDCT lung cancer screenings must be documented in the beneficiaries’ medical records and include patient date of birth, pack-year

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

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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Vaccine advised

PCV13 from page 1

VIEW ON THE NEWS

Dr. Dan Ouellette, FCCP,

comments: Every year in the fall, I recommend to my patients with respiratory disease that they receive the influenza vaccine. Often, they ask me “what about the pneumonia vaccine?” We then have a conversation about what the “pneumonia vaccine” is. I review their immunization record with them to try and figure out if they have received this vaccine before, and if so,



when. This year, the situation is both complicated and clear in my patients over 65 years of age. It is more complicated because the 13-valent pneumococcal vaccine must be administered in addition to the 23-valent pneumococcal vaccine, with those patients who have not received the PCV23 having to receive both. It is clearer, because all of my older patients must receive the PCV13. It is better for my patients, because they will have increased immunity to the pneumococcus.

atomic asplenia, cerebrospinal fluid leak, or cochlear implants. The new PCV13 recommendation for all older adults is based on a randomized, placebo-controlled trial of the vaccine in

about 85,000 adults aged 65 years and older in the Netherlands who had no prior pneumococcal vaccine exposure. The vaccine showed a moderate level of evidence for efficacy against community-acquired pneumonia in this cohort, ACIP determined. Efficacy against nonbacteremic vaccine-type pneumococcal pneumonia

was about 45%, while efficacy against vaccine-type invasive pneumococcal disease was about 75%, the reviewers wrote.

ACIP will reevaluate the recommendations in 2018.

Ms. Tomczyk and her colleagues disclosed no funding sources or conflicts of interest.

NOW APPROVED

STRIVERDI[®]
RESPIMAT[®]
 (olodaterol)
 INHALATION SPRAY



A New FDA-Approved Maintenance Treatment for COPD

Indication

Striverdi[®] Respimat[®] (olodaterol) Inhalation Spray is a long-acting beta₂-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations: STRIVERDI RESPIMAT is not indicated to treat acute deteriorations of COPD and is not indicated to treat asthma.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication.

STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life threatening condition, or used as rescue therapy for acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting beta₂ agonist.

STRIVERDI RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂ agonists as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. STRIVERDI RESPIMAT may produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, STRIVERDI RESPIMAT should be discontinued immediately and alternative therapy instituted.

STRIVERDI RESPIMAT can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms, and should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension. If cardiovascular symptoms occur, STRIVERDI RESPIMAT may need to be discontinued.

STRIVERDI RESPIMAT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.

Be alert to hypokalemia and hyperglycemia.

Immediate hypersensitivity reactions, including angioedema, may occur. If such a reaction occurs, therapy with STRIVERDI RESPIMAT should be stopped at once and alternative treatment should be considered.

The most commonly reported adverse reactions (≥2% incidence and more than placebo) with STRIVERDI RESPIMAT (and placebo) were nasopharyngitis, 11.3% (7.7%); upper respiratory tract infection, 8.2% (7.5%); bronchitis, 4.7% (3.6%); urinary tract infection, 2.5% (1.0%); cough, 4.2% (4.0%); dizziness, 2.3% (2.1%); rash, 2.2% (1.1%); diarrhea, 2.9% (2.5%); back pain, 3.5% (2.7%); and arthralgia 2.1% (0.8%).

STRIVERDI RESPIMAT should be used with extreme caution in patients treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated.

STRIVERDI RESPIMAT should be used with caution in patients treated with additional adrenergic drugs, non-potassium-sparing diuretics, and beta-blockers.

STRIVERDI RESPIMAT is for oral inhalation only.

Please see accompanying brief summary on following page, including boxed WARNING.
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Continued from previous page

smoking history, and current smoking status or the number of years since quitting smoking.

The order must also include a statement that the beneficiary is asymptomatic; and the National Provider Identifier of the ordering practitioner.

To be eligible to perform the screening, radiologists must be board certified and involved in the supervision and interpretation of at least 300 chest CT acquisitions in the past 3 years.

Medicare-eligible centers for lung cancer LDCT screening must have participated in past lung cancer screening trials, such as the National Lung Screening Trial, or be an accredited advanced diagnostic imaging center with training and experience in LDCT lung cancer screening. They must use LDCTs with an effective radiation dose less than 1.5 mSv, and they must collect and submit data to a CMS-approved national registry for each LDCT lung cancer screening performed.

Rapid prophylaxis didn't cut PEs

PE in trauma from page 1

chemical prophylaxis, and placement prophylactic filters in the inferior vena cava (IVC) in high-risk patients.

Overall, 1% of patients developed a pulmonary embolism. Comparing

rates of pulmonary emboli, deaths from pulmonary embolism, or mortality in the preprogram and postprogram time periods, however, showed no significant differences, he said at

the annual clinical congress of the American College of Surgeons.

One percent of patients in both time periods developed a pulmonary embolism. The rate of death from pulmonary embolism was 7% in the earlier period and 8% in the later period. Mortality rates were 4.5% in both periods.

That's despite great improvements in reducing the proportion of patients who got no prophylaxis from 45% in the earlier period to 11% under the improvement program. The use of prophylactic IVC filters increased from 3% in the earlier period to nearly 8% under the program. The time to initiation of prophylaxis decreased from 57 hours to 32 hours, on average.

The proportion of patients who missed a dose of thromboprophylaxis did not change significantly, from 39% in the earlier period to 36% under the program.

"Current prophylactic strategies and therapies for pulmonary embolism may be inadequate," Dr. Pommerening said, perhaps because of inadequate dosing or inadequate therapies. The utility or potential thrombogenicity of IVC filters is a topic of "serious discussion" at his institution, he said.

"There's still room for improvement," he added, by eliminating



SHERRY BOSCHERT/FRONTLINE MEDICAL NEWS

Because of the low rates of PE, the study may not have been powered to detect differences, Dr. Matthew J. Pommerening said.

missed doses and reducing the 11% of patients who got no prophylaxis.

The time to diagnosis of pulmonary embolism and the proportion of emboli located in the main pulmonary artery did not differ significantly by time period.

The size of the study may not have provided enough power to detect differences in rates of emboli between time periods with such a low overall rate of pulmonary emboli to begin with, he said.

The investigators have started to look at whether the performance-improvement program made any difference in the rate of deep vein thrombosis.

Dr. Pommerening reported having no financial disclosures.

STRIVERDI® RESPIMAT® (olodaterol) Inhalation Spray FOR ORAL INHALATION BRIEF SUMMARY OF PRESCRIBING INFORMATION Please see package insert for full Prescribing Information.

WARNING: ASTHMA-RELATED DEATH
Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Contraindications, Warnings and Precautions].

INDICATIONS AND USAGE: Maintenance Treatment of COPD: STRIVERDI RESPIMAT is a long-acting beta₂-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. **Important Limitations of Use:** STRIVERDI RESPIMAT is not indicated to treat acute deteriorations of COPD [see Warnings and Precautions]. STRIVERDI RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STRIVERDI RESPIMAT in asthma have not been established.

CONTRAINDICATIONS: All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication [see Warnings and Precautions]. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

WARNINGS AND PRECAUTIONS: Asthma-Related Death [see Boxed Warning]: Data from a large placebo-controlled study in asthma patients showed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists. A 28-week, placebo-controlled US study comparing the safety of another long-acting beta₂-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of long-acting beta₂-adrenergic agonists, including STRIVERDI RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STRIVERDI RESPIMAT has been conducted. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Contraindications]. **Deterioration of Disease and Acute Episodes:** STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STRIVERDI RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STRIVERDI RESPIMAT in this setting is inappropriate. STRIVERDI RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STRIVERDI RESPIMAT has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta₂-agonist. When beginning STRIVERDI RESPIMAT, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing STRIVERDI RESPIMAT, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used. Increasing inhaled beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If STRIVERDI RESPIMAT no longer controls symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalation of short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of STRIVERDI RESPIMAT beyond the recommended dose is not appropriate in this situation. **Excessive Use of STRIVERDI RESPIMAT and Use with Long-Acting Beta₂-Agonists:** As with other inhaled drugs containing beta₂-adrenergic agents, STRIVERDI RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. **Paradoxical Bronchospasm:** As with other inhaled beta₂-agonists, STRIVERDI RESPIMAT may produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, STRIVERDI RESPIMAT should be discontinued immediately and alternative therapy instituted. **Cardiovascular Effects:** STRIVERDI RESPIMAT, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STRIVERDI RESPIMAT may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Long acting beta₂-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension. **Co-existing Conditions:** STRIVERDI RESPIMAT, like other sympathomimetic amines, should be used with caution in patients

with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. **Hypokalemia and Hyperglycemia:** Beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta₂-adrenergic agonists may produce increases in plasma glucose. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment [see Drug Interactions], which may increase the susceptibility for cardiac arrhythmias. Clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical studies with long-term administration of STRIVERDI RESPIMAT with the rates similar to those for placebo controls. STRIVERDI RESPIMAT has not been investigated in patients whose diabetes mellitus is not well controlled. **Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including angioedema, may occur after administration of STRIVERDI RESPIMAT. If such a reaction occurs, therapy with STRIVERDI RESPIMAT should be stopped at once and alternative treatment should be considered.

ADVERSE REACTIONS: Long-acting beta₂-adrenergic agonists, such as STRIVERDI RESPIMAT, increase the risk of asthma-related death. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Boxed Warning and Warnings and Precautions]. Clinical Trials Experience in Chronic Obstructive Pulmonary Disease: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The STRIVERDI RESPIMAT clinical development program included seven dose-ranging trials and eight confirmatory trials. Four of the confirmatory trials were 6-week cross-over trials and four were 48-week parallel group trials. Adverse reactions observed in the dose-ranging trials and four 6-week cross-over trials were consistent with those observed in the 48-week parallel group trials, which formed the primary safety database. The primary safety database consisted of pooled data from the four 48-week double-blind, active and placebo-controlled, parallel group confirmatory clinical trials. These trials included 3104 adult COPD patients (77% males and 23% females) 40 years of age and older. Of these patients, 876 and 883 patients were treated with STRIVERDI RESPIMAT 5 mcg and 10 mcg once-daily, respectively. The STRIVERDI RESPIMAT groups were composed of mostly Caucasians (66%) with a mean age of 64 years and a mean percent predicted FEV₁ at baseline of 44% for both the 5 mcg and 10 mcg treatment groups. Control arms for comparison included placebo in all four trials plus formoterol 12 mcg in two trials. In these four clinical trials, seventy-two percent (72%) of patients exposed to any dose of STRIVERDI RESPIMAT reported an adverse reaction compared to 71% in the placebo group. The proportion of patients who discontinued due to an adverse reaction was 7.2% for STRIVERDI RESPIMAT treated patients compared to 8.8% for placebo treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation, pneumonia, and atrial fibrillation. Table 1 shows all adverse drug reactions reported by at least 2% of patients (and higher than placebo) who received STRIVERDI RESPIMAT 5 mcg during the 48-week trials.

Table 1: Number and frequency of adverse drug reactions greater than 2% (and higher than placebo) in COPD patients exposed to STRIVERDI RESPIMAT 5 mcg: Pooled data from the four 48-week, double-blind, active- and placebo-controlled clinical trials in COPD patients 40 years of age and older

Treatment	STRIVERDI 5 mcg once-daily	Placebo
Body system (adverse drug reaction)	n=876 n (%)	n=885 n (%)
Infections and infestations		
Nasopharyngitis	99 (11.3)	68 (7.7)
Upper Respiratory Tract Infection	72 (8.2)	66 (7.5)
Bronchitis	41 (4.7)	32 (3.6)
Urinary Tract Infection	22 (2.5)	9 (1.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	37 (4.2)	35 (4.0)
Nervous system disorders		
Dizziness	20 (2.3)	19 (2.1)
Skin and subcutaneous tissue disorders		
Rash*	19 (2.2)	10 (1.1)
Gastrointestinal disorders		
Diarrhea	25 (2.9)	22 (2.5)
Musculoskeletal and connective tissue disorders		
Back Pain	31 (3.5)	24 (2.7)
Arthralgia	18 (2.1)	7 (0.8)

* Rash includes a grouping of similar terms.

Additional adverse reactions that occurred in greater than 2% (and higher than placebo) of patients exposed to STRIVERDI RESPIMAT 10 mcg were pneumonia, constipation, and pyrexia. Lung cancers were reported in 6 (0.7%), 3 (0.3%), and 2 (0.2%) patients who received STRIVERDI RESPIMAT 10 mcg, 5 mcg, and placebo, respectively.

DRUG INTERACTIONS: Adrenergic Drugs: If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of STRIVERDI RESPIMAT may be potentiated [see Warnings and Precautions]. **Xanthine Derivatives, Steroids, or Diuretics:** Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of STRIVERDI RESPIMAT [see Warnings and Precautions].

Non-Potassium Sparing Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics. **Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs:** STRIVERDI RESPIMAT, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias. **Beta-Blockers:** Beta-adrenergic receptor antagonists (beta-blockers) and STRIVERDI RESPIMAT may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution. **Inhibitors of Cytochrome P450 and P-gp Efflux Transporter:** In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of maximum plasma concentrations and AUC was observed. STRIVERDI RESPIMAT was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment is necessary.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies with STRIVERDI RESPIMAT in pregnant women. STRIVERDI RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. STRIVERDI RESPIMAT was not teratogenic in rats at inhalation doses approximately 2,731 times the maximum recommended human daily inhalation dose (MRHDID) on an AUC basis (at a rat maternal inhalation dose of 1,054 mcg/kg/day). Placental transfer of STRIVERDI RESPIMAT was observed in pregnant rats. STRIVERDI RESPIMAT has been shown to be teratogenic in New Zealand rabbits at inhalation doses approximately 7,130 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 2,489 mcg/kg/day). STRIVERDI RESPIMAT exhibited the following fetal toxicities: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum. No significant effects occurred at an inhalation dose approximately 1,353 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 974 mcg/kg/day). **Labor and Delivery:** There are no adequate and well-controlled human studies that have investigated the effects of STRIVERDI RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of STRIVERDI RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. **Nursing Mothers:** Olodaterol, the active component of STRIVERDI RESPIMAT, and/or its metabolites are excreted into the milk of lactating rats. Excretion of olodaterol and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of STRIVERDI RESPIMAT on nursing infants. Caution should be exercised when STRIVERDI RESPIMAT is administered to nursing women. **Pediatric Use:** STRIVERDI RESPIMAT is not indicated for use in children. The safety and effectiveness of STRIVERDI RESPIMAT in the pediatric population have not been established. **Geriatric Use:** Based on available data, no adjustment of STRIVERDI RESPIMAT dosage in geriatric patients is necessary. Of the 876 patients who received STRIVERDI RESPIMAT at the recommended dose of 5 mcg once-daily in the clinical studies from the pooled 1-year database, 485 were less than or equal to 65 years of age and 391 (44.6%) were greater than 65 years of age. No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Hepatic Impairment:** Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed. **Renal Impairment:** Subjects with severe renal impairment showed no clinically relevant changes in C_{max} or AUC compared to their healthy controls. **OVERDOSAGE:** The expected signs and symptoms with overdose of STRIVERDI RESPIMAT are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., myocardial ischemia, angina pectoris, hypertension or hypotension, tachycardia, arrhythmias, palpitations, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of STRIVERDI RESPIMAT. Treatment of overdose consists of discontinuation of STRIVERDI RESPIMAT together with institution of appropriate symptomatic and supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdose of STRIVERDI RESPIMAT. Cardiac monitoring is recommended in cases of overdose.

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CPAP compliance compatible with good sexual QOL

BY WHITNEY MCKNIGHT
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Patients who consider themselves too sexy for their continuous positive airway pressure devices should reconsider, according to a presenter at the annual meeting of the American College of Chest Physicians.

“Despite the unsexy appearance of a positive airway pressure device in the bedroom, patients who don’t comply with their CPAP [protocols] do not have a better sexual quality of life,” said Dr. Salman Alim, who presented the research.

Sexual quality of life questionnaires were distributed to 52 men being treated at a single site with continuous positive airway pressure (CPAP) for obstructive sleep apnea. The 10-question survey used a scale of 1-8, with 80 being the highest score, to evaluate the participants’ emotional and physical satisfaction with their sex lives. Patients were considered CPAP-compliant if they used their device 4 or more hours nightly at least 70% of the time.

The compliant cohort of 27 men, whose average age was 59 years, had a sexual quality of life score

VIEW ON THE NEWS

Dr. Octavian C. Ioachimescu, FCCP, comments: Adherence to CPAP therapy for obstructive sleep apnea (OSA) remains a problem in day-to-day practice. Whenever a patient, often but not always a young patient, brings up the issue of CPAP not being “sexy” in the bedroom, I ask a simple question: “How sexy do you think it is to be snoring, snorting, gasping, choking, or drooling?” That realization seems to work, at least for a while ...

If validated, a sexual quality of life questionnaire may be a good instrument to assess this domain of OSA symptoms. If findings of better CPAP adherence being correlated with better sexual quality of life are reproduced in a rigorous trial, then we would welcome another tool in our armamentarium to motivate, engage, and empower our patients to participate in the act of therapy. Why not 6 hours and 80% of the nights? Or 8 hours and 100% of the nights?

of about 38. The noncompliant group of 25 men, average age 56 years, had a score of about 48.

After adjustment for variables such as age, body mass index, erectile dysfunction, use of phosphodiesterase inhibitors, and depression, CPAP compliance did not predict one’s sexual quality of life, reported Dr. Alim, who was with Rosalind Franklin University in North Chicago, Ill., at the time of the study and is now with Physicians Regional Healthcare System in Naples, Fla.

“Although this is not a validated survey ... the

study’s findings can be the basis to develop a hypothesis that can be tested more rigorously. At the least, the results provide clinicians with useful information on counseling patients on adherence with CPAP,” Dr. Mark Rosen, Master FCCP, medical director of the American College of Chest Physicians, said in an interview.

The study authors had no relevant disclosures.

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Obstructive sleep apnea seen in 8% of ICU patients

BY MARY ANN MOON
Frontline Medical News

FROM THE JOURNAL OF CRITICAL CARE

Obstructive sleep apnea is a common condition among patients in intensive care units, affecting nearly 8% treated at one large academic medical center during a 3-year period, according to a report published online in the *Journal of Critical Care*.

In what they described as the first study to document the prevalence of obstructive sleep apnea (OSA) in the ICU patient population, researchers

found that 1,183 of 15,077 patients (7.8%) aged 16 years and older who were treated between 2003 and 2006 had a physician-documented diagnosis of OSA at admission. Surprisingly, however, OSA did not raise mortality risk, even though it is a well-known predictor of cardiovascular disease and is associated with several comorbid conditions such as obesity, diabetes, and hypertension, said Dr. Enrique Bolona, of the Mayo Clinic, Rochester, Minn., and his associates.

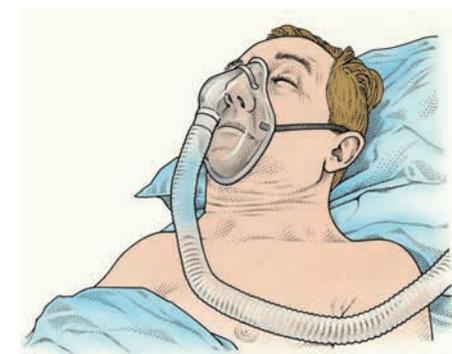
Patients treated in three medical, surgical, and mixed ICUs who had

comorbid OSA had significantly lower ICU mortality (2.4%) than did ICU patients without OSA (6.2%), as well as significantly lower hospital mortality (3.9% vs. 11.4%), the investigators reported (*J. Crit. Care* 2014 Oct. 10 [doi: 10.1016/j.jcrc.2014.10.001])

Patients with OSA had less severe illness than did ICU patients without OSA, as measured by their lower APACHE III scores (median, 45.3 vs. 54.9), lower scores on the Acute Physiology Scale (median, 35.3 vs. 41.8), and lower predicted mortality at admission (10.3% vs. 16.3%). But

even after the data were adjusted for this discrepancy in severity, OSA was still associated with significantly lower mortality (odds ratio, 0.40).

The reason for these “unexpected” findings is not yet known. Obesity, which strongly correlates with OSA,



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VIEW ON THE NEWS

Dr. Octavian C. Ioachimescu, FCCP, comments: Obstructive sleep apnea (OSA) is a prevalent condition in the general population. A recently published re-analysis of the Wisconsin Sleep Cohort (Peppard et al., 2013) showed that the incidence of sleep apnea (1) increased over the last decade [the 7.8% rate in this study may be too low!], (2) is dependent on OSA definition [apnea hypopnea index more than 5, more than 15, with or without excessive daytime sleepiness – needs to be clear and homogenous], and (3) went up significantly with body mass index in both genders [this study does not have data on BMI distributions].

Multiple publications indicate that OSA prevalence and cardiovascular mortality increase in parallel with age. As such, it is very likely that the lifetime cardiovascular risk attributable to OSA in a 40-year-old subject is very different than the one of a 65-year-old, even if corrected for life years, gender and comorbidities. The reasons include lead time lag or survival bias, i.e., patients

who were affected the most by OSA may have already died before age 65 because of OSA hence the cohort of 65-year-old patients may have lower cardiovascular or general attributable mortality.

Alternative explanations are that intermittent hypoxia of OSA may in fact be beneficial (ischemic preconditioning?), or we are dealing with ascertainment bias or maybe a Hawthorne effect, as awareness about OSA became more prevalent over the last decades.

While the reported findings by Bolona et al. are intriguing, we need to interpret the data with the above caveats in mind. We need to have the comorbidity load very well characterized; the BMI, gender, and age distributions to know; to rely less on cross-sectional data by introducing into our computations the time factor; and to conduct good epidemiological studies over long periods of time before we can give credence to any of these potential explanations. Let’s talk again in 10 years.

may exert a protective effect during critical illness by virtue of increased nutritional reserves. Also, patients diagnosed with OSA may have better access to health care than nonaffected patients, “resulting in closer follow-up and management of associated comorbidities.

“Once admitted to the ICU, stricter monitoring and a higher level of alertness with regard to detection of respiratory problems may also play a role, making patients with OSA more likely to receive therapies such as noninvasive positive pressure ventilation earlier,” they said.

Dr. Bolona and his associates had no relevant financial disclosures.

COPD: LAMA/LABA topped fluticasone/salmeterol

BY SHARON WORCESTER
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – Once-daily combination treatment with umeclidinium and vilanterol was more effective than twice-daily combination treatment with fluticasone and salmeterol in patients with moderate to severe chronic obstructive pulmonary disease in two 12-week double-blind, parallel-group, double-dummy studies.

In the two multicenter studies, 706 and 697 patients, respectively, were randomized to receive either 62.5 mcg of the long-acting muscarinic antagonist (LAMA) umeclidinium and 25 mcg of the long-acting beta₂ agonist (LABA) vilanterol – a recently approved combination bronchodilator maintenance treatment for COPD – or a combination of 250 mcg of the inhaled corticosteroid (ICS) fluticasone and 50 mcg of the LABA salmeterol, which is also indicated as a maintenance therapy for COPD.

The patients in the LAMA/LABA groups, who were treated once daily for 12 weeks, had significantly greater improvements on all lung function measures, compared with those in the ICS/LABA groups, who were treated twice daily. Dr. James F. Donohue, FCCP, of the University of North Carolina at Chapel Hill said at the annual meeting of the American College of Chest Physicians.

In the first study, the improvement from baseline to day 84 (the primary study endpoint) in 0- to 24-hour weighted mean forced expiratory volume in 1 second (FEV₁) was 165 mL

for the LAMA/LABA group, and 91 mL in the ICS/LABA group. In the second study, the improvement in the two groups was 213 mL and 112 mL.

The LAMA/LABA combination also improved trough FEV₁ on day 85

by 82 mL and 98 mL more than did the ICS/LABA combination.

Both combinations provided clinically meaningful improvements in dyspnea and quality of life scores.

Adverse events occurred during

treatment in a similar proportion of patients in both treatment groups in both studies: 26% and 27% in the LAMA/LABA and ICS/LABA patients in the first study, and 30% and 31%, respectively, in the second study.

Approximately 50% of individuals with narcolepsy are undiagnosed.¹

TIRED
ALL THE TIME

CATAPLEXY
HYPNAGOGIC
HALLUCINATIONS
EXCESSIVE DAYTIME
SLEEPINESS
SLEEP
PARALYSIS
SLEEP
DISRUPTION

Narcolepsy symptoms may be lurking beneath the surface.

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: These two studies demonstrated significant incremental benefit in lung function testing using a combination LAMA/LABA inhaler over ICS/LABA, and may represent a new approach when selecting a combination inhaler for COPD patients. However, the outcome measure reported is close to what is thought to be the minimal clinically important difference for FEV₁, and its “real world” effect on a patient’s daily life is unclear. Important clinical outcomes should receive equal or more attention – such as improvements in hospitalizations and symptoms/quality of life, which did not differ.

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JP-116-01 Rev0613

The most common adverse events were headache and nasopharyngitis.

In the first study, serious adverse events occurred in 2% of the LAMA/LABA patients and 3% of ICS/LABA patients, and in 3% and 4% of patients in the second study.

One death occurred in the ICS/LABA group in the first study, but

it was not considered study related. Five deaths occurred in the second study, including two in the LAMA/LABA patients and three in the ICS/LABA patients. One of the deaths in the ICS/LABA group was because of pneumonia and was reported as drug related.

Patients in both studies had FEV₁

between 30% and 70%, and had not experienced a COPD exacerbation within the previous year. The LAMA/LABA therapy was delivered via Ellipta inhaler, and the ICS/LABA therapy was delivered via Diskus inhaler.

The Food and Drug Administration approved umeclidinium/vilan-

terol combination therapy (Anoro Ellipta) in December 2013, the first LAMA/LABA therapy approved in the United States. Dr. Donohue and his colleagues conducted the regulatory trial of the drug combination, which was published in July 2013 (*Respir. Med.* 2013;107:1538-46).

The “really robust findings as befits two bronchodilators” suggest umeclidinium/vilanterol combination therapy is an effective treatment option that provides greater lung function than fluticasone/salmeterol for moderate to severe COPD in patients with infrequent exacerbations.

GSK developed the umeclidinium/vilanterol combination product with Theravance and funded the studies. Dr. Donohue reported receiving consultant fees and/or serving on an advisory committee for several drug companies including GlaxoSmithKline. He has also served as a member of drug safety monitoring boards for the National Institutes of Health and several drug companies.

Tiotropium spray okayed for COPD

BY ELIZABETH MEHCATIE
Frontline Medical News

The Food and Drug Administration has approved tiotropium bromide inhalation spray in the Respimat device for the treatment of chronic obstructive pulmonary disease.

The approved indication for the product, which will be marketed as Spiriva Respimat, is for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema, and for reducing exacerbations in COPD patients. The inhalation powder formulation of tiotropium, an anticholinergic, is provided in the Spiriva Handihaler device, and will remain on the market. The Respimat device delivers a 5-mcg dose, and the HandiHaler device delivers an 18-mcg dose, with similar pharmacokinetic effects and systemic exposure.

The Respimat device is used with two other FDA-approved inhaled bronchodilators manufactured by Boehringer Ingelheim. The company said that Spiriva Respimat will be available in January 2015.

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To identify the symptoms of narcolepsy, LOOK DEEPER

- C** **Cataplexy:** A sudden, temporary loss of muscle tone triggered by strong emotions^{1,2}
- H** **Hypnagogic Hallucinations:** Vivid dream-like experiences that occur during the transitions between wake and sleep^{1,2}
- E** **Excessive Daytime Sleepiness:** The inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep²
- S** **Sleep Paralysis:** The temporary inability to move or speak while falling asleep or waking up²
- S** **Sleep Disruption:** The interruption of sleep by frequent awakenings^{1,2}

C.H.E.S.S. is a useful mnemonic for recalling the 5 symptoms of narcolepsy,³ although not all patients experience all symptoms.² Narcolepsy is primarily characterized by excessive daytime sleepiness and cataplexy.² All patients with narcolepsy have excessive daytime sleepiness.² The presence of cataplexy is pathognomonic for narcolepsy.²

Narcolepsy Is a Chronic, Life-Disrupting Neurologic Disorder^{2,3}

Narcolepsy is a chronic, life-disrupting neurologic disorder in which the brain is unable to regulate sleep-wake cycles normally, resulting in sleep-wake state instability.¹⁻⁴

Narcolepsy Is Underdiagnosed

It is estimated that approximately 50% or more of individuals with narcolepsy remain undiagnosed.¹ Initial onset of symptoms typically occurs between the ages of 15-25,² although an accurate diagnosis can take more than 10 years.¹

Narcolepsy Symptoms Can Be Difficult to Recognize

Narcolepsy symptoms may overlap with those of other conditions, such as obstructive sleep apnea and depression.^{1,2} The initial and presenting symptom is typically some manifestation of excessive daytime sleepiness such as tiredness, fatigue, difficulty concentrating, or mood changes.^{1,2,5} Individual symptoms should be evaluated carefully to determine whether they are due to narcolepsy or another condition. Looking deeper at the symptoms can help healthcare professionals establish a differential diagnosis.

Get a Deeper Look, at www.NarcolepsyLink.com

Narcolepsy Link contains resources to help identify narcolepsy symptoms and facilitate communications with your patients.



Pneumonia causes most emergency surgery deaths

BY RICHARD M. KIRKNER
Frontline Medical News

PHILADELPHIA – Emergency surgery accounts for a disproportionate share of surgery-related deaths and complications, and while quality programs focus on prevention of surgical site infections, investigators at Duke University, Durham, N.C., found that pneumonia is the most consequential sequelae of emergency surgery, accounting for more than half of all deaths.

Dr. C. Cameron McCoy, presenting the paper at the annual meeting of the American Association for the Surgery of Trauma, called on the organization to lead efforts to focus quality improvement measures on pneumonia after emergency surgery. “Given their large contribution to postoperative morbidity and mortality, emergency surgery patients in general surgery represent ideal targets for quality improvement programs, but little is

known about the incidence of complications and their association with subsequent mortality,” Dr. McCoy said.

He cited the Michigan Surgical Quality Collaborative, which reported that while emergency operations account for approximately one-tenth (11%) of surgeries, they represented almost half (47%) of all postoperative deaths and more than a quarter (28%) of surgical complications (Ann. Surg. 2013;257:596-602).

The Duke investigators reviewed 100,829 emergency operations in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) performed from 2005 to 2011 for eight diagnoses: acute appendicitis, gallbladder disease, gastroduodenal ulcer, diverticulitis, abdominal wall hernia, and intestinal ischemia, obstruction, or perforation.

They analyzed the data for rates of five complications, including urinary tract infection, deep vein thrombosis, and pulmonary embolism, in addi-



The data suggest efforts should be focused on prevention, recognition, and treatment of postoperative pneumonia following emergency general surgery.

Incidence and risk of selected emergency surgery complications

Complication	Complication rate	Death rate	End organ dysfunction (adjusted odds ratio)	30-day mortality (adjusted odds ratio)
Incisional surgical site infection	4.2%	3.0%	1.11	0.41
Pneumonia	2.8%	19.7%	9.80	1.58
Urinary tract infection	1.6%	7.9%	2.59	0.52
Deep vein thrombosis/pulmonary embolism	1.2%	10.7%	2.71	0.71
Myocardial infarction	0.5%	30.9%	2.81	2.80

Note: Based on analysis of 100,829 emergency operations performed from 2005 to 2011.

Source: Dr. McCoy

VIEW ON THE NEWS

Dr. Frank Podbielski, FCCP, comments: The authors have identified prevention and early treatment of pneumonia as an opportunity to decrease complications and length of stay after emergency surgery. Pneumonia, however, is often a subjective diagnosis with an unclear etiology. We look forward to the authors’ ongoing work on identifying suspected causes of this problem – whether preexist-



ing (prior to the surgical illness), direct sequelae of the surgical illness (e.g., aspiration pneumonia), or hospital acquired (no predisposing etiology). For the best strategy to reduce the complications of pneumonia associated with emergency surgery, it would be helpful to assign a provisional etiology in each case, as well as define “pneumonia” with specific radiographic and clinical parameters.

tion to pneumonia, heart attack, and surgical site infection (SSI), and then factored three outcome measures: end organ dysfunction, death, and hospital length of stay. Demographics among the analyzed population were similar.

“Postoperative pneumonia and postoperative myocardial infarction are the only two of our variables to be associated with a significant increase in 30-day postoperative mortality,” Dr. McCoy said. “Of note, pneumonia is also associated with the absolute greatest number of deaths.”

The Duke investigators’ findings were consistent with previous studies, Dr. McCoy said: Emergency operations accounted for 15% of all surgeries and 53% of postoperative deaths. “SSI was the most frequent complication, in 4.2% of our study patients; in second was pneumonia, occurring in about 2.8%. The most infrequent complication was myocardial infarction at 0.5%,” Dr. McCoy said.

However, the consequences of those complications varied significantly. “Surgical site infection was the only studied complication of the five not to be associated with end organ dysfunction,” Dr. McCoy said. All complications resulted in longer postoperative hospital stays, but again, the results varied. “Postoperative pneumonia was associated with the longest postoperative length of stay, with a median of 18 days; surgical site infection was associated with the shortest, with a median of 7 days, for patients with one of the five complications,” he said.

“The data presented here suggest we should focus our efforts on the prevention, recognition, and treatment of postoperative pneumonia

following emergency general surgery,” Dr. McCoy said. “Assuming we only have finite resources to pursue quality improvement in acute care surgery, this makes SSI potentially the least relevant to critical care surgeons. In addition, as quality improvement measures are being utilized in pay-for-performance models, it is necessary to validate these measures prior to their application in acute care surgery.”

He added, “The American Association for the Surgery of Trauma is the most appropriate organization to lead the development of quality improvement measures targeting postoperative pneumonia following emergency general surgery.”

Dr. McCoy noted a couple potential limitations of the study: While it did adjust for a wide array of preexisting diseases or conditions that could have affected outcomes, a disproportionate number of cases involved appendectomy.

Dr. McCoy had no financial conflicts to disclose.

Giants in Chest Medicine

Hear thought-provoking interviews from some of the biggest contributors to chest medicine.

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Good results from lungs donated after drowning

BY AMY KARON
Frontline Medical News

FROM THE ANNALS OF THORACIC SURGERY

Patients who received lung transplants from donors who died of asphyxiation or drowning had similar survival rates and clinical outcomes as those whose donors died of other causes, according to a large registry analysis in *The Annals of Thoracic Surgery*.

“Asphyxiation or drowning as a donor cause of death should not au-



Survival curves did not vary based on donor cause of death for asphyxiation compared with all other causes.

DR. WHITSON

tomatically exclude the organ from transplant consideration,” said Dr. Bryan A. Whitson of Ohio State University, Columbus, and his associates.

Donor death from asphyxiation or drowning did not significantly affect rates of airway dehiscence, transplant rejection, posttransplant stroke or dialysis, or long-term survival.

Lungs donated after asphyxiation or drowning should be carefully evaluated for parenchymal injury, microbial contamination, and the possibility of primary graft dysfunction, the researchers cautioned. For example, asphyxiation and drowning can alter lung surfactant levels (*Ann. Thorac. Surg.* 2014;98:1145-51).

The analysis included 18,205 U.S. adults who underwent lung transplantation between 1987 and 2010, including 309 patients whose donors had reportedly died from drowning or asphyxiation.

Patients were identified from

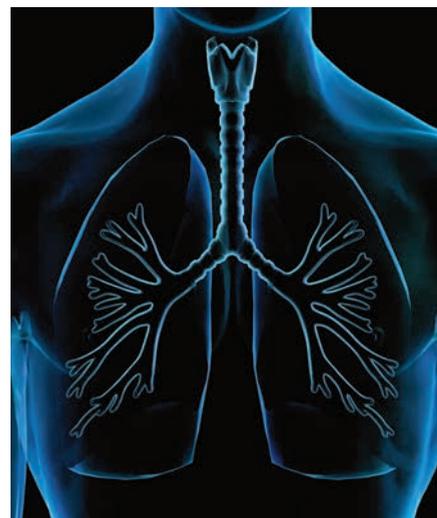
the UNOS/OPTN STAR (United Network for Organ Sharing/Organ Procurement and Transplantation Network Standard Transplant Analysis and Research) database, which is overseen by the U.S. Department of Health & Human Services.

Ten-year survival curves did not vary based on donor cause of death, either when analyzed individually or when asphyxiation or drowning was compared with all other causes ($P = .52$), the researchers said.

In fact, pulmonary deaths were significantly less common (5.8%) among recipients whose donors had died of asphyxiation or drowning compared with other causes (9.5%; $P = .02$).

Donor death from drowning and asphyxiation also did not significantly affect rates of treatment for transplant rejection within the first year after surgery (50.8% vs. 47.4% for all other causes of donor death), or posttransplant rates of stroke (0.7% vs. 2.1%) or dialysis (5.4% vs. 5.2%), the investigators said.

However, hospital length of stay averaged 0.8 days longer when donors had died of asphyxiation or drowning as compared with other causes (27.3 vs. 26.5 days; $P < 0.001$), they reported.



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Cardiac death doesn't preclude lung donation

BY WHITNEY MCKNIGHT
Frontline Medical News

AT CHEST 2014

AUSTIN, TEX. – The risk of death at 1 year after lung transplantation with organs donated either after cardiac arrest or after brain death was virtually the same, an analysis of the literature has shown.

“Donation after cardiac death appears to be a safe and effective method to expand the donor pool,” said Dr. Dustin Krutsinger of the University of Iowa, Iowa City, who presented the findings during the Hot Topics in Pulmonary Critical Care session at the annual meeting of the American College of Chest Physicians.

Over the years, the demand for organ donations for lung transplant candidates has steadily increased while the number of available organs has remained static. This is due, in part, to physicians being concerned about injury to the organs during the ischemic period, as well as what can often be as much as an hour before organ procurement after withdrawal of life support. However, Dr. Krutsinger said the similarities between the two cohorts could result from the fact that before procurement, systemic circulation allows the lungs to oxygenate by perfusion, and so there is less impact during the ischemic period.

“There is also a thought that the ischemic period might actually protect the lungs and the liver from reperfusion injury. And we’re avoiding brain death, which is not a completely benign state,” he told the audience.

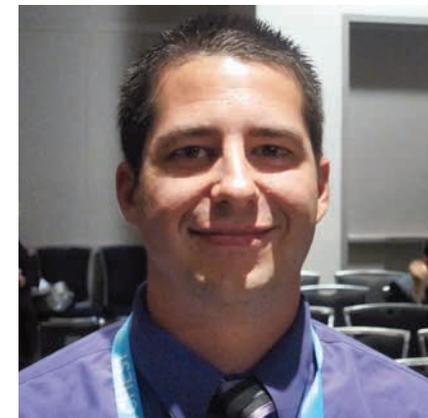
After conducting an extensive review of the literature for 1-year survival rates post lung transplantation, the investigators found 519 unique citations, including 58 citations selected for full text review, 10 observational cohort studies for systematic review, and another 5 such studies for meta-analysis.

Dr. Krutsinger and his colleagues found no significant difference in 1-year survival rates between the donation after cardiac death and the donation after brain death cohorts ($P = .658$). In a pooled analysis of the five studies, no significant difference in risk of death was found at 1 year after either transplantation procedure (relative risk, 0.66; 95% confidence interval, 0.38-1.15; $P =$

.15). Although he thought the findings were limited by shortcomings in the data, such as the fact that the study was a retrospective analysis of unmatched cohorts and that the follow-up period was short, Dr. Krutsinger said in an interview that he thought the data were compelling enough for institutions to begin rethinking organ procurement and transplantation protocols. In addition to his own study, he cited a 2013 study which he said indicated that if lungs donated after cardiac arrest were included, the pool of available organs would increase by as much as 50% (*Ann. Am. Thorac. Soc.* 2013;10:73-80).

But challenges remain.

“There are some things you can do to the potential donors that are



WHITNEY MCKNIGHT/FRONTLINE MEDICAL NEWS

“Donation after cardiac death appears to be a safe and effective method to expand the donor pool,” Dr. Dustin Krutsinger said.

questionable ethicswise, such as administering heparin pre-mortem, which would be beneficial to the actual recipients. But, up until they are pronounced dead, they are still a patient. You don’t really have that complication with a donation after brain death, since once brain death is determined, the person is officially dead. Things you then do to them to benefit the eventual recipients aren’t being done to a ‘patient.’”

Still, Dr. Krutsinger said that if organs procured after cardiac arrest were to become more common than after brain death, he would be “disappointed” since the data showed “the outcomes are similar, not inferior.”

Dr. Krutsinger said he had no relevant disclosures.

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VIEW ON THE NEWS

Dr. Jacques-Pierre Fontaine, FCCP, comments: The shortage of suitable donor lungs remains an important problem. Less than 20% of lungs being offered for donation are being used. The notion that asphyxiation or drowning excludes a patient from being a potential donor is widespread among some clinicians. This extensive retrospective review of the robust UNOS

Database demonstrates that recipients of lungs from donors who died from asphyxiation or drowning have similar 10-year survival and posttransplant complication rates. In carefully selected donors, these lungs may be successfully used. Furthermore, “optimization” of marginal donor lungs may become more prevalent as ex-vivo lung perfusion technology evolves.

PULMONARY PERSPECTIVES: Is 3D printing of organs the future?

Creating a biologic 3D trachea

BY DR. ADNAN M. AL-AYOUBI
AND DR. FAIZ Y. BHORA, FCCP

Imagine the day when organs are produced in the lab and are available for transplant, a scenario often repeated by doctors, patients, and medical reporters alike. What seems like a scene from a science-fiction movie may one day become reality—and sooner than we may imagine. Our understanding of biological systems and cellular mechanisms is rapidly expanding, accompanied and supported by advances in bioengineering. 3D printing, now a household word, has been hailed among the most exciting inventions of this decade with hardly a week passing by without new “firsts” using 3D printing technology. This novel technology has vast potential for multiscale innovations in almost every discipline: health-care, industry, academia, and the arts. In health-care, 3D printing is often called a game changer. It has already customized prosthetic and implant design and impacted the pharmaceutical industry and drug delivery systems, medical education, and most of all—tissue engineering and regenerative medicine. Here we briefly describe the basic concepts of this technology for the busy clinician and how it can be applied to tissue engineering with a special focus on airway regeneration.



DR. AL-AYOUBI

3D printing process

3D printing, also known as rapid prototyping or additive manufacturing, was introduced in the 80s for industrial purposes. Not until a miniaturized “desktop” version of the printer was developed did its role in medicine begin to expand. All 3D printers, regardless of their types, follow similar principles. Products of 3D printers are objects made by sequential addition (z-stacking) of 2D layers creating three-dimensional structures. The objects of interest can be designed using computer-aided design (CAD) software or taken directly from 3D-reconstructed images of CT scans and MRIs. The image files are saved as a (.STL) file and processed by “slicer” software to generate G-code files that relay the control instructions to the printer. Depending on the size of

the printer, the “ink” used, and the size and geometrical complexity of the desired object, it can take from a few minutes to several hours or days to print. Unlike the monochromatic older generations of 3D printers, newer devices are emerging on the market with either multiple printing heads or “ink” chambers. The latter provides greater freedom in materials choice and is of particular interest in tissue regeneration for its ability to print and compartmentalize different cellular components.

Types of 3D printers

There are multiple types of 3D printers available commercially, benefiting from an open-source platform that allows customization and improvement of the current devices. Similarly, different types of “inks” are utilized depending on the printer’s design but also on the desired end-product. We mention some of the common types of printers and direct our focus to the last two, given their particular application in regenerative medicine:

- Selective laser sintering
- Electron beam melting
- Direct laser metal sintering
- Selective heat sintering
- Electron beam freeform fabrication
- Fused deposition modeling
- Photopolymerized extrusion stereolithography

Fused deposition modeling printers

Fused deposition modeling (FDM) printers utilize a heated extrusion head and are closely similar to a desktop inkjet printer. FDM printers benefit from their wide commercial availability and relatively low cost, making them among the most popular 3D printers currently in use. The “ink” utilized is a thermoplastic material typically prepared as a thread spool fed to the heated head and sequentially deposited as droplets with an approximate 100-micron resolution. The thermoplastics hardened within few seconds, allowing fast and precise 3D object production. Several thermoplastics are used, some of which are also biocompatible and have been traditionally used in implant manufacturing and have shown promise for tissue engineering, such as polylactic acid (PLA), polylactic-glycolic acid (PLGA),

and polycaprolactone (PCL). PCL has attracted substantial interests within the medical community given its low inflammatory profile, slow rate of hydrolysis, and ability to promote cellular attachment and growth (Shimao. *Curr Opin Biotechnol.* 2001;12[3]:242). In fact, PCL has been successfully printed as a splint for bronchial malacia in a baby suffering from repeated bouts of pneumonia and difficulty breathing (Zopf et al. *N Engl J Med.* 2013;368[21]:2043). FDM printers are thus most suitable for manufacturing prosthetic devices and possibly tissue scaffolds for cellular growth.

Photopolymerized extrusion stereolithography printers

In this form of 3D printing, the extrusion head consists of a motorized syringe-plunger containing the liquid ink. This is polymerized into a solid shape after extrusion and upon exposure to UV light (or another light source depending on the chemical content of the mixture). Polymerizable liquid inks are grouped under the term hydrogels, formerly defined by the International Union of Pure and Applied Chemistry (IUPAC) as “nonfluid colloidal network or polymer network that is expanded throughout its whole volume by a fluid.” Several formulations of hydrogels exist, and we have used varying combinations of polyethylene glycol diacrylate and alginate to create hydrogels with different mechanical properties. Photopolymerization is slower than FDM; however, it has the added benefit of incorporating the cells into the prepolymerized liquid mix, which allows cellular inclusion into the final product. In essence, this type of printing will likely represent the future of “bioprinting” with its ability to compartmentalize cellular components within the scaffold. 3D printed ears (Manoor et al. *Nano Lett.* 2013;13[6]:2634) and aortic valves (Hockaday et al. *Biofabrication.* 2012;4[3]:035005) were generated using this approach. 3D printing was successful in replicating the shape of the desired organs with high fidelity while permitting maintained cellular growth, ushering a new era for regenerative medicine.



DR. BHORA

However, the current mechanical properties of these structures do not permit organ transplantation and lack the necessary vascularized network for maintained in vivo growth.

Tracheal regeneration

In the setting of large segment tracheal pathologies, both benign and malignant, surgical resection and reconstruction may be challenging. Our lab has been working on creating a bioengineered tissue alternative for repair and/or replacement of large tracheal defects. The ideal material should have longitudinal flexibility, while maintaining lateral rigidity and concurrently supporting chondrogenesis, neovascularization, and re-epithelialization. Using a combination of mesenchymal stem cells, biologic collagen membranes, and 3D printing, we have achieved preliminary and encouraging results in large animal models. 3D-reconstructed CT scan of the neck and chest is obtained, and we isolate the tracheobronchial tree below the cricoid cartilage extending toward the carina and the major bronchi. Large tracheal defects, long segment airway stenosis, or tracheobronchomalacia can then be corrected virtually using CAD software applications. The improved anatomical 3D image is next converted to a (.STL) file readable by the printer, which generates the tracheal scaffold. The latter is subsequently incubated with mesenchymal stem cells, which are

allowed to grow and differentiate to chondrogenic progenitor cells in a bioreactor in vitro. Chondrogenesis is a complex and well-orchestrated process. We incubate the stem cells in growth media containing a specific mixture of TGF- β ; BMP-2, -4, and -7; and FGF-2 to induce the formation of the chondrogenic lineage. Additionally, the scaffold with the adherent cells is mounted on a mandrel in a bioreactor and subjected to slow and continuous rotation to improve chondrogenesis via mechanical stimulation. In the early phases of differentiation, collagen I and fibronectin are deposited around the cells creating the earliest form of extracellular matrix for chondrocytes growth. With this approach, we have seen maintained cellular growth and

Continued on page 16

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

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST $>3\times$ ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet 2403 mg/day in the three phase 3 trials had a higher incidence of elevations in ALT or AST ($\geq 3\times$ ULN) than placebo patients (3.7% vs 0.8%, respectively). Elevations $\geq 10\times$ ULN in ALT or AST occurred in 0.3% vs 0.2% of patients in the Esbriet 2403 mg/day group and placebo group, respectively. Increases in ALT and AST $\geq 3\times$ ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet 2403 mg/day in the three phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Most photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Instruct patients to avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: In clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported by patients in the Esbriet treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% vs 5.8% of patients in the 2403 mg/day group compared with the placebo group, respectively; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event vs 1.0% in the placebo group. The most common ($>2\%$) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions ($\geq 10\%$) were nausea (36% vs 16%), rash (30% vs 10%), abdominal pain (24% vs 15%), upper respiratory tract infection (27% vs 25%), diarrhea (26% vs 20%), fatigue (26% vs 19%), headache (22% vs 19%), dyspepsia (19% vs 7%), dizziness (18% vs 11%), vomiting (13% vs 6%), anorexia (13% vs 5%), gastroesophageal reflux disease (11% vs 7%), insomnia (10% vs 7%), weight decreased (10% vs 5%), and arthralgia (10% vs 7%) in the Esbriet and placebo treatment groups, respectively.

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

The concomitant administration of Esbriet and fluvoxamine or other strong CYP1A2 inhibitors (eg, enoxacin) is not recommended because it significantly increases exposure to Esbriet. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of Esbriet and avoided during Esbriet treatment. If fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

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

The concomitant use of Esbriet and a CYP1A2 inducer may decrease the exposure of Esbriet, and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to Esbriet treatment and avoid concomitant use of Esbriet and a strong CYP1A2 inducer.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to InterMune at 1-888-486-6411.

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

Continued from page 14

differentiation of the stem cells into chondrogenic progenitors in vitro and chondrocytes in vivo in the animal model (Al-Ayoubi et al. Presented at the STS 51st Annual Meeting. Orlando, FL 2013). Efforts are underway to understand the airway dynamics, mucosal epithelial function, and long-term effects of the bioengineered trachea.

Final word

3D printing is an exciting technology with significant impact on regenerative medicine. It particularly allows precise and customized reproduction of the engineered tissue while maintaining form and function. Further identification of suitable biomaterials is warranted, as well as the biological interactions of the stem cells with their potential environments. While substantial information remains to be discov-

ered and technical challenges overcome, the field of tissue engineering is undoubtedly heading toward amazing findings, hoping to find cures for many debilitating illnesses.

Drs. Al-Ayoubi and Bhora are with the Department of Thoracic Surgery; Mount Sinai St. Luke's Hospital and Mount Sinai Roosevelt Hospital; Icahn School of Medicine at Mount Sinai, New York.

Esbriet[®]
pirfenidone capsules 267mg

Rx only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Disorders

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

ADVERSE REACTIONS

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

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

ESBRIET[®] (pirfenidone)

Clinical Trials Experience

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

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

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

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

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

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

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

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

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

Postmarketing Experience

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

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

Tobacco use remained high among teens in 2013

BY MIKE BOCK
Frontline Medical News

FROM MMWR

Although cigarette use among middle and high school students

continues to decrease, overall tobacco use is still high, with 23% of high school students using tobacco products in 2013, the Centers for Disease Control and Prevention reported.

Overall, 46% of high school students reported ever using a tobacco product, and 31% reported ever trying two or more tobacco products, according to data from the National Youth Tobacco Survey

(MMWR 2014;63:1021-6).

In 2013, 23% of high school students reported current use of a tobacco product; in 2012, 23% of high school students reported current tobacco use, and 24% used a tobacco product in 2011.

Combustible tobacco products were the most popular form of tobacco ingestion among current and former users, as 9 out of 10 high school students reporting using them. Cigarettes were the most regularly used tobacco products at 13%, followed by cigars (12%), smokeless tobacco (5.7%), hookah (5.2%), e-cigarettes (4.5%), and pipes (4.1%).

The authors, led by CDC epidemiologist René A. Arrazola, noted the data could be influenced by self-reporting bias. The National Youth Tobacco Survey is a school-based, self-administered questionnaire.

Of 250 schools selected for the 2013 National Youth Tobacco Survey,



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187 (75%) participated, with a sample of 91% of 20,301 eligible students; the response rate was 68%.

The increasing number of teens using e-cigarettes could be cause for concern, because there are few data on the long-term impact of e-cigarette use. However, the 2014 Surgeon General's report found that adolescent nicotine use can have adverse effects on brain development.

"Considering how trends in tobacco product use and tobacco marketing change, rigorous surveillance of all available forms of tobacco use by youths, particularly use of emerging products such as e-cigarettes, is essential," the researchers said.

Among middle school students, 17.7% had ever used tobacco. Middle school students were more likely to smoke cigars instead of cigarettes, with 3.1% reporting current use of cigars, and 2.9% reporting current use of cigarettes; 1.1% reported recently using e-cigarettes.

Cigarettes were the most prevalent tobacco product used by white and Hispanic high school students (14% and 13%), although cigars were close behind (11% and 12%).

ESBRIET® (pirfenidone)

DRUG INTERACTIONS

CYP1A2 Inhibitors

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

Strong CYP1A Inhibitors

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

Moderate CYP1A Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

CYP1A2 Inducers

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

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

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m² basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m² basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m² basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ESBRIET® (pirfenidone)

Hepatic Impairment

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

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment [see *Clinical Pharmacology section 12.3 in full Prescribing Information*].

Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.3 in full Prescribing Information*]. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

Smokers

Smoking causes decreased exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*], which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Events

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

Smokers

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

Take with Food

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

Manufactured for:

InterMune, Inc.
Brisbane, CA 94005 USA

Reference: 1. ESBRIET full Prescribing Information. InterMune, Inc. October 2014.



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ICU meds can bring on serotonin syndrome

BY MICHELE G. SULLIVAN
Frontline Medical News

EXPERT ANALYSIS FROM ANA 2014

BALTIMORE – Serotonin syndrome can easily develop in the intensive care unit, particularly when patients receive opiates and antiemetic medications in addition to the serotonin-enhancing medications they may already be taking.

“These medications are pervasively present, and they are notorious for drug-drug interactions,” Dr. Alejandro Rabinstein said at the annual meeting of the American Neurological Association. “And, in the ICU, we often use them without even realizing it. The combination can be enough to cause serotonin syndrome, which is sometimes recognized too late, and can have serious consequences.”

Because there are scant data on the phenomenon, Dr. Rabinstein, a critical care neurologist at the Mayo Clinic, Rochester, Minn., conducted a literature search to identify cases and examine their outcomes. His series comprised 33 patients, 22 of whom were seen at the Mayo facility.

The patients were a median of 22 years old. Four of them had been admitted with serotonin syndrome as their primary diagnosis, but it was either unsuspected or had not yet de-

veloped in the remainder.

For 17 patients (52%), the primary reason for admission was a change in mental status or altered consciousness. Four were admitted for sepsis syndrome. Other reasons included resuscitation after cardiac arrest (three), severe pneumonia (two), tumor-related complications (two), emergency surgery (two), graft vs. host disease (one), liver



When patients enter the ICU on an SSRI, opiates and antiemetics put them at risk for serotonin syndrome.

DR. RABINSTEIN

failure (one), and trauma (one).

At admission, the mean APACHE-III score was 67, although the range was wide (11-146). A total of 18 patients required mechanical ventilation, and 6 had undergone surgery before serotonin syndrome developed.

All of the patients showed altered mental status, a key characteristic of serotonin syndrome. Agitation was present in 14 patients. Other common signs were tachypnea (23), tachycardia (20), clonus (29), hyperreflexia (24), and rigidity (26). Mydriasis

was present in 14 and tremor in 12. Seven patients were markedly diaphoretic. Fever was present in 14.

About 40% of the group (13 patients) developed signs of serotonin syndrome only after they were hospitalized (mean day 4). Dr. Rabinstein said 22 drugs with a direct serotonin-enhancing action were involved in the cases. In fact, almost all were taking at least one such drug on admission, and 70% got new serotonergic medications while in the ICU.

About 75% of the patients were taking a selective serotonin reuptake inhibitor when admitted (citalopram, fluoxetine, sertraline, escitalopram, and paroxetine). Almost a third were taking a selective norepinephrine reuptake inhibitor (venlafaxine and duloxetine). About a fourth were taking some other antidepressant with serotonergic activity (trazodone, mirtazapine, buspirone, clomipramine). While in the ICU, three patients received a new serotonergic antidepressant.

Four patients were taking an antiemetic upon admission, and seven started a new antiemetic when admitted. Three were taking an opioid upon admission, and 21 started an opioid when admitted.

All of the patients received benzodiazepine treatment, and 24% had to be paralyzed while their serotonergic

symptoms resolved. The anticholinergic antihistamine cyproheptadine was given to the 13 most severely affected patients. However, Dr. Rabinstein said, its efficacy couldn't be reliably assessed because of this selection bias.

It took a mean of 56 hours for patients to recover to the point where they could interact normally, but the range of recovery time was very wide (8-288 hours). Despite some increases in creatinine kinase and lactic acid, none of the patients developed rhabdomyolysis-related kidney failure. Although serotonin syndrome can be fatal, there were no related deaths in this group.

The review points to how easily ICU treatment can precipitate a very serious neurologic disorder. “Almost everyone came into the ICU on one of these medications, and almost everyone got at least one more after arriving,” Dr. Rabinstein said.

“It's something we have to be on the alert for. The reason I did this study was simply to raise awareness, because this diagnosis is blown all the time. You don't have to be a neurologist to make this diagnosis, but you need to be very attentive to these signs,” Dr. Rabinstein said.

He had no financial disclosures.

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Larger plasma volumes increase transfusion thrombosis

BY M. ALEXANDER OTTO
Frontline Medical News

AT THE ACS CLINICAL CONGRESS

SAN FRANCISCO – Venous thromboembolism is about 50% more likely when trauma patients are transfused with more than 1 unit of fresh frozen plasma for every 2 units of red blood cells, according to a retrospective review of 139,842 adult patients in the National Trauma Data Bank, all of whom received at least 1 unit of red blood cells from 2007 to 2012.

The risk quadrupled when patients received 6 or more red blood cell (RBC) units; for those patients, the only independent risk factor for venous thromboembolism (VTE) was transfusion with more than 1 unit of fresh frozen plasma (FFP) per 2 units of RBCs (odds ratio, 4.12; $P = .011$).

When patients get that much plasma, they “should be monitored closely for deep vein thrombosis [DVT] and pulmonary embolism [PE], and started on VTE prophylaxis as soon as possible,” said lead investigator Dr. Gregory Magee, a trauma and critical care fellow at the University of Southern California, Los Angeles.

The findings complicate an emerging idea of how best to transfuse trauma patients. A 2013 investigation found that 6-hour survival is signifi-

cantly higher when patients get more plasma with their RBCs than they might have in the past, at least 1 FFP unit for every 2 RBC units. Some research suggests that a 1:1 ratio might be even better (JAMA Surg. 2013;148:127-36).

“You need to do what you need to do to help your patients survive,” but there should be a “balancing act to make sure they have enough clotting factors [onboard] to stop the bleeding, but not enough to cause thrombosis,” Dr. Magee said at the annual clinical congress of the American College of Surgeons.

The rate of transfusion-associated PEs in his study was 0.4%, and the rate of DVTs 0.8%. How serious they were is not known; the information was unavailable in the database review. Though low, the incidence of thrombosis increased with increasing volumes of transfused RBCs.

In addition to the 50% increased risk of VTE with higher volumes of transfused plasma (OR, 1.47; $P < .001$), VTE was independently associated with transfusions of 6 or more RBC units (OR, 2.10; $P = .001$); blunt trauma (OR, 1.49; $P = .001$); male gender (OR, 1.29; $P < .001$); and Abbreviated

Injury Scale (AIS) scores of 3 or higher for chest injuries (OR, 1.30; $P < .001$), head injuries (OR, 1.18; $P = .032$), and lower extremity injuries (OR, 1.16; $P = .034$).

Several of Dr. Magee's colleagues are coinvestigators on a recently concluded randomized transfusion trial that pitted plasma, platelet, and RBC ratios of 1:1:1 and 1:1:2 against each other, looking for survival and complication differences. They hope to publish their results soon, he said. The randomized study was the only way to counter the survival bias that might have been at work in the 2013 investigation, which was a prospective cohort study. Higher volumes

of plasma might have improved survival, but it's possible that patients who lived longer were more likely to get FFP, since it's often administered well after RBC transfusions are underway.

For now, “we don't know which one is best or if it makes a difference,” Dr. Magee said.

Dr. Magee had no disclosures. The work was funded in part by the National Institutes of Health.



It's a balance. ... Clotting factors are needed to stop bleeding, but not so much as to cause thrombosis.

DR. MAGEE

oatto@frontlinemedcom.com

First and only treatment approved for both **PAH** and inoperable or persistent/recurrent **CTEPH** after surgery[†]

Stimulating



*Soluble Guanylate Cyclase

What could Adempas mean to your patients?

[†]INDICATIONS

- Adempas (riociguat) tablets are indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO 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 predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

[‡]Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

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

FOR PAH. FOR CTEPH.

Adempas[®]
riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

Adempas-US.com

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Adempas could mean moving from the couch to the kitchen

Patients walked farther with Adempas at Week 12: results from Week 2 onward

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; $p < 0.0001$) for PAH (WHO Group 1) patients.

WHO FUNCTIONAL CLASS

50%

more PAH patients improved WHO Functional Class vs placebo ($p = 0.0033$); Adempas: $n = 53/254$ [21%], placebo: $n = 18/125$ [14%] at Week 12.

Deteriorated

4% for Adempas ($n = 9/254$)

14% for placebo ($n = 18/125$)

Stable

76% for Adempas ($n = 192/254$)

71% for placebo ($n = 89/125$)



PATENT-1: 443 PAH patients were studied. (Adempas 2.5 mg $n = 254$, 1.5 mg $n = 63$, placebo $n = 126$)

Baseline characteristics:

- PAH defined as: pulmonary vascular resistance (PVR) > 300 dyn·sec·cm⁻⁵, mean pulmonary arterial pressure (mPAP) > 25 mm Hg
- Mean age: 51 years (approximately 80% female)
- PAH etiologies: idiopathic (61%), familial (2%), associated with connective tissue disease (25%), congenital heart disease (8%), portal hypertension (3%), or anorexigen or amphetamine use (1%)
- Mean 6MWD was 363m
- Concomitant medications: Oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed

Patient population was: 50% treatment-naïve, 44% pretreated with an endothelin receptor antagonist (ERA), and 6% pretreated with a prostacyclin analogue (PCA). The majority of patients had WHO Functional Class II (42%) or III (54%) at baseline. Patients with systolic blood pressure < 95 mm Hg were excluded.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Patients walked farther with Adempas at Week 16: results from Week 2 onward

46m improvement (mean) in 6MWD over placebo at Week 16
(95% CI: 25m-67m; $p < 0.0001$) for CTEPH* (WHO Group 4) patients.

WHO FUNCTIONAL CLASS

2x

as many CTEPH patients improved WHO Functional Class vs placebo ($p = 0.0026$;
Adempas: $n = 57/173$ [33%],
placebo: $n = 13/87$ [15%])
at Week 16.

Deteriorated

5% for Adempas
($n = 9/173$)

7% for placebo
($n = 6/87$)

Stable

62% for Adempas
($n = 107/173$)

78% for placebo
($n = 68/87$)



CHEST-1: 261 CTEPH patients were studied. (Adempas $n = 173$, placebo $n = 88$)
Baseline characteristics:

*Inoperable or recurrent/persistent CTEPH after surgery.

- Mean age: 59 years (range: 18–80)
- Mean 6MWD was 347m
- Concomitant medications: Stable dosages of oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed, but not nitric oxide donors, endothelin receptor antagonists, prostacyclin analogues, specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil), and nonspecific PDE inhibitors (for example, dipyridamole or theophylline)

Patient population was: 72% inoperable by pulmonary endarterectomy (PEA) (pulmonary vascular resistance [PVR] > 300 dyn-sec- cm^{-5} and mean pulmonary arterial pressure > 25 mm Hg measured at least 90 days after the start of full anticoagulation); 28% recurrent or persisting pulmonary hypertension (PH) following PEA (PVR > 300 dyn-sec- cm^{-5} measured at least 180 days following PEA). The majority of patients were WHO Functional Class II (31%) or III (64%) at baseline. Patients with systolic blood pressure < 95 mm Hg were excluded.

WARNINGS AND PRECAUTIONS

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.



FOR PAH. FOR CTEPH.
Adempas[®]
riociguat tablets
0.5mg | 1mg | 1.5mg | 2mg | 2.5mg
Adempas-US.com

More than 90% of Adempas patients survived at 2 years*

*Data from CHEST-2 and PATENT-2 open-label extension studies. Without a control group, these data must be interpreted cautiously.

PAH

93%

PROBABILITY OF SURVIVAL
AT 2 YEARS

CTEPH

94%

PROBABILITY OF SURVIVAL
AT 2 YEARS

**At 1 year,
probability
of survival was
97% in both
open-label
extension
studies.**

WARNINGS AND PRECAUTIONS

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 and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

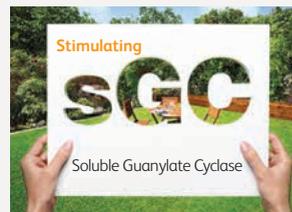
Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic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

Pulmonary Veno-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.

MOST COMMON ADVERSE REACTIONS

- The most common adverse reactions occurring more frequently ($\geq 3\%$) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).
- Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.



Visit
Adempas-US.com
for more information

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400-10-0003-14b September 2014



FOR PAH. FOR CTEPH.
Adempas[®]
riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

ADEMPAS (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)**
- **For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).**

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), (WHO 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), (WHO 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 (61%) or PAH associated with connective tissue diseases (25%) [see *Clinical Studies* (14.2)].

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see *Use in Specific Populations* (8.1)].

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.2)].

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.2) and *Use in Specific Populations* (8.1, 8.6)].

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program [see *Warnings and Precautions* (5.1)].

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations* (8.6)].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 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 and P-gp/BCRP inhibitors [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, 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 Veno-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 ($\geq 3\%$) are displayed in Table 1 below. Most adverse reactions 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 ($\geq 3\%$) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas 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) in any form is contraindicated because of hypotension [see *Contraindications* (4.2) and *Clinical Pharmacology* (12.2)].

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

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

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 who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. 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 antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. 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 hypotension 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 hypotensive 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 was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 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 hazard to the fetus [see *Boxed Warning and Contraindications (4.1)*].

Animal Data

In rats administered riociguat orally (1, 5, and 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 in which no adverse effects were observed is approximately 0.4 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) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 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 4 times and 13 times, respectively, the human exposure at the MRHD.

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 [see *Nonclinical Toxicology (13.2)*].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% 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 healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see *Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)*].

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 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*].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis [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 OVERDOSAGE

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 her 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 nitrates 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 multi pathway CYP inhibitors 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.

Manufactured for:



Bayer HealthCare

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Whippany, NJ 07981

Manufactured in Germany

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6710501BS

CRITICAL CARE COMMENTARY: Delirium in the ICU

BY DR. ELIZABETH AWERBUCH

Delirium, as defined by the DSM-V, is a set of diagnostic criteria that includes a disturbance in attention, awareness, and cognition that develops over a short period of time and tends to fluctuate in severity throughout the day (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 2013). The incidence of delirium in the ICU has been reported to range from 16% to 89% (Reade & Finfer. *N Engl J Med*. 2014;370[5]:444; Pun & Ely. *Chest*. 2007;132[2]:624). Delirium is now recognized as a product of our treatments for patients in the ICU and may, therefore, lend itself to methods of prevention. We have unknowingly increased the risk of cognitive and psychological decline in our patients. With this realization, preventing delirium in patients in the ICU has become an integral part of daily rounds.

It is well established that physicians are poor at diagnosing and recognizing delirium. There is a multitude of tests that has been validated as a screening tool to monitor for the presence of delirium in the ICU population. Two of the popular tools are the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Unit Delirium Screening Checklist (ICDSC). The CAM-ICU can be used on nonverbal patients, translated in multiple languages, and takes an average of less than a minute to complete. It can be administered by any staff member with a high compliance and accuracy rate. It has

a specificity and sensitivity of greater than 90%. The ICDSC is an eight item checklist with a specificity of 64% and sensitivity of 99% and with an inter-rater reliability of 0.94 (Pun & Ely). Choice of a screening tool is institution-dependent, but using the tool is imperative in order to recognize delirium and intervene early.

We have begun to observe the many adverse effects that our critically ill patients attain from being mechanically ventilated, deeply sedated, and even paralyzed at times. Patients identified as having delirium while in the ICU have more than a three-fold increased risk of reintubation and are more likely to have more than 10 days added to

their length of stay (LOS) in the hospital. Each day of delirium correlates to an almost 20% increased risk of increased LOS and 10% increased risk of death. All of these factors together equate to an increased LOS, which is associated with an increased cost per admission (Pun & Ely).

Recent studies have shown that delirium causes further decline in not only the current hospitalization but also extends well beyond their discharge. With prolonged hospitalizations, we see patients' physical abilities deteriorate and a higher incidence for posthospitalization rehabilitation. Pandharipande and colleagues showed that the cognitive impairments found in patients with ICU delirium were similar to those with mild Alzheimer disease or moderate traumatic brain injury (Pandharipande et al. *N Engl J Med*. 2013;369[14]:1306).

These long-term cognitive defects involve difficulties in attention, memory, and executive function. These may affect each patient differently but can contribute to an inability to return to work or perform the normal activities of daily living, which overall will decrease their quality of life. They are also at an increased risk for requiring institutionalization (Pun & Ely).

Prevention is the only effective way to decrease the risk of delirium. There are some innate features that serve as risk factors for a higher frequency of delirium, but there are some aspects of care that we as physicians have control over. Examples of these baseline risk factors include advanced

age, dementia, depression, hypertension, alcoholism, severity of illness, and APACHE II score (Pun & Ely; Ouimet et al. *Intensive Care Med*. 2007;33[1]:66). Any type of coma increases the likelihood of developing delirium, including those that are medically induced (Ouimet et al.).

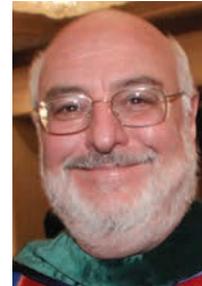
There is no level 1 evidence for pharmacologic intervention to prevent or treat delirium. In regards to pharmacologic intervention, most physicians consider avoidance of medication rather than giving a specific medication as a treatment. It has been well studied that benzodiazepines have a high incidence in causing delirium, especially when compared with



DR. AWERBUCH

EDITOR'S COMMENT

In this the final commentary of my tenure, Dr. Awerbuch describes a most disturbing and severe consequence of critical care—delirium. All the ramifications of delirium and long-term sequelae are not yet known, but it again appears that merely survival should not be our only significant metric. In the last few commentaries, we have discussed early mobilization, ARDS, and now delirium, with its inherent long-term problems. Prevention, as our mothers would have said, is worth a pound of cure, as there is no definitive therapy for this condition per se: So preventive approaches as spelled out



here should be an important part of our daily ICU care.

Again, as this is my final commentary as section editor,

I wish only success to my successor, Dr. Lee E. Morrow, and I thank the readers for their interest and attention, of course all the authors for their time and expert effort, and to Pamela L. Goorsky, our publication editor, for all her help and making sure that I was timely and absolutely correct.

I wish all the readers a happy, healthy, and productive 2015 and again thank all of you and CHEST for this opportunity of service.

Dr. Peter Spiro, FCCP

other sedatives, including dexmedetomidine or propofol (Reade & Finfer; Jones & Pisani. *Curr Opin Crit Care*. 2012;18[2]:146). Dexmedetomidine is an alpha-2 receptor agonist that also inhibits the release of norepinephrine, and its actions resemble a normal

sleep pattern. This may be the reason that patients have a lower incidence of delirium when it is used for both sedation and pain control (Reade & Finfer, Pun & Ely). Treating pain has been a slightly controversial area in

Continued on following page

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Continued from previous page

delirium. To simplify it, using opioids for a sedative purpose and not an analgesic one has been shown to increase the incidence of delirium. However, if it is used correctly to remove pain, then it has been shown to reduce the risk of delirium (Brummel & Girard. *Crit Care Clin.* 2013;29[1]:51).

The ABCDE method is just one approach that pulls together all aspects of critical care in the prevention of delirium. It highlights the important aspects of daily awakenings and breathing trials, adequate pain management, improvement of sleep cycle, daily monitoring of delirium, and early mobilization and exercise.

Once delirium is recognized, the use of pharmacologic medication may be better in decreasing the symptoms. Haloperidol and atypical antipsychotics have been suspected to have potential benefits in the treatment of delirium; however, this has yet to be proven. Olanzapine vs. haloperidol vs. placebo has shown no difference in the number of delirium-free days. Quetiapine has shown a shorter time to resolution of delirium when compared with placebo; however, there was not a significant difference in LOS or days with mechanical ventilation (Jones & Pisani). There is only anecdotal evidence

of the use of haloperidol in treating delirium; nevertheless, it may be the medication preferred for preventive treatment. Surgical literature has shown that low dose haloperidol or risperidone has been successful in decreasing the incidence of delirium. Whether this can be generalized to a critically ill medical population still remains to be demonstrated (Reade & Finfer).

Nonpharmacologic modalities should be used in a preventive manner, but some of these methods have been shown to decrease the duration of delirium in those already exhibiting its signs and symptoms. The full medical team should take an active part in helping to minimize disruption of sleep architecture or sleep deprivation; reorientation of the patient to the time, date, and their surroundings throughout the day; timely removal of catheters and physical restraints; use of eye glasses or hearing aids; adequate hydration; scheduled pain control; minimization of unnecessary noise or stimuli; and use of a nonpharmacologic sleep protocol. Allowing a patient to sleep comfortably at night with the lights off, no noise, no cleaning or labs being drawn, will help to prevent disruption of the natural circadian rhythm (Pun & Ely).

The ABCDE method is just one approach that pulls together all aspects of critical care in the prevention of delirium. It highlights the important aspects of daily awakenings and breathing trials, adequate pain management, improvement of sleep cycle, daily monitoring of delirium, and early mobilization and exercise. All aspects of this model have been proven to reduce or lessen the negative course of delirium in the ICU patient as well as positive outcomes in the number of days of mechanical ven-

tilation, LOS in the ICU and the hospital, functional outcomes, and overall survival (Brummel & Girard).

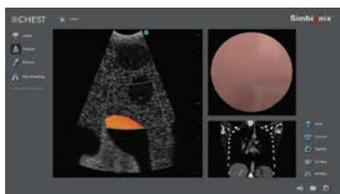
In summary, delirium has become a prominent issue in the care of the critically ill. Implementing a strategy for daily screening and then acting on those results to change treatable risk factors and avoid problematic ones, should become standard practice in the modern day ICU. We are still in the early phases of identifying the full, long-term effects of delirium, but we do recognize that there are detrimental cognitive effects. Delirium is a large burden, not just on the patients lifestyles, but on their families and society as a whole. The future requires us to take a more proactive course in the prevention of delirium and make prevention an integral part of the daily critical care tasks.

Dr. Awerbuch is attending physician, Division of Pulmonary and Critical Care Medicine, Clinical Instructor of Medicine, Icahn School of Medicine, Elmhurst Hospital Center, Elmhurst, New York.

Erratum

In the Critical Care Commentary by Dr. Martin E. Warshawsky, "ARDS: The past, present, and future?" in the October issue of *CHEST Physician*, the first sentence in the second paragraph of the article should have read: "ARDS is characterized by PO_2/FiO_2 less than 300, bilateral radiographic opacities not fully explained by effusions, collapse, or nodules, and respiratory failure not fully explained by cardiac failure or fluid overload (ARDS Definition Taskforce. *JAMA.* 2012;307[23]:2526)."

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Dialysis device reduced viral load in Ebola patient

BY SHARON WORCESTER
Frontline Medical News

FROM KIDNEY WEEK 2014

PHILADELPHIA – An experimental dialysis device safely and dramatically reduced the viral load in a critically ill Ebola patient treated in Frankfurt, Germany.

Dialysis performed using the device resulted in a reduction in viral load from 400,000 copies/mL to 1,000 copies/mL in the 36-year-old patient, said Dr. Helmut Geiger, chief of nephrology at Frankfurt University Hospital, at Kidney Week 2014.

The patient, a pediatrician who had treated Ebola patients in Sierra Leone, was diagnosed in September. He was transferred in October to Frankfurt University Hospital, where he presented with fever, chills, and weakness, and rapidly deteriorated. He developed multiorgan failure – including kidney failure – despite treatment with various experimental therapies.

The patient was placed on dialysis. The experimental device – the Hemopurifier, made by Aethlon Medical of San Diego – was incorporated into the treatment, with special approval from Germany's Federal Institute for Drugs and Medical Devices, Dr. Geiger said at the meeting, which was sponsored by the American Society of Nephrology.

The Hemopurifier is a first-in-class biofiltration device designed to eliminate viruses and immunosuppressive proteins from the circulatory system of infected individuals, according to Aethlon.

The company has been testing the device in patients with hepatitis C and in HIV patients in India. Aethlon plans to initiate U.S. clinical studies under an investigational device exemption approved by the U.S. Food and Drug Administration.

The Hemopurifier is a cylindrical cartridge that attaches to an existing dialysis machine. Inside, a glue-like protein selectively binds to viral particles and fragments, removing them from blood circulation.

The patient treated in Frankfurt by Dr. Geiger and his team underwent a 6.5-hour dialysis procedure using the device, and an analysis performed at a laboratory equipped to handle Ebola virus showed that the device had trapped 242 million viral copies.

The patient is now out of isolation, off dialysis, and in very good condition, he said.

Although additional study is needed, it appears that the Hemopurifier device may have contributed to the

patient's recovery, Dr. Geiger said, and no adverse events occurred during the treatment.

The device ultimately could play a role in treating multiple types of viral infection, he added.

Use of the Hemopurifier is safe and feasible, the device can be used with intermittent hemodialysis or in the setting of continuous renal replacement therapy, and it represents a promising new supportive tool for

severe Ebola infection, he concluded.

Dr. Geiger reported having consultancy agreements with AbbVie, Amgen, and Otsuka, and receiving research funding from Fresenius Medical Care.

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FROM THE EVP/CEO: Reflecting on a banner year

BY PAUL A. MARKOWSKI, CAE

It's December—the end of the calendar year, which often means a time of reflection. Depending on how things have gone during a given year, reflection can bring on a range of emotions. However, when I look back at our goals and accomplishments for CHEST, I'm nothing but proud of the work we've done and honored to have been part of this banner year.

To help focus our work in 2014, we concentrated our efforts around the five main goals from our strategic plan. There are many accomplishments, and I'll highlight just a few.

Goal 1: CHEST provides the total education solution with content customized to fit individual learner needs and schedules.

This past year, we developed and hosted 15 live-learning simulation courses in our new Innovation, Simulation, and Training Center. We held our first course in April and have since provided simulation education to approximately 1,000 attendees. We offered advanced technology learning tools and materials, including high-fidelity mannequin simulators and cadavers, to enhance these live-learning courses.

We're on track to continue providing quality education in 2015. We already have 19 courses scheduled, and people have begun registering. Check out the calendar at chestnet.org/live-learning.

Goal 2: CHEST has an array of new, relevant, and useful guidelines, standards, and complementary programs that guide the profession.

To be more responsive in the release of guidelines and consensus statements, we began publishing updates to topics as new evidence was evaluated. Following this model, we released several updates to our Diagnosis and Management of Cough: Evidence-Based Clinical Practice Guidelines from 2006. Remaining topics will be updated over the next few years. We published two new guidelines: Pharmacological Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline; and Care of the Critically Ill and Injured During Pandemics and Disasters: CHEST



MR. MARKOWSKI

Consensus Statement. More is in the works for 2015. We're partnering with the Canadian Thoracic Society to publish new guidelines for management of acute exacerbation of COPD, expected to be available early next year.

Goal 3: CHEST has a meaningful impact on global lung health and patient care.

We continue to host premier international education events to advance patient care. We hosted 1,800+ health-care professionals at CHEST World Congress 2014 and 4,000+ professionals at CHEST 2014 in Austin, Texas. Each program was carefully designed so that attendees could put the latest clinical advances into immediate practice and positively impact global lung health. In addition to education opportunities for health professionals, we provide education resources for patients and their families. This year, CHEST Foundation revised or wrote all new patient education materials. These resources are available on chestnet.org, where they are accessible to patients and clinicians around the world.

Goal 4: CHEST optimizes its assets to achieve its mission and ensure execution of its strategic plan.

By optimizing our print and electronic assets, our journal *CHEST* now reaches over 350,000 readers in print and online. In July, improved online content became available with the addition of Online Exclusives. In 2014, we continued to advance our mission through social media. We use social media outlets as a means for establishing ourselves as thought leaders in chest medicine, and we post and share content accordingly. Over the past year, our Twitter followers doubled and our Facebook fans grew

from 30,000 to 70,000. Those with an interest in chest medicine are taking note and engaging with us, and we expect those numbers to continue climbing.

Goal 5: CHEST has a strong and diverse financial base.

Our big news here is we successfully completed building our new CHEST Global Headquarters within budgetary and financing parameters. We now have an amazing facility that allows us to elevate our education offerings and advance our mission. Also contributing to our revenue base and attesting to the quality of our print publications, both subscription and advertising revenue for the journal *CHEST* hit all-time highs in 2014, and advertising revenue for *CHEST Physician* hit an all-time high. Our valued assets are lending to our financial stability.

CHEST accomplished much more during 2014, and I invite you to read the details in our Advancement and Impact Report, available on chestnet.org under the "About" tab. The report recaps our accomplishments during the presidential term of Michael H. Baumann, MD, MS, FCCP, but it also represents a culmination of the work of all our Past Presidents. CHEST has a proud history of dedicated leaders committed to advancing patient care and chest medicine. Their mentorship and work have been groundbreaking, and these have laid the foundation that enables us to accomplish all we do. Their contributions have led us to where we are today and will, no doubt, continue to guide us. I look forward to beginning another banner year in 2015.

As always, feel free to connect with me. I invite you to follow me on Twitter (@PMarkowskiACCP), or look for me at upcoming CHEST events.

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The end of the year is a time for many of us to make charitable contributions to the causes we care about most. This year, we ask you to include the CHEST Foundation on your list of organizations worthy of support.

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NAMDRC's 2015 conference

BY DR. TIMOTHY A. MORRIS, FCCP;
AND PHIL PORTE, NAMDRC EXECUTIVE
DIRECTOR

The NAMDRC meeting and educational conference is a most informative, productive, and fun professional gathering. The 38th annual meeting awaits you in Scottsdale, Arizona, March 12-14, 2015. The NAMDRC conference is unique in several important ways. The venue is small enough to allow personal interactions with world-class experts. It is tailor-made to enhance your clinical acumen, improve the productivity of your practice, and inform you of regulatory and legislative issues that have direct effects on your patients' access to care and on your practice's bottom line. The conference's setting is magnificent, and there are ample opportunities for you and your guest to have fun and to enjoy the beauty of this premier destination in the Southwest (at a time of year when you might enjoy a little thawing). Finally, it is a great chance to see the NAMDRC organization in action.

NAMDRC, the National Association for the Medical Direction of Respiratory Care, interests extend far beyond respiratory care departments. Formed by the American College of Chest Physicians, the American Thoracic Society, and the American Society of Anesthesiologists in the mid-

1970s, NAMDRC is an agile group of thought leaders from academic and private practice who can respond quickly to legislative and regulatory matters unique to pulmonary, critical care, and sleep medicine. For over 3 decades, it has earned a reputation for insightful and decisive leadership and has represented our profession through proactive, direct contact with policymakers on Capitol Hill and at federal regulatory agencies. The origin of our actions and the heart of our organization is the practicing physician.

Our educational conference is eclectic and all the sessions are plenary. Expert speakers interact personally with the audience, and we encourage real-time participation through the conference's audience response system. The program offers up to 13.5 AMA PRA Category 1 credits™ but concise enough to be done by midday. You and your guest will have the afternoon and evening to enjoy the beauty of the Scottsdale/Phoenix area at your leisure.

Another unique feature of the NAMDRC conference is the absence of an exhibit hall. NAMDRC's corporate partners actually support that aspect of the conference, since it affords them the opportunity to mingle with registrants in a more casual setting. Without the sales atmosphere (and expense) associated with an exhibit hall, partners tell NAMDRC that our approach is unique simply

because that casual atmosphere has fostered many long-term relationships for both physicians attending the conference and corporate representatives.

The program is filled with nationally recognized speakers committed to NAMDRC's educational goals. The topics include clinical updates, practice management advice, and health policy issues important to pulmonary, critical care, and sleep medicine. This year's theme is on individualization of patient care: the characteristics among patients with similar disorders that might warrant different approaches to diagnosis or therapies. Examples include the following:

- COPD Phenotypes

Robert Benzo, MD, Director Mindful Breathing Laboratory, Mayo Clinic, Rochester, MN

- Patients in Whom CPAP and Bi-Level Devices Might Reduce Hospital Readmissions

Sairam Parthasarathy, MD, University of Arizona College of Medicine, Tucson, AZ

- The Financial Implications of the Affordable Care Act – Luncheon

Don Moran, President, The Moran Company, Arlington, VA

- Selection of Respiratory Failure Patients for Acute Application of ECMO, ECCOR, etc.

J. Christopher Farmer, MD, FCCP, Professor of Medicine and Chair of Critical Care Medicine, Mayo Clinic, Scottsdale, AZ

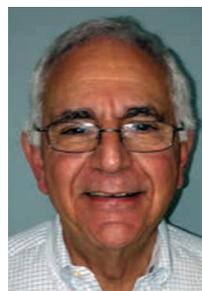
- Coding Update 2015

Alan Plummer, MD, FCCP, Professor of Medicine, Emory University Medical Center, Atlanta, GA.

Continued on following page



DR. MORRIS



MR. PORTE

Innovation, Simulation, and Training Center



2015 Education Calendar



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Management
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Methodology
March 12-13

Ultrasonography:
Essentials in Critical Care
March 26-28

Advanced Clinical
Training in Pulmonary
Function Testing
April 10-11

Focused Thoracic and
Vascular Ultrasound
April 30-May 1

Critical Care
Echocardiography
May 2-3

Advanced Critical Care
Echocardiography
June 4-6

Celebration of
Pediatric Pulmonology
June 12-13

Comprehensive
Pleural Procedures
June 18-20

Difficult Airway
Management
July 16-18

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

Pulmonary Procedures
for the Intensivist
August 7-8

Ultrasonography:
Essentials in Critical Care
September 10-12

Comprehensive
Bronchoscopy With
Endobronchial
Ultrasound
September 24-26

Focused Thoracic and
Vascular Ultrasound
November 12-13

Critical Care
Echocardiography
November 14-15

Ultrasonography:
Essentials in Critical Care
December 3-5

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

Critical Care Medicine
August 21-24

Sleep Medicine
August 21-24

Pulmonary Medicine
August 26-30

CHEST Annual Meeting

CHEST 2015
October 24-28
Montreal, Quebec,
Canada



> Learn More chestnet.org/live-learning

CHEST publishes policy statement; CMS releases preliminary decision

The “Online First” section of the journal *CHEST* has published Components for High Quality Lung Cancer Screening: American College of Chest Physicians and American Thoracic Society Policy Statement. The effort, led by lung cancer experts from the American College of Chest Physicians (CHEST), Gerard Silvestri, MD, FCCP, Peter Mazzone, MD, FCCP, and Frank Detterbeck, MD, FCCP, in collaboration with the American Thoracic Society (ATS), American Cancer Society, and American College of Radiology, aims to provide the framework and background to establish safe and effective lung cancer screening programs. The policy statement was presented to the Centers for Medicare & Medicaid Services (CMS) and was received positively.

The statement outlines nine components required for a safe and effective lung cancer screening program. Components include recommended population for lung cancer screening, screening frequency and duration, specification of CT scanning, nodule identification, reporting, management of algorithms, smok-

ing cessation, patient and provider education, and data collection.

On November 10, CMS released a preliminary decision to cover lung cancer screening with low-dose computed tomography (LDCT) for eligible patients. The decision was welcomed by a number of professional societies, including CHEST and ATS.

Dr. Silvestri noted, “We recently released a policy statement, which articulates what was special about these institutions and provides a roadmap for bringing best practices to patients at risk. We’re very eager to see the benefits of this important technology brought in a thoughtful way to people at risk throughout the United States. We feel this statement positively impacted the decision made today to cover screening in eligible patients.”

Components for High Quality Lung Cancer Screening: American College of Chest Physicians and American Thoracic Society Policy Statement can be viewed free of charge in the Online First section of *CHEST* at <http://journal.publications.chestnet.org>.

This Month in *CHEST*: Editor’s picks

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

EDITORIAL

Improving the Management of Children With Bronchiolitis: The Updated American Academy of Pediatrics Clinical Practice Guideline.

By Drs. S. C. Su and A. B. Chang.



ORIGINAL RESEARCH

Assessment of the Safety and Efficiency of Using an Age-Adjusted D-dimer Threshold to Exclude Suspected Pulmonary Embolism. By Dr. S. C. Woller et al.

Comparative Effectiveness of Robotic-Assisted vs Thoracoscopic Lobectomy.

By Dr. S. Paul et al.

The Association of Weight With the Detection of Airflow Obstruction and Inhaled Treatment Among Patients With a Clinical Diagnosis of COPD.

By Dr. B. F. Collins et al.

Continued from previous page

•Legislative & Regulatory Issues

Phil Porte, Executive Director, NAMDRRC, Vienna, VA

Please visit the NAMDRRC website to download the program at www.namdrcc.org/pubs/NAMDRCC_2015_BROCHURE.pdf. The brochure will give you conference and membership information, as well as hotel rates and more. Physicians who join NAMDRRC after July 1, 2014, and have never attended a NAMDRRC conference, enjoy complimentary conference registration, up to a \$425 value.

For additional information, contact NAMDRRC at 703/752-4359.

Dr. Morris is Professor of Medicine and Clinical Service Chief, Division of Pulmonary, Critical Care and Sleep Medicine, University of California, San Diego School of Medicine; and NAMDRRC President-Elect and Program Chairperson. Mr. Porte is NAMDRRC Executive Director.

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Medicare inches toward pay for advance care plan

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Medicare won't pay physicians for counseling their patients on advance care directives in 2015, but they are open to doing it sometime in the future.

In the 2015 Medicare Physician Fee Schedule, federal officials said they "will consider" whether to pay for codes related to advance care planning services after they have had the

opportunity to go through notice and comment rulemaking.

The final physician payment rule, which was released on Oct. 31, highlights two codes recently created by the American Medical Association's Relative Value Update Committee. The CPT code 99497 covers the first 30 minutes of a face-to-face discussion with the patient, family member, or surrogate about advance directives, as well as the completion of forms. The add-on CPT code 99498 covers each

additional 30 minutes.

Physicians can use the new codes, but Medicare will not pay for them in 2015, according to the rule.

Dr. Diane E. Meier, director of the Center to Advance Palliative Care, said the agency's decision not to move forward immediately with payment is not a surprise.

"I think it's promising," she said. "I think it's not surprising that they are being extremely cautious and hesitant given the political firestorm that an effort to do this created in 2009."

Public opinion on end-of-life care is beginning to shift, Dr. Meier said, which could bode well for future Medicare payment. But payment is only one barrier to making counseling available to all patients. Training physicians and other health care providers in how to have conversations about the end of life is a far bigger hurdle, she said.

"If the clinician is afraid, uncomfortable, doesn't even know how to begin, it doesn't matter if there's a payment," she said. "They're not going to do it."

There has been some momentum building for Medicare payment for end-of-life counseling, including pressure from Congress. In September, 34 members of the U.S. House of Representatives wrote to CMS urging



It's not surprising that CMS is being cautious given the political firestorm that an effort to do this created in 2009.

DR. MEIER

them to begin paying for the newly created codes 99497 and 99498.

The Institute of Medicine in its September report, *Dying in America*, also recommended that physicians be compensated for counseling patients on end-of-life planning.

mschneider@frontlinemedcom.com
On Twitter @maryellenny

VIEW ON THE NEWS

Dr. Michael E. Nelson, FCCP, comments: Pulmonary and critical care physicians counsel patients and offer advance directives as part of routine care, as do many other physicians. It is appropriate to expect reimbursement for providing this often time-consuming process. However, CMS occasionally chooses not to reimburse for CPT

codes until it has an opportunity to study the financial implications of this decision. While CMS cannot be compelled to decide in favor of physicians, contacting your senators and representatives at the federal level and requesting their support for payment is a good way to help CMS decide to "do the right thing."

Malpractice climate: 'Stable, but still dysfunctional'

BY ALICIA GALLEGOS
Frontline Medical News

Fewer malpractice suits are resulting in paid claims against physicians while malpractice insurance premiums have remained stable or declined over the last 12 years, according to an analysis published Oct. 30 in *JAMA*.

Since 2002, the rate of paid malpractice claims against doctors of medicine has decreased by an estimated 6% annually; for doctors of osteopathy, the rate has declined about 5% annually, Michelle M. Mello of Stanford (Calif.) University and her colleagues reported (*JAMA* 2014 Oct. 30 [doi:10.1001/jama.2014.10705]).

Dr. Mello and her colleagues analyzed paid legal claims against MDs and DOs between 1994 and 2013 from the National Practitioner Data Bank and the American Medical Association's Physician Masterfile. They also evaluated premium data from the Medical Liability Monitor's Annual Rate Survey.

The rate of paid malpractice claims against MDs fell from 18.6 to 9.9 paid claims per 1,000 physicians between 2002 and 2013, they found. For DOs, rates dropped from about 19 in 2002 to about 12.2 paid claims per 1,000 physicians in 2013.

The median compensation paid to plaintiffs rose by 63% between 1994 and 2007, from \$133,799 to \$218,400, in adjusted 2013 dollars. However, since 2007, that number has declined, reaching \$195,000 in 2013. Only 3.4% of payments made during the 20-year period resulted from jury verdicts; the others stemmed from settlements.

For the premiums review, Dr. Mello and colleagues analyzed insurance data from 2004 to 2013 from five geographical areas: Los Angeles, Orange,

Kern, and Ventura counties in California; Nassau and Suffolk counties in New York; Cook, Madison, St. Clair, and Will counties in Illinois; and the states of Tennessee and Colorado. The locations were selected based on geographic diversity and because each had an insurer with a dominant market share.

In California, Illinois, and Tennessee, internists and ob.gyns. saw a 36% decrease in premiums charged by each state's largest medical malpractice insurer from 2004 to 2013. Premiums charged to general surgeons fell by 30% in these states. In Colorado, internists saw a 20% decrease in premiums



over the same time period, but general surgeons saw an increase of 13% and ob.gyns. experienced an 11% rise. In New York, rates charged by the largest insurer rose by 12% for ob.gyns, 16% for internists, and 35% for general surgeons.

It remains unclear why the rate of paid claims has decreased and why premiums have remained fairly stable, Dr. Mello and colleagues said. While medical organizations like to point to tort reform, traditional reforms such as award caps do not address problems within the malpractice system's core functions – compensating negligently injured patients and deterring substandard care, they added.

"The weight of evidence suggests that the sys-

tem's effectiveness as both a compensation and a deterrence mechanism is mediocre at best, and there is little to suggest it has improved over the past decade," they wrote. "Thus, 'stable but still dysfunctional' might describe today's liability environment."

The authors offered alternatives to traditional tort reform, such as communication and resolution programs, mandatory presuit notification laws, and judge-directed negotiation.

In communication and resolution programs, clinicians and institutions openly discuss adverse outcomes with patients and proactively seek resolution, including offering an apology, and, if the standard of care was not met, compensation. Mandatory presuit notification refers to requiring plaintiffs to give defendants advance notice that they intend to sue. Judge-directed negotiation centers on court policies in which malpractice litigants meet early and often with judges to discuss settlement. In such negotiations, the court employs an attorney with clinical training to help judges understand clinical issues.

The authors conclude that action to improve the medical liability system is necessary while the legal climate is stable, and not after a crisis.

"During malpractice crises, interest in liability reform intensifies, but one lesson of the last 40 years is that an atmosphere of crisis is not conducive to thoughtful and enduring solutions," study authors said. "Action now to reduce the amplitude of the next medical liability cycle is both prudent and feasible. Further testing of nontraditional reforms, followed by wider implementation of those that work, holds the most promise."

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Medicare finalizes monthly pay for care coordination

The 2015 final Medicare Physician Fee Schedule also addresses Open Payments and allows telemedicine for annual wellness visits, psychoanalysis, psychotherapy, and prolonged E&M services.

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Time spent on care coordination outside of the face-to-face visit will receive pay recognition in 2015, as a result of a regulation from the Centers for Medicare & Medicaid Services.

CMS officials have released the final 2015 Medicare Physician Fee Schedule rule, which lays out how much, and under what conditions, payment will be made for providing care coordination services to Medicare patients with multiple chronic conditions.

Starting Jan. 1, about \$40 per patient per month can be earned for non-face-to-face chronic care management services, such as developing and revising the care plan, communicating with other treating providers, and managing medications.

The billing codes – CPT codes 99490 and 99487 and 99489 – apply only to Medicare patients with two or more significant, chronic conditions. CMS plans to make a bundled

The billing codes – CPT codes 99490 and 99487 and 99489 – apply only to Medicare patients with two or more significant, chronic conditions.

payment for codes 99487 and 99489, according to the rule.

CMS will also allow more “flexibility” in the supervision of clinical staff who provide care coordination services. Under the rule, physicians can bill “incident to” services provided by clinical staff members, even if they are not direct employees and are under general, but not direct, supervision.

CMS said the rules for “incident to” services are somewhat looser than usual because of the nature of non-face-to-face care coordination, which often involves after-hours contact with nurses and coordination with providers who are not direct employees of the physician practice.

The fee schedule final rule also expands access to telehealth services for Medicare beneficiaries. Medicare will now allow annual wellness visits, psychoanalysis, psychotherapy, and prolonged evaluation and management services to be performed via telemedicine.

CMS is also finalizing changes to the Open Payments Program, which aims to increase transparency by requiring

drug, device, and biological manufacturers to report on their payments to physicians and teaching hospitals. CMS published the first round of payment data on Sept. 30, 2014.

The most significant change for



physicians is the elimination of the continuing education exclusion.

Currently, manufacturers do not have to report payments made indirectly to speakers at continuing medication education (CME) courses, provided the events are organized by certain accredited groups (the Accreditation Council for Continuing Medical Education, the American Academy of Family Physicians, the American Medical Association, or the American Osteopathic Association) and that the manufacturer has not had a role in recruiting or influencing the speakers.

Under the change finalized in the rule, CMS would no longer provide the exemption only for CME events run by accredited groups. Instead, indirect CME payments will be excluded from reporting across the board, provided the payments meet other rules about lack of industry interference.

The new rules will take effect Jan. 1, 2016.

The CME change “will create a more consistent reporting requirement, and will also be more consistent for consumers who will ultimately have access to the reported data,” CMS wrote in a fact sheet on the rule.

The agency will also require manufacturers to report stocks, stock options, or any other ownership interest as distinct categories. The changes aren’t expected to be implemented until the 2016 data collection period, according to CMS.

The final fee schedule rule also reminds physicians of the looming Sustainable Growth Rate cut.

Unless Congress acts to avert the cut before March 31, 2015, physicians will face on average a 21.2% across-the-board Medicare fee reduction.

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Medicare begins bundled hospital outpatient payments

BY MARY ELLEN SCHNEIDER
Frontline Medical News

After a year-long delay, Medicare officials are implementing bundled payments for a number of services performed in hospital outpatient departments.

The new payments, which were finalized in

the 2015 Medicare Hospital Outpatient Prospective Payment System rule, will take effect on Jan. 1, 2015.

The Centers for Medicare & Medicaid Services selected 25 primary services and their adjunctive services and supplies as comprehensive ambulatory payment classifications (C-APCs) and will provide a single payment under Medicare Part B.

Medicare beneficiaries will pay a single copayment for the C-APC services.

The 25 C-APCs fall within 12 clinical families:

- automatic implantable cardiac defibrillators, pacemakers, and related devices
- breast surgery
- ENT procedures
- cardiac electrophysiology
- ophthalmic surgery
- gastrointestinal procedures
- neurostimulators
- orthopedic surgery
- implantable drug delivery systems
- radiation oncology
- urogenital procedures
- vascular procedures

For instance, Medicare has designated implantation of a drug infusion device as a C-APC (0227) with a bundled Part B Medicare payment of \$15,566.

The final rule, which was released by CMS on Oct. 31, also reversed the CMS policy of requiring physician certification for all Medicare Part A hospital admissions.

Starting Jan. 1, a formal physician certification is required only for long-stay cases of 20 days or more, or in costly outlier cases.

For most patients, the admission order, medical record, and progress notes will contain “sufficient information to support the medical necessity of an inpatient admission without a separate requirement of an additional, formal, physician certification,” according to the final rule.

The revision of the physician certification policy does not remove any of the requirements associated with Medicare’s controversial 2-midnight policy, which governs short-stay hospitalizations.

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GR14_194

South Florida Critical Care Medicine - Nocturnist

An MHS representative will be attending the CHEST2014 Conference, visit us at booth#740

About the Opportunity:

Memorial Healthcare System's Intensivist program is expanding. The program is currently comprised of 21 full time intensivists, providing 24/7 ICU coverage at multiple locations within The Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple Board Certifications including infectious diseases, pulmonology, surgery and neuro-critical care. This is a full-time employed position with competitive benefits and compensation package, "sovereign immunity", paid CME, state of the art equipment (including EPIC EMS, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds etc)

Qualifications & Responsibilities:

The program is seeking four (4) dedicated critical-care nocturnists to join the existing team. The nocturnists will integrate into the existing operational structure as the program expands to cover additional critical care units. Critical care coverage is provided in 12 hour in-house shifts, 7pm to 7am - averaging approximately 15 shifts per month. The successful candidates will have excellent clinical skills, a broad knowledge base in critical care and be dedicated to providing high quality, evidence based care. Candidates must be BC/BE.

About Memorial Healthcare System:

Memorial Healthcare System is a 1,900-bed healthcare system located in South Florida and is highly regarded for its exceptional patient- and family-centered care. Memorial's patient, physician and employee satisfaction rates are among the most admired in the country, and the system is recognized as a national leader in quality healthcare.

About South Florida:

South Florida offers quality of life, is rich in cultural and recreational amenities, and offers pristine beaches, top-rated golf courses, museums and world-class dining. The greater Ft. Lauderdale area offers numerous communities in which to raise a family. In addition, Florida has no state income tax.

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Annual echo screening for allograft vasculopathy

BY BRUCE JANCIN
Frontline Medical News

AT THE HFSA ANNUAL SCIENTIFIC MEETING

LAS VEGAS – The experience at one major heart transplantation center indicates that annual screening dobutamine stress echocardiography to detect cardiac allograft vasculopathy renders annual coronary angiography unnecessary.

“This noninvasive method has very good specificity and is associated with a negative predictive value of 94%-97%. It can be used in our experience in lieu of annual invasive coronary angiography,” Dr. Jerry D. Estep declared at the annual meeting of the Heart Failure Society of America.

Cardiac allograft vasculopathy (CAV) is a unique, highly aggressive form of CAD. After 3 years post transplant, it becomes the No. 1 cause of cardiac retransplantation and mortality. Guidelines recommend consideration of annual screening coronary angiography to detect it early to institute aggres-

sive countermeasures. That’s the practice at most transplant centers.

However, at Houston Methodist Hospital, where Dr. Estep is medical director of the heart transplant and LVAD program, annual dobutamine stress echocardiography (DSE) is used instead. Because there is a scarcity of published data on this noninvasive alternative approach, he presented a retrospective study of the Houston transplant center’s experience over a recent 5-year period.

The study included 144 heart transplant recipients who underwent screening DSE for CAV annually for the first 4 years post transplant and coronary angiography at year 5.

During years 1-4, DSE detected CAV in 19% of patients. They didn’t differ in terms of baseline characteristics from those who remained free of this serious complication.

The good news: Ninety-four percent of patients with normal DSEs during years 1-4 had no CAV upon angiography at year 5. Moreover, the 5% who did have CAV at year 5 after earlier negative

Ninety-four percent of patients with normal DSEs during years 1-4 had no CAV upon angiography at year 5.

VIEW ON THE NEWS

Dr. Hossein G. Almassi, FCCP, comments:

Among solid organ transplants, cardiac transplant is rather unique in its need for invasive biopsy and angiography in following up the cardiac allograft. The search for noninvasive monitoring tools has been ongoing for a number of years. The report by the Houston group is a positive development in the right direction awaiting further confirmation by other cardiac transplant centers.

DSEs had mild to moderate disease.

The investigators documented the performance of annual screening DSE in predicting the development of major adverse cardiac events, defined as readmission for acute coronary syndrome, heart failure, revascularization, repeat heart transplantation, or cardiac death.

Dr. Estep reported having no financial conflicts regarding this study.

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Job Opportunity in South Florida Critical Care Intensivists

About the Opportunity:

Memorial Healthcare System’s Intensivist Program has expanded. The program is currently comprised of 23 full time intensivists and five critical care ARNPs, providing 24/7 ICU coverage at multiple locations within the Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple board certifications including infectious diseases, pulmonology, surgery and neuro-critical care.

The available positions are full-time employed positions with competitive benefits and compensation package, sovereign immunity, paid CME and state-of-the-art equipment (including EPICEMS, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds, etc).

Qualifications and Responsibilities

The program is seeking dedicated critical care physicians to join the existing team. The successful candidates will integrate into the existing operational structure that includes two different ICU staffing models. Two separate opportunities exist, at different locations within Memorial Healthcare System.

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- Approximately 15 shifts per month (more if desired)
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- 15 total shifts per month (in house 7am-7pm, availability/on call 7pm-7am)

The successful candidates will have excellent clinical skills, a broad knowledge base in critical care and be dedicated to providing high quality, evidence-based care. Applicants must be board certified/board eligible in critical care medicine.

About Memorial Healthcare System:

Memorial Healthcare System is a 1,900-bed healthcare system located in South Florida and is highly regarded for its exceptional patient- and family-centered care. Memorial’s patient, physician and employee satisfaction rates are some of the most admired in the country, and the system is recognized as a national leader in quality healthcare.

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Mechanical heart valves create pregnancy risks

BY MITCHEL L. ZOLER
Frontline Medical News

AT ESC 2014

BARCELONA – Women with mechanical heart valves who become pregnant face a very-high-risk pregnancy, with a 58% rate of an uncomplicated pregnancy resulting in a live birth, according to international registry data collected since 2007.

Pregnant women at high risk because of a mechanical heart valve need management by a multidisciplinary team at a referral center that focuses on these cases, a type of care that many of these women do not receive today, Dr. Jolien W. Roos-Hesselink said at the annual congress of the European Society of Cardiology.

“We believe management of these women needs to be better structured and organized,” said Dr. Roos-Hesselink, professor and head of the department of congenital cardiology at Erasmus Medical Center in Rotterdam, the Netherlands. “Pregnancy is a time of risk for any woman with structural heart disease, but for those with a mechanical valve are really high-risk patients,” she said in an interview.

“Most of these women are now cared for by a general cardiologist. They need a specialist in obstetric cardiology,” as well as care from

other experts with experience in the types of complications these women develop, said Dr. Roger J.C. Hall, professor of cardiology at Norfolk and Norwich (England) University Hospital.

The data also showed that physicians around the world used any one of seven different anticoagulant regimens during these pregnancies, a strikingly high number that highlights uncertainty about which

Risks faced by women with mechanical heart valves far exceeded the risk seen in women with tissue valves.

regimen is best, although heparin use during the first trimester was linked with a higher rate of valve thrombosis. The various regimens use different combinations of periods of treatment with unfractionated heparin, low-molecular-weight heparin, or a vitamin K antagonist drug during the first trimester, during weeks 14-36, and during the last weeks of pregnancy.

“We found large differences in management among different countries, physicians, and among individual patients. All the regimens have advantages and disadvantages” and are based on expert opinion with no prospect for a randomized, controlled trial, said Dr. Roos-Hesselink. For now, the numbers of women receiving each of the seven regimens remains too small for statistical analysis, but the researchers hope that eventually larger numbers may start to reveal which regimens work best, said Dr. Hall.

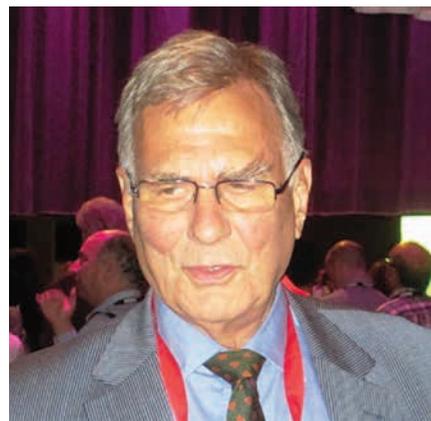
However, the available data showed two clear trends: Treatment with vitamin K antagonists was tied to an increased rate of miscarriages, and treatment with heparin during the first trimester was associated with an increased rate of valve thrombosis, noted Dr. Roos-Hesselink.

One other notable finding was that the risks faced by women with mechanical heart valves far exceeded the risk seen in women with tissue valves, and in women with other forms of mechanical heart disease but no valve prostheses. Adolescents and young women who need a heart valve should be part of a shared decision process that reviews the pros and cons of a mechanical and tissue valve, said Dr. Roos-Hesselink and Dr. Hall.

A tissue valve is less durable, and so typically requires replacement

sooner than does a mechanical valve. But in the current study, the pregnancy loss and complication rates among the 134 women with a tissue valve roughly matched the rates among the 2,620 women with no valve prosthesis, while the rates among 212 women with a mechanical valve ran much higher.

The Registry of Pregnancy and Cardiac Diseases began in 2007 through an initiative of two interest groups of the European Society of Cardiology, the valve group and the congenital heart disease group (Eur. Heart J. 2013;34:657-65). By



The researchers hope that eventually larger numbers may start to reveal which regimens work best, said Dr. Roger J. C. Hall.

September 2014, the registry had enrolled more than 3,600 pregnancies. The current report focused on the first 2,966 women enrolled, with an average age of 29 years. Slightly more than half the enrolled women had congenital heart disease, slightly fewer than a third had valvular heart disease (usually because of rheumatic heart disease), 7% had cardiomyopathy, and smaller number of women had other etiologies.

Maternal mortality averaged 1.4% for women with mechanical valves, 1.5% for those with tissue valves, and 0.2% for everyone else. Miscarriage rates were 16% for mothers

VITALS

Key clinical point: Pregnant women with mechanical heart valves have a very high rate of pregnancy complications and miscarriages.

Major finding: The rate of live births without complications was 58% in women with a mechanical heart valve.

Data source: ROPAC registry of 2,966 pregnant women with structural heart disease from 132 centers in 48 countries.

Disclosures: Dr. Roos-Hesselink and Dr. Hall had no disclosures.



“We believe management of these women needs to be better structured and organized,” Dr. Jolien W. Roos-Hesselink said.

with mechanical valves and 2% for everyone else, including those with tissue valves. Fetal mortality was 3% among women with mechanical valves and less than 1% for everyone else. Thrombotic and hemorrhagic events occurred in about 29% of women with mechanical valves, compared with less than 6% in everyone else. Ten of the women with mechanical valves (5%) developed valve thrombosis. The live birth rate was 80% for women with mechanical valves and 95% or better for everyone else.

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VIEW ON THE NEWS

Dr. G. Hossein Almassi, FCCP, comments: One of the toughest decisions in valvular heart surgery is the selection of a valve prosthesis for a young female. Historically, age has been the major deciding factor in selecting a mechanical valve over a tissue valve. The current report is a testament to this difficulty, showing a lack of a standardized anticoagulation regimen and a much higher rate of pregnancy loss and complications with mechanical heart valves. Availability of transcatheter valve technology may make the tissue valves more attractive for this group of patients. Clearly, the care for these women would be best provided by a multidisciplinary team of specialists.

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CHEST

The screenshot shows the CHEST Physician website interface. At the top, there's a navigation bar with 'HOME', 'CLINICAL NEWS', 'NEWS FROM THE ACCP', 'FEATURES', 'PRACTICE ECONOMICS', and 'MUL'. Below this, a 'Featured Topic' section highlights 'PULMONARY MEDICINE' with a sub-headline 'Biological gender does not improve cardiovascular risk in men'. Other news items include 'High schoolers smoking more often, pipes, e-cigarettes', 'Pulmonologist holds up to real world, pragmatic studies', 'Biologics inch ahead in asthma treatment', and 'Clinical phenotypes in COPD lead to better diagnosis, more targeted treatments'. A 'Features' section includes 'Point/Counterpoint: Will Choosing Wisely in care?' and 'Campaign pushes doctors to be the best "YES" of all the tools, part - and now the rescue - is among the most powerful, in a system that rewards you no surprise that more it...'. At the bottom, there's a 'Connect with the ACCP' link.

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