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THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

A macrolide might once again be available for empiric oral treatment of severe CAP, Dr. Carlos Barrera said.

Solithromycin shows efficacy in pneumonia

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2015

MONTREAL – A new, next-generation macrolide, solithromycin, showed safety and efficacy as a once-daily oral agent that was noninferior to the comparator oral antibiotic, the fluoroquinolone moxifloxacin, in a phase III trial.

Macrolide resistance among strains of *Streptococcus pneumoniae* that cause many U.S. cases of severe community-acquired pneumonia has become common, complicating treatment of this common infection with a macrolide, Dr. Carlos M. Barrera explained at the annual meeting of the American College of Chest Physicians.

The SOLITAIRE-ORAL (Efficacy and Safety Study of Oral Solithromycin [CEM-101] Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia) trial enrolled 860 patients with moderate to moderately severe community-acquired pneumonia.

About half of the patients enrolled in the trial underwent microbiologic assessment of their infect-

See **Solithromycin** • *page 8*

High-flow nasal cannula scores CCU success

No change in escalation rates, mortality

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2015

MONTREAL – A relatively new system for delivering noninvasive respiratory support, high-flow nasal cannula therapy, appeared well suited to ventilation therapy for coronary care unit patients, according to a single-center experience in New Zealand with 497 adult patients.

"The high-flow nasal cannula largely replaced noninvasive ventilation in our CCU patients with no change in escalation rates or mortality. The high-flow nasal cannula should be considered a first-line treatment in this setting," said Dr. Troy S. Browne at the annual meeting of the American College of Chest Physicians.

He and his associates at Tauranga (New Zealand) Hospital compared their experience using standard noninvasive ventilation on 249 CCU patients who needed respiratory support during May-November 2012 with 248 patients who received ventilation with a high-flow nasal cannula once it became the default strategy in the coronary care unit.

The high-flow nasal

See **High-flow cannula** • *page 9*

INSIDE

Catheter-directed thrombolysis for PE

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2015

MONTREAL – Catheter-directed thrombolysis surpassed systemic thrombolysis for minimizing in-hospital mortality of patients with an acute pulmonary embolism in a review of more than 1,500 U.S. patients. The review also found evidence that U.S. pulmonary embolism (PE) patients increasingly undergo catheter-directed thrombolysis, with usage jumping by more than 50% from 2010 to 2012, although in 2012 U.S. clinicians performed catheter-directed thrombolysis on 160 patients with an acute pulmonary embolism (PE) who were included in a national U.S. registry of hospitalized patients, Dr. Amina Saqib said at the annual meeting of the American College of Chest Physicians.

Catheter-directed thrombolysis resulted in a 9% in-hospital mortality rate and a 10% combined rate

See **Catheter-directed** • *page 9*

CHEST Physician
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CHANGE SERVICE REQUESTED

In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

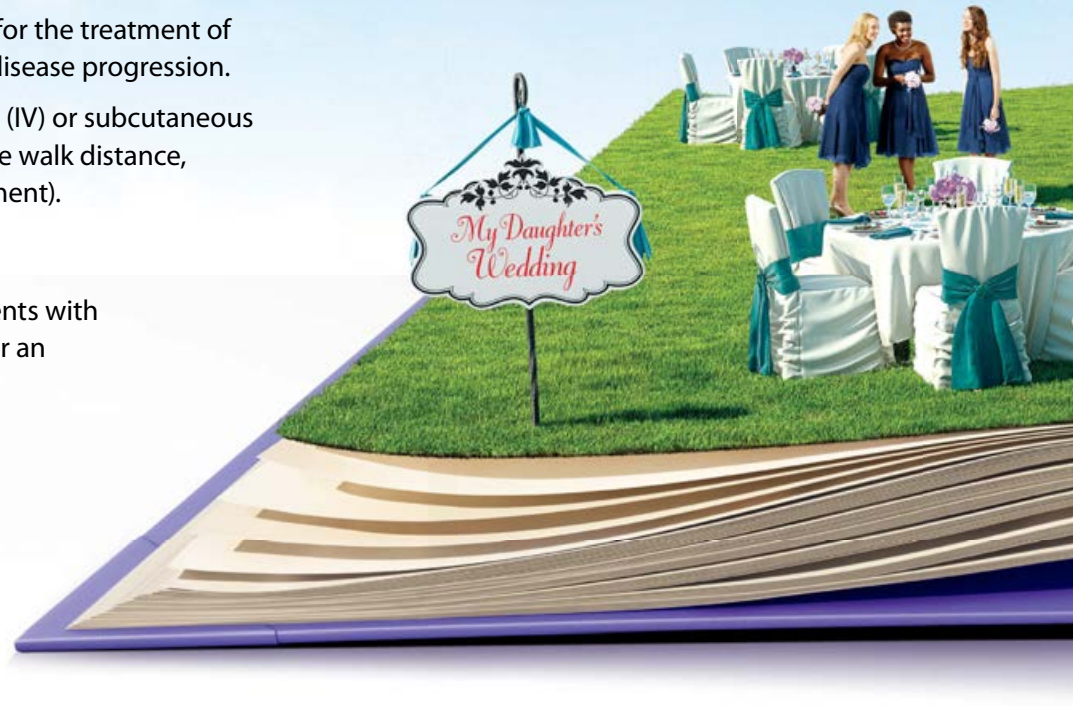
OPSUMIT® (macitentan) is the only ERA approved to delay disease progression as both monotherapy and in combination with PDE-5 inhibitors or inhaled prostanoids[1]

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.

6MWD: 6-minute walk distance; ERA: endothelin receptor antagonist; IV: intravenous; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase type 5; SC: subcutaneous; SERAPHIN: **S**tudy with an **E**ndothelin **R**eceptor **A**ntagonist in **P**ulmonary Arterial **H**ypertension to **I**mprove Cli**N**ical Outcome; ULN: upper limit of normal; WHO: World Health Organization.

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

Patient dramatization

SERAPHIN: The first long-term outcome trial in PAH (average treatment 2 years) to demonstrate the use of both monotherapy and combination therapy to delay disease progression[1,2]

Patients were treated with OPSUMIT monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

- SERAPHIN included both incident (recently diagnosed) and prevalent (previously diagnosed) patients[3]
- Overall, the median time from diagnosis was 15 months, ranging from 1 day to 36 years[3]
- 25% of patients were diagnosed less than 6 months prior to enrollment in the study[3]

SERAPHIN was a randomized, double-blind, placebo-controlled, event-driven outcome study to assess the effect of OPSUMIT on disease progression (time to first significant morbidity or mortality event), as defined by death, atrial septostomy, lung transplantation, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).[1,2]

WARNINGS AND PRECAUTIONS (continued)

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN was 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN was 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 × 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.

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

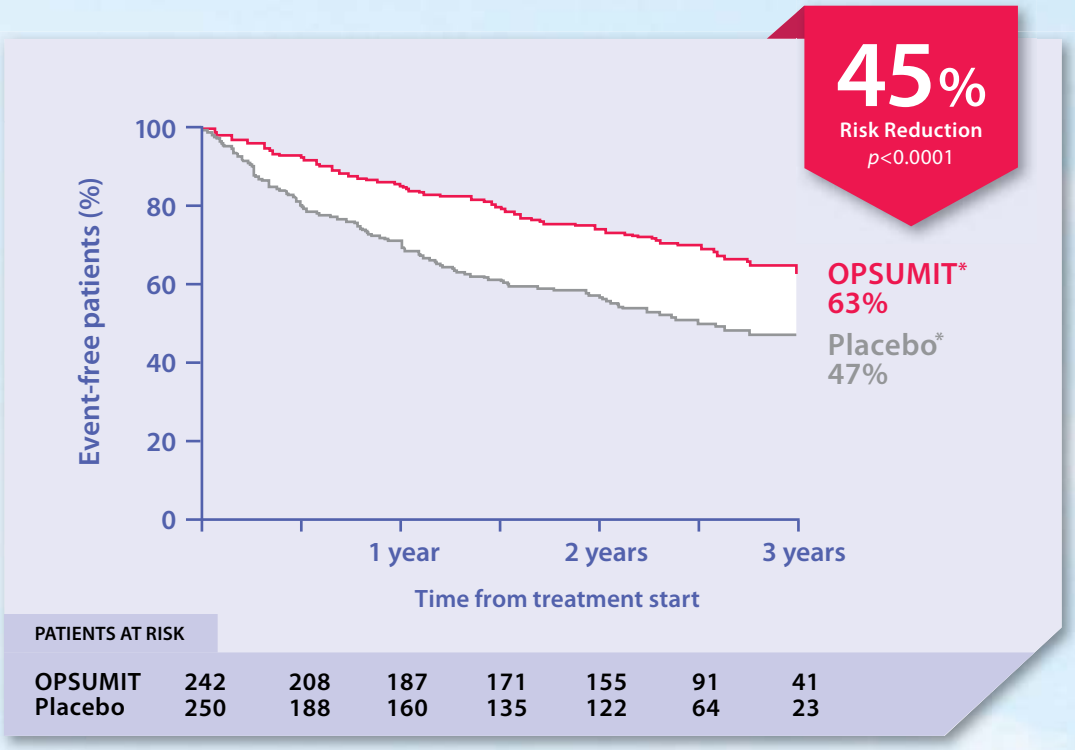
FUTURE. FORWARD. Opsumit® macitentan tablets 10 mg

INDICATION

OPSUMIT® (macitentan) 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.

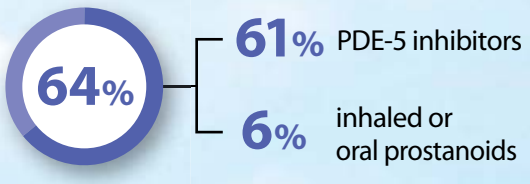
Keep disease progression in mind from the start of therapy: OPSUMIT is the only ERA approved to delay disease progression in FC II and III patients[1]

Kaplan-Meier estimates of risk of first primary endpoint event in SERAPHIN



Disease progression included: death, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms and need for additional PAH treatment).[1]

***Patients on PAH-specific background therapy at baseline**



Summary of primary endpoint events

	OPSUMIT 10 mg (n=242) n (%)	Placebo (n=250) n (%)
Patients with a primary endpoint event†	76 (31.4)	116 (46.4)
Component as first event		
Worsening PAH	59 (24.4)	93 (37.2)
Death	16 (6.6)	17 (6.8)
IV/SC prostanoid	1 (0.4)	6 (2.4)

The beneficial effect of OPSUMIT was primarily attributable to a reduction in clinical worsening events (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).[1]

†No patients experienced an event of lung transplantation or atrial septostomy in the placebo or OPSUMIT 10 mg treatment groups.

WARNINGS AND PRECAUTIONS (continued)

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.

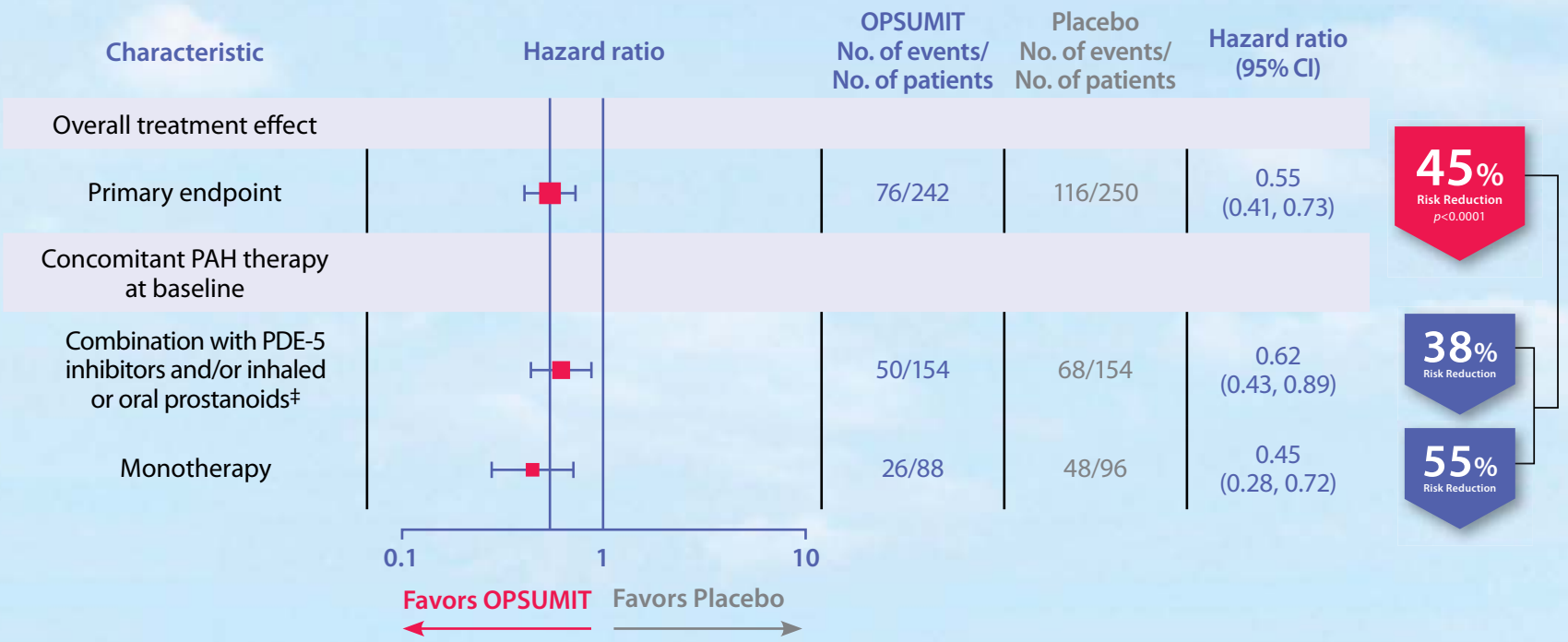
Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

INDICATION (continued)

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%).

OPSUMIT provided consistent efficacy on the primary endpoint as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

Subgroup analysis of the primary endpoint in the SERAPHIN study



‡The OPSUMIT indication includes combination with phosphodiesterase-5 inhibitors or inhaled prostanoids, but not oral prostanoids.

In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)...

Don't delay, treat today—keep disease progression in mind from the start of therapy in FC II and III patients.

OPSUMIT is approved for use as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids[1]

ADVERSE REACTIONS

- Most common adverse reactions (more frequent than placebo by ≥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.

References: 1. OPSUMIT full prescribing information. Actelion Pharmaceuticals US, Inc. February 2015. **2.** Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809-818. **3.** Center for Drug Evaluation and Research, Food and Drug Administration. Opsumit (macitentan) NDA 204410. Medical Review(s). 19 October 2013. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000MedR.pdf. Accessed April 15, 2015.

CI: confidence interval; CYP: cytochrome P450; FC: functional class; HIV: human immunodeficiency virus.

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

FUTURE. FORWARD. Opsumit® macitentan tablets 10 mg

ACTELION

Opsumit
macitentan tablets 10 mg

Rx only

BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

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

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

CONTRAINDICATIONS

Pregnancy

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

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

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

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

OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include the following:

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

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

Hepatotoxicity

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

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

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

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

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

Hemoglobin Decrease

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

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

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

Table 2: Adverse Reactions

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

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OPSUMIT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity reactions (angioedema, pruritus and rash)
Respiratory, thoracic and mediastinal disorders: nasal congestion

DRUG INTERACTIONS

Strong CYP3A4 Inducers

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

Strong CYP3A4 Inhibitors

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

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

Animal Data

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

Nursing Mothers

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

Pediatric use

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

Geriatric use

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

Females and Males of Reproductive Potential

Females

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

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

Males

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

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

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

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

OPSUMIT® (macitentan)

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.

Drug Interactions

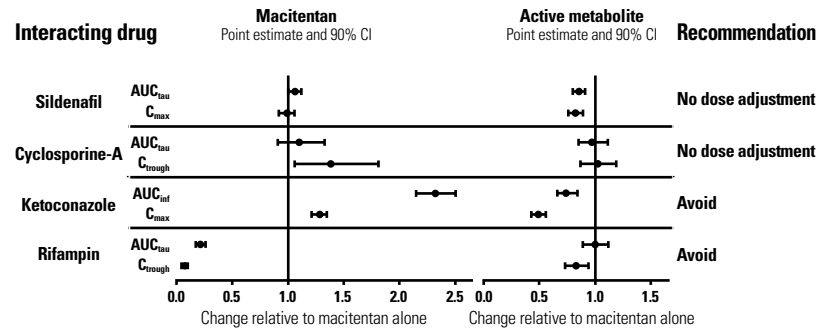
In vitro studies

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

ACT20150219

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. February 2015.

Novel Macrolide for Pneumonia

Solithromycin *from page 1*

ing pathogen, and about 40% of cases in each treatment arm had infections caused by *S. pneumoniae*. In this subgroup, the 5-day regimen of solithromycin tested in the study succeeded in clearing the infection in 89% of patients, comparable to the 83% success rate achieved with a 7-day course of moxifloxacin (Avelox), said Dr. Barrera, a pulmonologist who practices in Miami.

The study's primary endpoint for Food and Drug Administration approval of solithromycin was early clinical response, defined as an improvement in at least two listed symptoms at 72 hours after onset of treatment.

That endpoint occurred in 78% of patients enrolled in each of the two arms of the study.

The data make solithromycin look like a promising way to once again have a macrolide available for empiric oral treatment of more severe community-acquired pneumonia, pending full peer review of the data, commented Dr. Muthiah P. Muthiah, a pulmonologist at the University of Tennessee Health Science Center in Memphis.

"A couple of decades ago, you could comfortably treat a patient with severe community-acquired pneumonia with a macrolide, but you can't do that anymore," Dr. Muthiah said in an interview.

If the newly reported data on oral solithromycin hold up under further review, it would mean that solithromycin was as effective as a potent quinolone, which remains an effective monotherapy for community-acquired pneumonia in patients who do not require treatment in an intensive care unit, Dr. Muthiah noted.

A companion study, SOLITAIRE-IV, is a phase III pivotal trial assessing the safety and efficacy of solithromycin when begun intravenously for treating community-acquired pneumonia, followed by a switch to oral dosing, in comparison with intravenous followed by oral treatment with moxifloxacin.

Once those data are fully collected and analyzed, the company will submit the information from both trials to the FDA, said Dr. David Oldach, who is the chief medical officer for Cempra.

Results from the intravenous trial, reported in a preliminary way by Cempra in a press release, showed that the solithromycin treatment regimen tested in SOLITAIRE-IV met its noninferiority targets, compared with moxifloxacin.

The safety results, however, showed that solithromycin produced a higher number of patients with a liver-enzyme elevation, compared with patients treated with moxifloxacin.

In SOLITAIRE-IV, Cempra reported that grade 3 increase in levels of alanine transaminase (ALT) occurred in 8% of patients on solithromycin and in 3% of patients on moxifloxacin. Grade 4 increases in ALT occurred in less than 1% of patients in both treatment arms.

In the current, orally administered trial, grade 3 ALT increases occurred in 5% of patients treated with solithromycin and in 2% of patients treated with moxifloxacin.

Grade 4 ALT increases occurred in 0.5% of patients treated with solithromycin and in 1.2% of those treated with moxifloxacin.

No patients in either arm developed an elevation of both ALT and bilirubin, and the ALT increases seen were reversible and asymptomatic, Dr. Barrera said.

By other assessments, the safety profiles of solithromycin and moxifloxacin were similar: 7% of patients on solithromycin and 6% on moxifloxacin had a serious adverse event, and 4% of patients in each study arm discontinued treatment because of an adverse event.

SOLITAIRE-ORAL was sponsored by Cempra, the company developing solithromycin.

Dr. Barrera has received research funding from Cempra. Dr. Muthiah had no disclosures.

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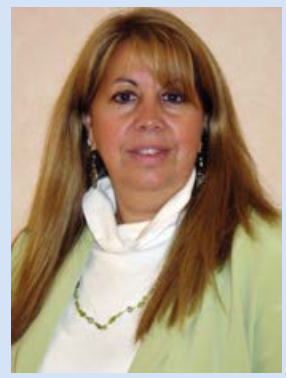
VIEW ON THE NEWS

Dr. Vera A. DePalo, MBA, FCCP comments: It is always good to add more antibiotics for patients with significant infection to our antimicrobial armamentarium. It is equally important to remember that the antibiogram can be a very useful tool in understanding the local resistance pattern of microbes and to guide antimicrobial selection.

IN THIS ISSUE



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

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Better-tolerated ventilation

High-flow cannula *from page 1*

cannula produced similar outcomes while being "better tolerated and less of a burden for the nursing staff to manage," said Dr. Browne, who is an anesthesiologist and critical care medicine specialist at the Tauranga Hospital.

A key feature of the high-flow nasal cannula system is the warmed and humidified mix of oxygen and air that it pumps.

'It's high enough flow to open the lungs but much better tolerated' than standard noninvasive ventilation.

DR. FUHRMAN

"If you run a nasal cannula without this, you dry out the patient's nose at 5 or 6 L/min, and it's very uncomfortable. But I've worn a high-flow nasal cannula with 30 L/min flow and I couldn't tell I was wearing it," commented Dr. Thomas Fuhrman, FCCP, chief of anesthesiology at the Bay Pines (Fla.) VA Healthcare System.

"It's high enough flow to open the lungs but much better tolerated" than standard noninvasive ventilation, Dr. Fuhrman said in an interview.

Patients can open their mouths, swallow, and eat while wearing the high-flow nasal cannula, he noted.

"This report is a step forward and will help spur adoption" of the high-flow nasal cannula, Dr. Fuhrman predicted. Many cardiologists are not yet aware of it as it's usually placed by intensivists. Over time, additional indications for the device will develop, he added.

The specific system used in Tauranga Hospital"s coronary care unit is the Optiflow high-flow nasal cannula along with the Airvo pumping system, both marketed by Fisher & Paykel Healthcare. During the 6 months preceding November 2012, 107 of 249 (43%) CCU patients underwent noninvasive ventilation during the first 40 hours following CCU admission. During the subsequent period ventilation started on 67 of 248 (27%) during the first 40 hours. Of those, 60 (90%) received sufficient treatment with a high-flow nasal cannula, while 7 (10%) required standard noninvasive ventilation.

Patient outcomes during the two study periods were similar.

A more definitive comparison of noninvasive ventilation and high-flow nasal cannula treatment requires a prospective, randomized study, Dr. Browne said.

FRONTLINE MEDICAL NEWS

The high-flow nasal cannula produced similar outcomes while being 'better tolerated and less of a burden for the nursing staff to manage,' said Dr. Browne.

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Reduced mortality, higher cost

Catheter-directed thrombolysis *from page 1*

of in-hospital mortality plus intracerebral hemorrhages, rates significantly below those tallied in propensity score–matched patients who underwent systemic thrombolysis of their acute PE. The matched group with systemic thrombolysis had a 17% in-hospital mortality rate and a 17% combined mortality plus intracerebral hemorrhage rate, said Dr. Saqib, a researcher at Staten Island (N.Y.) University Hospital.

"To the best of our knowledge, this is the first, large, nationwide, observational study that compared safety and efficacy outcomes between systemic thrombolysis and catheter-directed thrombolysis in acute PE," Dr. Saqib said.

The U.S. data, collected during 2010-2012, also showed that, after adjustment for clinical and demographic variables, each acute PE treatment by catheter-directed thrombolysis cost an average $9,428 above the cost for systemic thrombolysis, she said.

"We need to more systematically identify the patients with an acute PE who could benefit from catheter-directed thrombolysis, especially patients with a massive PE," commented Dr. Muthiah P. Muthiah, FCCP, a critical-care medicine physician at the University of Tennessee Health Science Center in Memphis. "This may be something to offer to patients who have an absolute contraindication for systemic thrombolysis, such as recent surgery, but it is not available everywhere," Dr. Muthiah said in an interview.

Dr. Saqib and her associates used data collected by the Federal National Inpatient Sample. Among U.S. patients hospitalized during 2010-2012 and entered into this database, they identified 1,169 adult acute PE patients who underwent systemic thrombolysis and 352 patients who received catheter-directed thrombolysis. The patients averaged about 58 years old and just under half were men.

The propensity score–adjusted analysis also showed no statistically significant difference between the two treatment approaches for the incidence of intracerebral hemorrhage, any hemorrhages requiring a transfusion, new-onset acute renal failure, or hospital length of stay.

Among the patients treated by catheter-directed thrombolysis, all the intracerebral hemorrhages occurred during 2010; during 2011 and 2012 none of the patients treated this way had an intracerebral hemorrhage, Dr. Saqib noted.

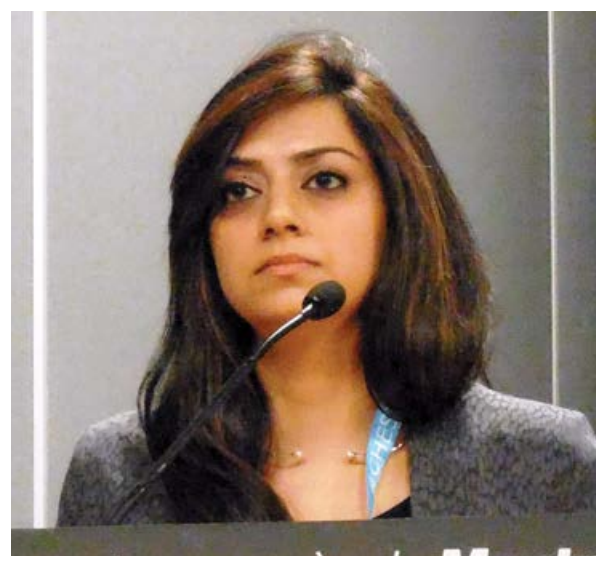
Although the findings were consistent with results from prior analyses, the propensity-score adjustment used in the current study cannot fully account for all unmeasured confounding factors.

The best way to compare catheter-directed thrombolysis and systemic thrombolysis for treating acute PE would be in a prospective, randomized study, Dr. Saqib said.

Dr. Saqib and Dr. Muthiah had no relevant financial disclosures.

FRONTLINE MEDICAL NEWS

Dr. Muthiah: This may be an option for patients in whom systemic thrombolysis is contraindicated.



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Dr. Saqib: Catheter-directed thrombolysis cost an average $9,428 more than systemic thrombolysis

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Radiation dose exceeds 50 mSv in 2% of ICU patients

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2015

MONTREAL – Some of the sickest patients treated at U.S. hospitals receive high levels of radiation exposure, based on a review of more than 4,000 medical ICU patients treated recently at one U.S. quaternary-care center.

During 2013, 98 patients admitted to the medical ICU at the Cleveland Clinic – 2% of the 4,155 patients who passed through the medical ICU that year – had cumulative radiation exposure of at least 50 mSv while in the ICU, thereby exceeding the U.S. standard for maximum annual workplace exposure, Dr. Sudhir Krishnan said at the annual meeting of the American College of Chest Physicians. The finding raises questions of whether all these exposures are appropriate and whether they reflect overuse of certain imaging modalities.

Dr. Krishnan and his associates ran a retrospective review of case records for the medical ICU–admitted patients at the Cleveland Clinic during 2013 (Chest. 2015 Oct 25. doi: 10.1378/chest.2278486). During their ICU stay, 3,490 patients (84%) received some amount of radiation exposure. Exposure averaged 7 mSv, with a median of 1.5 mSv. The radiation exposure came primarily from imaging and more specifically from CT examinations, which produced more than half of all radiation-exposure episodes. Other sources included x-rays, nuclear scans, and interventional procedures.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Sudhir Krishnan and his associates ran a retrospective review of case records for the medical ICU–admitted patients at the Cleveland Clinic.

Based on typical radiation dosages received during each type of procedure, the researchers calculated an estimated total radiation dosage received by each patient during their ICU stay. Nearly two-thirds of patients had an exposure of less than 3 mSv, the average annual exposure a person receives from ambient radiation. A quarter of the patients had an exposure of 3-14 mSv, 11% had an exposure of 15-49 mSv, and 2% – 98 patients – had exposure during their ICU stay that ran to 50 mSv or greater, exceeding the U.S. workplace annual maximum. Thirteen patients had an exposure level during their ICU stay that reached 100 mSv or higher; the maximum exposure level was in a patient with cumulative exposure of 176 mSv, said Dr. Krishnan, a critical-care medicine specialist at the Cleveland Clinic.

He and his coworkers did a multivariate analysis to identify factors that linked with a higher likelihood of having high radiation exposure. Patients at greatest risk for high exposure levels were sicker patients with higher APACHE 3 scores, longer stays in the ICU, and the presence of cirrhosis, but those most at risk also tended to be younger.

Rates of both ICU deaths and deaths during the entire hospitalization were significantly higher among those with radiation exposure that was 50 mSv or greater.

Dr. Krishnan cautioned that he has not run any analysis that assessed the appropriateness of the imaging that the ICU patients received, nor did he have any data documenting the clinical consequences to the patients who had higher radiation exposure. Despite that uncertainty, he suggested that efforts focus on avoiding unnecessary radiation exposure to patients.

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Hypothermia after nonshockable-rhythm cardiac arrest

BY MARY ANN MOON
Frontline Medical News

Therapeutic hypothermia significantly raises the rate of survival with a good neurologic outcome among patients who are comatose after a cardiac arrest with a nonshockable initial rhythm, according to a report published online in Circulation.

Many observational and retrospective cohort studies have examined the possible benefits of therapeutic hypothermia in this patient population, but they have produced conflicting results. No prospective randomized clinical trials have been published as yet. This has led to controversy. Some clinicians insist the treatment should be reserved only for patients who meet the narrow criteria for which there is good supportive evidence; others, eager for any clinical strategy that can improve the outcomes of these critically ill patients, routinely expand its use to comatose patients regardless of their initial heart rhythm or the location of the cardiac arrest, wrote Dr. Sarah M. Perman of the department of emergency medicine, University of Colorado, Aurora, and her associates.

They studied the issue using data from a national registry of patients treated at 16 medical centers that sometimes use therapeutic hypothermia after cardiac arrest. The researchers assessed the records of 519 adults during a 3-year period who had a nontraumatic cardiac arrest and initially registered either pulseless electrical activity or asystole, then had a return of spontaneous circulation but remained comatose.

Approximately half of these comatose survivors (262 patients) were treated with therapeutic hypothermia according to their hospital's usual protocols, and the other half (257 control subjects) received standard care without therapeutic hypothermia.

Patients who received the intervention were significantly younger (62 vs 69 years), had a longer duration of cardiac arrest (23 vs 13 minutes), had a higher incidence of asystole as their primary cardiac rhythm (45% vs 35%), and were much more likely to have a an out-of-hospital cardiac arrest (82% vs 39%).

To account for these marked differences and to control for confounding by indication, the investigators used propensity matching and identified 200 matched pairs of patients.

In the propensity-matched cohort, the rate of survival to hospital discharge was significantly higher with therapeutic hypothermia (29%) than without it (15%), as was the rate of survival with a favorable neurologic outcome (21% vs 10%). And in a multivariate analysis of factors contributing to positive patient outcomes, the intervention was associated with a 3.5-fold increase in favorable neurologic outcomes. A further analysis of the data showed that therapeutic hypothermia was associated with improved survival, with an OR of 2.8.

The rate of survival to hospital discharge was significantly higher with therapeutic hypothermia (29%) than without it (15%), as was the rate of survival with a favorable neurologic outcome (21% vs 10%).

In addition, an analysis of outcomes across various subgroups of patients showed that regardless of the location of their cardiac arrest, patients were consistently more likely to survive to hospital discharge neurologically intact if they received therapeutic hypothermia (OR, 2.1 for out-of-hospital and OR, 4.2 for in-hospital cardiac arrest).

"These results lend support to a broadening of indications for therapeutic hypothermia in comatose post-arrest patients with initial nonshockable rhythms," Dr. Perman and her associates said.

CPR guide: Compression limits, no vasopressin

BY SHANNON AYMES
Frontline Medical News

New guidelines on cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) set upper limits on chest compression rate and depth, add naloxone to the care of suspected opioid abusers, and remove vasopressin from the advanced cardiac life support (ACLS) algorithm.

The American Heart Association published its revised guidelines in Circulation. The AHA released its previous guidelines in 2010.

"Everyone has a role to play in the chain of survival – from bystanders to dispatchers, emergency responders to health care providers," Dr. Mark Creager said in a statement.

"When everyone knows their role, knows CPR, and works together, we can dramatically improve cardiac arrest victims' chances of survival," said Dr. Creager, AHA president and director of the Heart and Vascular Center at Dartmouth-Hitchcock Medical Center, Lebanon, N.H.

The 2015 guidelines' new recommendations include the following:

• **Resuscitation pathways.** The guidelines note that the resuscitation pathways are very different for patients who experience cardiac arrest present in a hospital setting (IHCA) as compared to an out-of-hospital setting (OHCA). In OHCA, the patient depends on lay rescuers to not only recognize the situation but also call for help, initiate CPR, and, if available, administer defibrillation until emergency medical personnel arrive. However, IHCA involves prevention of cardiac arrest and smooth delivery of care in a multidisciplinary setting.

• **Layperson CPR.** Untrained lay rescuers should provide compression-only CPR for OHCA. Trained lay rescuers who are able to provide rescue breaths should begin CPR with compressions followed by breaths at a ratio of 30 compressions to two breaths. Compression-only CPR is easier to perform for untrained lay rescuers, the guidelines note, and survival rates are similar using CPR with or without rescue breaths in adult cardiac arrest with a cardiac etiology.

• **Compression rate and depth.** The guidelines set upper limits on chest compression depth and heart rate, recommending a compression rate of 100-120 compressions per minute with a depth of at least 2 inches, not to exceed 2.4 inches in adults.

• **Social media dispatching.** Despite limited evidence, the authors said that it may be reasonable for communities to use social media technologies to alert lay rescuers with mobile phones about nearby OHCA cases.

• **Naloxone and opioid addiction.** Also new is the recommended use of naloxone for patients with suspected or known opioid addiction by appropriately trained lay rescuers or basic life support (BLS) providers.

• **CPR training.** The guidelines highlight several changes to simplify health care provider training in CPR. For example, trained rescuers can simultaneously perform some tasks

Continued on following page

Continued from previous page

to reduce the time to initiate chest compressions.

Likewise, in a team of trained rescuers, multiple steps such as activating the emergency response system, chest compression, ventilation, and defibrillator retrieval can be accomplished simultaneously.

• **High-quality CPR.** Finally, the guidelines focus on emphasizing high-quality CPR with adequate compression rate and depth, complete chest recoil, few interruptions to compressions, and appropriate ventilation.

The guidelines offer several changes to advanced cardiac life support (ACLS).

The algorithm was simplified by removing vasopressin, because the authors note that "the combined use of vasopressin and epinephrine offers no advantage to using standard-dose epinephrine in cardiac arrest."

Likewise, the guidelines note conflicting studies to support the use of lidocaine after return of spontaneous circulation (ROSC).

"However, the initiation or continuation of lidocaine may be considered immediately after ROSC from VF/pulseless ventricular tachycardia cardiac arrest," the guideline authors wrote.

Finally, the guidelines highlight updates in post–cardiac arrest care, including a wider range of target temperatures, between 32° C and 36° C, to be maintained for at least 24 hours in comatose adults with ROSC after cardiac arrest.

In comparison, the 2010 guidelines called for a target temperature range of 32° C to 34° C for 12-24 hours.

The guidelines also detail new updates for acute coronary syndrome, pediatric BLS, pediatric ACLS, and neonatal resuscitation.

As the AHA updates its CPR guidelines, it's also important for lay rescuers and health providers to update their own training, noted Dr. Clifton Callaway, chair of the AHA's Emergency Cardiovascular Care (ECC) committee.

"Research shows resuscitation skills can decline within a few months after training – far before the 2-year period in which basic and advanced life support skills are currently evaluated," cautioned Dr. Callaway, professor of emergency medicine at the University of Pittsburgh.

"Frequent training with shorter intervals of basic and advanced cardiovascular life support skills may be helpful for providers who are likely to encounter a cardiac arrest to ensure the patient receives high-quality CPR," he added.

No pull-out pneumothorax with 'party balloon Valsalva'

BY M. ALEXANDER OTTO
Frontline Medical News

CHICAGO – Investigators have come up with a simple way to reduce and maybe even eliminate pull-out pneumothoraces during chest tube removal.

Instead of standard inhale or exhale Valsalva maneuvers, they have their patients blow up a party balloon as the tube is pulled.

That produces the same Valsalva effects as the standard maneuvers, but with two significant advantages. First, it's easy to explain and for patients to understand and do – not much more instruction is required than "blow up the balloon" – and, secondly, the inflating balloon is a visual check to make sure patients are doing the maneuver correctly. "It's easy. Everyone can do it," said lead investigator Dr. Puwadon Thitivara-

porn, who developed the technique with Dr. Kritaya Kritayakirana and colleagues at King Chulalongkorn Memorial Hospital in Bangkok, Thailand.

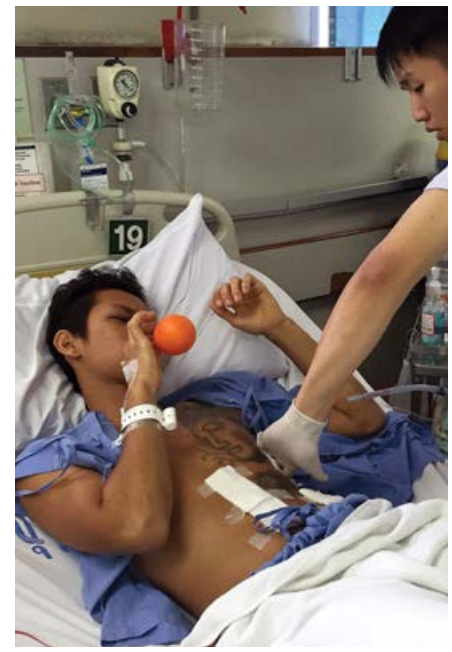
To see how well it works, the team randomized 10 women and 38 men about equally to four removal techniques: the standard expire Valsalva, the standard inspire Valsalva, and two balloon maneuvers – blowing the balloon up after a deep breath and blowing it up with residual lung volume after an initial exhalation.

The subjects were trauma patients 15-64 years old, with a mean age of 38 years. Lung injuries, rib fractures, and tube suction were a bit more common in the standard maneuver groups. Patients with tracheotomies, chronic lung disease, and Glasgow Coma Scores below 13 were excluded from the study. Hemopneumothorax was the most common indication for tube placement.

Two patients in each of the standard groups (16%) developed a pullout pneumothorax within 24 hours of tube removal, confirmed by x-ray. One required chest tube reinsertion, and all four ended up spending extra time in the hospital. Similar problems have been reported in American medicine (J Trauma. 2001 Apr;50[4]:674-7).

Meanwhile, not a single balloon patient had a lung collapse when their tube was pulled.

Because of the small number of subjects, the differences weren't statistically significant, but they came close in a group comparison of standard patients with balloon patients ($P = .11$). The investigators estimated they would need almost 600 hundred subjects to reach statistical significance.



COURTESY DR. PUWADON THITIVARAPORN

Inflating a balloon during tube removal may trump standard Valsalva.

Even so, the party balloon technique appears to be "easier and safer" than standard maneuvers, as well as "reproducible and cheap, and it can prevent recurrent pneumothorax. It can be used as an alternative to the classic Valsalva," said Dr. Thitivaraporn, a cardiothoracic surgery resident at the Bangkok hospital.

The balloon method is being used there now in nontrauma patients, as well, but the standard maneuvers are also being used until the balloon technique shows statistically significant benefits, he said.

With manometry, the team found that a party balloon's internal pressure builds quickly as it's inflated from a starting diameter of about 4.5 cm to about 9 cm, peaking at about 60 mm Hg; pressure trails off to about 40 mm Hg as inflation continues past 9 cm.

The investigators have no relevant disclosures.

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CRITICAL CARE COMMENTARY: Utilization management programs

BY DR. ARIEL M. MODRYKAMIEN, FCCP

The vast majority of health-care providers would recognize that medical resources are limited. The expectation to provide every effective therapy to every single patient is certainly unrealistic. As medicine providers, we frequently face the conflicting dilemma of providing evidence-base medical care vs allocating resources wisely. This dilemma becomes more complicated when evidence in medical literature is absent.

Utilization management programs may be needed to address policy change.

Resource allocation may be influenced by a number of personal, community, or society values. Consequently, the result of the previously described conflict is variation of patient care.

Practice variation has been characterized as one of the most common reasons for overuse, underuse, or misuse of health-care services, with well-described financial impact. In order to avoid practice variation, health-care organizations have adopted lean methods, which were previously used in the auto industry, such as the well-known Toyota manufacturing model. Lean methods use standardized processes to obtain a final product but also remove activities that absorb resources and create no value.

Not surprisingly, our medical profession has recently seen a growing use of protocols and checklists, obtaining impressive results in terms of patient safety and practice standardization. Despite these important efforts, costs in health care remain a major concern. The National Health Expenditure Projections 2013-2023 estimates an annual growth rate in hospital costs of 6.2% (Centers for Medicare & Medicaid Services. http://www.cms.gov).

Therefore, many organizations moved the concept of standardization one step further and created utilization management programs. These programs use a mix of clinical, administrative, and financial methods to evaluate facility structure, standardization of processes, clinical outcomes, and resource allocation.

This integrative approach aims at optimizing quality of care, safety, and cost-containment by creating links between multiple organizational stakeholders and initiatives. (Table 1 shows the key fundamental steps for an effective Utilization Management Program.)

In 2012, a survey of directors of respiratory therapy departments administered by the American Association for Respiratory Care (AARC) showed that the vacancy rate of surveyed hospitals was only 0.81 full-time equivalents (FTEs) (Kacmarek et al. *Respir Care.* 2012;57[5]:710).

The calculation of FTEs for a particular department often depends on staffing models that usually assign a daily number of therapists according to the daily number of chargeable activities (also known as productivity).

Despite the common use of the aforementioned models, it has been reported that unscheduled respiratory therapist activities (patient transports, rapid response calls, etc – nonchargeable) may account for up to 40% of the daily workload. Therefore, the existent gap between actual number of FTEs and real-life RT workload may result in compromised delivery of quality care, reduction in patient satisfaction, and unsafe practices.

Utilization management programs, with involvement of respiratory therapy leadership, hospital administrators, and other institutional stakeholders, are ideal forums to address these gaps.

As an example, in an attempt to reduce overuse of RT resources and prevent eventual underuse, many organizations standardized delivery of respiratory care by switching from physician-directed treatments to RT-driven protocols. In this model, respiratory therapists use guidelines to allocate treatments according to specific clinical indications and determine the frequency of those therapies based on severity scores.

In 1998, a landmark study published by Stoller and colleagues (*Am J Respir Crit Care Med.* 1998;158[4]:1068) showed that the use of RT-driven protocols had greater concordance with clinical practice guidelines. Two years later, Kollef and colleagues (*Chest.* 2000;117[2]:467) demonstrated that similar strategies significantly reduced respiratory therapy utilization.

Our own experience, published almost 15 years later, revealed that applying an RT-driven bronchodilator strategy, rather than a physician-directed one, resulted in reduction of utilization equivalent to 0.38 FTEs (Kallam et al. *Respir Care.* 2013;58[3]:431).

Unpublished data from our organization showed that expanding RT-driven protocols beyond bronchodilator therapy (ie, lung-expansion therapy, bronchopulmonary hygiene, etc) may reduce costs equivalent to 1.2 FTEs.

These findings reveal that standardization of practice not only positively impacts quality of care; it also improves allocation of labor resources and alleviates staffing shortage.

The existent gap between actual number of FTEs and real-life RT workload may result in compromised delivery of quality care, reduction in patient satisfaction, and unsafe practices.

Utilization management programs may be needed to address changes of multidisciplinary polices and procedures.

Institutional policies and procedures are usually regarded as rules or guidelines that determine the actions and day-to-day operations of an organization. Modification of existent polices or creation of new ones may greatly affect respiratory therapy utilization. Specifically, a recent study showed that the absence of an institutional policy in ventilator manipulation (any provider was able to manipulate ventilators) was associated with multiple changes of modes of mechanical ventilation per patient. Furthermore, each major ventilator change was associated with an increase in the odds of tracheostomy of 4.95 times and an 18.6% reduction of ventilator-free days (Modrykamien et al. *Respir Care.* 2015;Sept 22:abstract).

Evidently, application of new polices and procedures may have direct impact on quality of care and hospital costs.

Re-allocation of resources, reduction of costs, and improvement of quality of patient care are only a few goals of utilization management programs applied to respiratory therapy. The creation of new service lines and capital investment in new technologies may successfully be achieved if cost savings were redirected toward those goals.

In our experience, the shift in paradigm from physician-directed therapy to RT-driven protocols, associated with change in mechanical ventilator manipulation policy, allowed reassignment of FTEs to a bedside bronchoscopy service line.

In conclusion, delivery of evidence-based medicine and allocation of resources are not mutually exclusive concepts. Standardization of processes of patient care, creation and modification of organizational policies, and prioritization of institutional goals may help align both objectives to provide realistic quality medicine.

Table 1. Tasks for effective utilization management

1. Determination of priorities
2. Identification of needed information and critical stakeholders
3. Establish benchmarks
4. Design method for data collection
5. Implement data collection
6. Assess data and present results
7. Develop policies and procedures
8. Implement policies and procedures
9. Review task list periodically

FRONTLINE MEDICAL NEWS

Dr. Modrykamien is Clinical Associate Professor of Medicine, Health Science Center, Texas A&M University; Medical Director, Respiratory Therapy and Pulmonary Function Laboratory, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas.

Antibiotics don't prevent poststroke pneumonia

BY MARY ANN MOON
Frontline Medical News

Prophylactic antibiotics don't prevent poststroke pneumonia or reduce mortality, even in patients who have stroke-induced dysphagia and are at high risk of aspiration, according to a report published in the Lancet.

Routine use of antibiotics to prevent poststroke pneumonia "cannot be recommended and should be used judiciously ... in patients after stroke who are managed on stroke units, even if they are at high risk of aspiration," said Lalit Kalra, Ph.D., of the Institute of Psychiatry, Psychology, and Neuroscience at King's College, London, and his associates.

In a prospective open-label cluster-randomized clinical trial, researchers assigned 37 stroke units in the United Kingdom to give new patients either prophylactic antibiotics for 7 days plus standard stroke care (564 patients) or standard stroke care alone (524 patients). All study participants were considered "unsafe to swallow" because they had impaired consciousness, they failed a bedside swallow test, or had a nasogastric tube.

Each hospital was allowed to choose which antibiotics to use according to their local guidelines, as well as which dosage and route of administration. The primary outcome was the incidence of post-stroke pneumonia within 2 weeks of hospitalization, which was assessed by two separate methods: a statistician masked to treatment assignment diagnosed pneumonia according to a criteria-based hierarchical algorithm, and a local treating physician diagnosed pneumonia according to clinical findings.

According to the algorithm, poststroke pneumonia developed in 13% of patients given prophylactic antibiotics and 10% of the control group, for an OR of 1.21. According to the clinical findings, poststroke pneumonia developed in 16% of the intervention group and 15% of the control group, for an OR of 1.01, the investigators said (Lancet 2015;386:1835-44).

In addition, all-cause mortality at 14 days (10%) and at 90 days (39%) was not significantly different for the two study groups. And there was no significant difference in the percentage of patients with good functional outcomes. Prophylactic antibiotics were associated with longer hospital stays than standard treatment.

Prophylactic antibiotics did reduce the number of nonpneumonia infections, especially urosepsis. Adverse effects, including cases of *Clostridium difficile*-positive diarrhea and MRSA colonization, were rare and occurred in equal numbers.

Prophylactic antibiotics likely "do not add to existing preventive measures such as positioning, regular suction, swallowing techniques, modified diets, and early initiation of antibiotics" if patients are suspected of developing pneumonia. Further, poststroke pneumonia is probably not just a straightforward infection but a complex respiratory syndrome.

This study was funded by the U.K. National Institute for Health Research. The researchers reported having no relevant financial disclosures.

Statins may inhibit flu vaccine response

BY MATT MAHADY
Frontline Medical News

Statins may have the unintended consequence of reducing immunotherapeutic response to and effectiveness of influenza vaccination. Potential mitigation strategies for statin-induced immunosuppression suggested by the research team include preferential use of high-dose or adjuvanted vaccines.

In a post-hoc analysis (J Infect Dis. 2015 Oct 29. doi: 10.1093/infdis/jiv456), Dr. Steven Black of Cincinnati Children's Hospital Medical Center and colleagues derived data from an international, multisite, randomized, controlled, influenza vaccine clinical trial population of 6,961 subjects over the age of 65. At 3 weeks post vaccination, the researchers measured the level of antibodies to flu vaccine strains in the blood of statin and non–statin taking participants. Hemagglutination-inhibiting geometric mean titers to influenza A (H1NI), A (H3N2), and B strains were 38% (95% confidence interval, 27%-50%), 67% (95% CI, 54%-80%) and 38% (95% CI, 28%-29%) lower, respectively, in the statin therapy arm as compared with the non–statin therapy cohort. The effects were greater in patients on synthetic as opposed to fermentation-derived statin therapies.

Influenza vaccine effectiveness against medically attended acute respiratory illness was decreased in statin users compared with nonusers.

In addition, a separate retrospective investigation (J Infect Dis. 2015 Oct 29. doi: 10.1093/infdis/jiv457.) tracking 137,488 patients from a Georgia managed care organization database over nine flu seasons from 2002 to 2011 also generated data implying a connection between statin use and compromised influenza vaccine efficacy and immune response.

Dr. Saad Omer of the Emory Vaccine Center at Emory University in Atlanta and his colleagues analyzed the impact of statins on influenza vaccine efficacy against medically attended acute respiratory illness (MAARI). MAARI incidence is routinely employed as an influenza impact marker, although not all MAARI incidence is influenza related.

The Emory research team found that influenza vaccine effectiveness against MAARI was decreased in statin users compared with nonusers during periods of local (14% vs. 23%; mean difference, 11%; 95% CI, −1.7%-26%) and widespread (13% vs. 26%; mean difference, 18%; 95% CI, 2.9%-36%) influenza circulation.

"Even after adjustment for several covariates … the observed reduction in influenza vaccine effectiveness among statin users remained statistically significant for periods of widespread influenza circulation with a nonsignificant trend toward reduced vaccine effectiveness during

Continued on following page

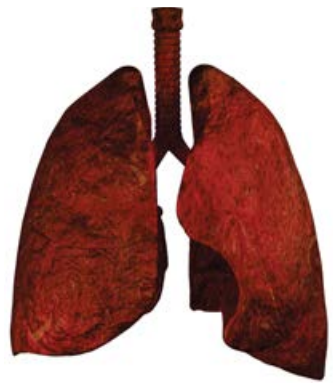
Heroin smoking linked to early-onset emphysema

BY DEEPAK CHITNIS
Frontline Medical News

FROM CHEST

Inhalation or smoking of heroin can lead to early onset chronic obstructive pulmonary disease (COPD), according Dr. Paul P. Walker and his colleagues from the University Hospital Aintree and the University of Liverpool, England.

"We believe that we have accumulated sufficient evidence of both physiologic impairment and structural damage to identify a discrete form of early onset COPD, commonly involving emphysema, which can be attributed to inhaled opiate use," the researchers wrote. "The widespread use of opiates as recreational drugs in some communities means that we are likely to see more obstructive lung disease in the future."



THINKSTOCK/TAGOTA

Recreational use of opiates has been linked to asthma, but "little is known about the association between heroin inhalation and COPD beyond a study by Buster et al. [and] no previous study has examined measures of emphysema, such as detailed lung function testing or CT scan," the researchers wrote (Chest. 2015 Nov;148[5]:1156-1163).

The researchers studied 73 individuals who were aged 40 years or younger when they developed symptoms, were diagnosed with COPD, and smoked heroin regularly within the last 2 years. The mean history of smoking heroin was 14 years. The study participants additionally were regular smokers for at least 5 years, most were heavy smokers, and did not have a primary clinical diagnosis of asthma. All completed spirometry on at least one occasion when clinically stable.

Data was collected during 2005-2013, via lung function testing done when subjects were both clinically stable and a minimum of 4 weeks postexacerbation. Lung function testing was done in 12 subjects via spirometry, either prebronchodilator or postbronchodilator. High-resolution CT scans (slice thickness was no greater than 2 mm) were performed in 32 subjects each analyzed by two thoracic radiologists. Emphysema was scored on a scale of 1-5 based on guidelines produced by Sakai et al., which requires examination of a cranial level taken 1 cm above the superior margin of the aortic arch, a middle level taken 1 cm below the carina, and a caudal level taken about 3 cm above the top of the diaphragm.

Data were available from 44 of the initial 73 subjects. In the 32 who had high-resolution CT scans, their mean score – taking into account the scans of the upper, middle, and lower lung – was 2.3, indicating a 5%-25% chance of emphysema; 15 of 32 individuals had a score greater than 3, indicating a 25%-50% likelihood of emphysema, in the upper lung alone.

In the 12 subjects who underwent lung function testing, the range of the diffusing capacity of the lung for carbon monoxide was 35.5-63.0, with a median of 48 and a mean of 51. Eleven subjects had a score that qualified as "abnormal."

Due to "lifestyle and varying motivation" not all subjects completed the investigation or returned for follow-up spirometric measurement, the researchers wrote. "Taking a history of inhaled drug use is important in patients with early-onset COPD, as is the provision of appropriate education about this new hazard of opiate use." In some areas and populations there may be a role for case finding using spirometry.

Dr. Walker and his coauthors did not report any relevant financial disclosures.

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VIEW ON THE NEWS

Emphysema from sources other than cigarettes

This case series of heroin smokers who developed early-onset emphysema may offer insights into the development of COPD and emphysema in cigarette smokers who don't smoke opiates.

How might narcotic use contribute to the development of COPD and emphysema? There are several possible explanations. Smokers of heroin and other illicit substances typically take a deep inhalation, combined with a Valsalva maneuver to enhance absorption of the drug into the body. This behavior has been described previously in heroin users and users of other smoked substances. In addition, these agents often burn at a very high temperature, with the potential to cause damage deep within the lung.

The depth of inhalation, dynamic hyperinflation, and barotrauma may be important factors in some patients who develop emphysema related to cigarette smoking or other factors, as well. Physicians should be aware of this problem, and the public must be educated about the dangers associated with the inhalation of these and other burned substances.

Dr. David M. Mannino, FCCP, is the chair of preventative medicine and environmental health in the department of epidemiology at the University of Kentucky in Lexington. He disclosed having served as a consultant for Boehringer Ingelheim GmbH, GlaxoSmithKline, AstraZeneca, Novartis AG, Merck, and Forest Pharmaceuticals, and has received research grants from GSK, Novartis, Boehringer Ingelheim, Forest Pharmaceuticals, and Pfizer. He is also compensated by Up-to-Date, has served as an expert in tobacco-related cases, and is on the board of the COPD Foundation. He made his remarks in an editorial published with the study.

Continued from previous page

periods of local circulation, as well ... (with) potential implications for clinical guidelines regarding statin use around the time of routine vaccinations," the researchers wrote.

Dr. Black is a consultant for Novartis Vaccines, GSK, Takeda Vaccines, Protein Sciences, and the World Health Organization. His coauthors – Dr. Uwe Nicolay, Dr. Giuseppe Del Giudice, and Dr. Rino Rappuoli – are employees of Novartis Vaccines.

Novartis Vaccines funded the post-hoc analysis, as well as the original clinical trial that developed the data utilized for the analysis. Dr. Omer and his colleagues were funded by Emory University and the National Institute of Allergy and Infectious Diseases and had no disclosures.

VIEW ON THE NEWS

Important questions raised; more research required

The findings that statin use adversely affects IIV (inactivated influenza vaccine) immunogenicity and vaccine effectiveness are biologically plausible, based on known immunomodulatory effects of these drugs and raise important questions about the use of these important medications. Should these results affect a physician's care of patients? Should statins be stopped for a period while influenza vaccine is administered? Should IIV not be administered to statin users? The answer to all of these questions is no.

Instead the results of these studies should be viewed as hypothesis generating and should prompt further investigation. If statins are found to reduce immunogenicity, then potentially transient interruption of statin therapy could be considered for testing. The effect of chronic statin use on the immunogenicity of other vaccines also needs to be evaluated further. Future studies could also evaluate whether alternative vaccination strategies with improved immunogenicity, such as high-dose, intradermally delivered, or adjuvanted vaccines will overcome the effects of statin use (if any).

The results also underscore the need for the development of influenza vaccines with improved efficacy and effectiveness.

Dr. Robert L. Atmar is a professor of medicine and interim chief of medicine-infectious disease at the Baylor College of Medicine, Houston, Texas. Dr. Wendy A. Keitel is an associate professor of molecular virology and microbiology at the Baylor College of Medicine, Houston, Texas. Dr. Atmar reported receiving grants from Takeda Vaccines. Dr. Keitel reported no relevant disclosures. Dr. Atmar and Dr. Keitel made these remarks in an editorial commentary (J Infect Dis. 2015 Oct 29. doi: 10.1093/infdis/jiv459.) that accompanied the data furnished by Dr. Black and colleagues and Dr. Omer and colleagues.

Reduce lung function decline

Delay IPF progression with Esbriet

Indication

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

Select Important Safety Information

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

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

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

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

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

Esbriet®
(pirfenidone) capsules 267 mg

Proven to delay progression in IPF[1]

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

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

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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

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

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

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

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

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

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

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

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

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

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Legionellosis cases continue to increase nationwide

BY DEEPAK CHITNIS
Frontline Medical News

Data from the first 3 years of the Center for Disease Control and Prevention's Active Bacterial Core surveillance (ABCs) program on legionellosis confirm that incidences of disease caused by the bacteria are increasing across the United States, according to the Morbidity and Mortality Weekly Report (MMWR. 2015 Oct 30;64[42]:1190-1193).

The ABCs program, which launched in 2011, identified 1,426 cases of legionellosis over the 3-year time span, and incidence rates of 1.3 (2011), 1.1 (2012), and 1.4 (2013) cases per 100,000 individuals in the general population. This corroborates similar findings made by the National Notifiable Diseases Surveillance System (NNDSS) between 2000 and 2011, which reported an increase in the

VITALS

Key clinical point: Data from the first 3 years of the CDC's Active Bacterial Core surveillance program provides evidence confirming that legionellosis rates across the United States are steadily rising.

Major finding: ABCs identified 1,426 legionellosis cases during 2011-2013, for an incidence of 1.3 cases per 100,000 population over the 3 years.

Data source: Analysis of 1,426 legionellosis cases from 2011-2013 collected by the CDC's ABCs program.

Disclosures: Study supported by the CDC.

crude incidence rate of legionellosis nationwide from 0.39 to 1.36 cases per 100,000 individuals.

The two main clinical syndromes associated with legionellosis are Legionnaires' disease, which is a severe form of pneumonia; and Pontiac fever, a milder illness without pneumonia.

"During 2000-2011, passive surveillance for legionellosis in the United States demonstrated a 249% increase in crude incidence, although little was known about the clinical course and method of diagnosis," says the report, led by Dr. Kathleen I. Dooling of the CDC's National Center for Immunization and Respiratory Diseases.

The report also states that "ABCs data during 2011-2013 showed that approximately 44% of patients with legionellosis required intensive care, and 9% died." Furthermore, incidence increased with age among the ABCs program cohort. Those younger than 50 years of age had a 0.4 incidence rate per 100,000 individuals; patients between 50 and 64 years old had a 2.5 per 100,000 incidence rate; those who were 65-79 years old had a 3.6 per 100,000 incidence rate; and individuals 80 years and older had an incidence rate of 4.7 per 100,000 individuals.

"Among cases identified during 2011-2013, 79% occurred in persons aged >50 years, 65% were in males, and 72% of patients were white," says the report, adding that "1,300 (91%) received a diagnosis of legionellosis on the basis of urine antigen testing, which only detects Lp1 species."

The ABCs program defined a confirmed case of legionellosis as "the isolation of *Legionella* from respiratory culture, detection of *Legionella* antigen in urine, or seroconversion (a more than fourfold rise in antibody titer between acute and convalescent sera) to Lp1."

Unlike NNDSS, ABCs recorded clinical and race data for each patient found to have legionellosis, finding that incidence rates among blacks were higher than among whites per 100,000 individuals: 1.0 vs. 1.5, respectively.

The report concludes by calling for further research into the disparities in legionellosis cases based on race, age, and geography, as well as the need for "more sensitive laboratory tests for legionellosis because proper diagnosis is needed for treatment and public health action."

This study was supported by the CDC.

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RSV antiviral reduces viral load, symptoms

BY MARY ANN MOON
Frontline Medical News

An oral inhibitor of respiratory syncytial virus replication, currently called ALS-008176, significantly reduced total viral load, peak viral load, duration of viral shedding, and clinical symptoms in a small proof-of-concept study funded by the drug's manufacturer and published online Nov. 18 in the New England Journal of Medicine.

These findings are particularly encouraging because at present, the standard of care for RSV infection is limited to supportive care only, said Dr. John P. DeVincenzo of the departments of pediatrics, microbiology, immunology, and biochemistry, University of Tennessee, and the Children's Foundation Research Institute at Le Bonheur Children's Hospital, both in Memphis.

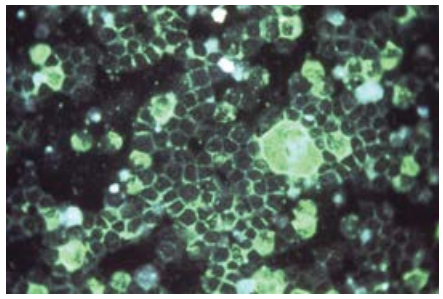
Dr. DeVincenzo and his colleagues performed this randomized, double-blind trial during three separate study periods in which up to 22 healthy adults were confined to a special quarantine unit for 2 weeks at a time. All 62 participants were inoculated intranasally with a clinical strain of RSV and monitored twice daily for the development of RSV infection via assays of fresh nasal washings. The participants were randomly assigned to receive the first dose of ALS-008176 or a matching placebo about 12 hours after the detection of RSV, or on the morning of day 6, whichever came first.

The active drug or the placebo were administered orally every 12 hours for 5 days, for a total of 10 doses. Three dosing regimens were assessed: In the first study period, participants were given a single loading dose of 750 mg followed by nine maintenance doses of 500 mg; in the second period, participants were given a single loading dose of 750 mg followed by nine maintenance doses of 150 mg; and in the third period, participants were given 10 doses of 375 mg each. A total of 35 study participants developed RSV infection.

Compared with placebo, all three dosing regimens significantly reduced viral load within 12 hours of starting treatment: by 88.0% in the first study period, by 85.3% in the second, and by 73.4% in the third. The mean interval until RSV RNA became undetectable ranged from 1.3 to 2.3 days for the three active-treatment groups, compared with 7.2 days for placebo. RSV RNA became undetectable within 4.5 days for all participants who received ALS-0081, compared with 11 days for those who received placebo.

In addition, mean peak viral loads were lower for all three dosing regimens than for placebo. "At the time that the peak viral load occurred in the placebo group, the mean viral load in each of the 3 ALS-008176 treatment groups was more than 1,000 times as low," wrote Dr. DeVincenzo and his associates (N Engl J Med. 2015 Nov 19;373:2048-58. doi:10.1056/NEJMoa1413275).

As important, RSV symptoms were much less severe in all three active-treatment groups than in the placebo group, as assessed subjectively



©Dr. Craig Lyerla/CDC

via symptom scores and objectively via the quantity of nasal mucus produced.

The small study population limited the ability to detect potential safety concerns. Nevertheless, "no serious adverse events, premature discontinuation of the study drug, or clinically significant, treatment-related adverse events were observed in any participants in the intention-to-treat population," the investigators added.

They noted that people who are infected with RSV under natural circumstances, particularly infants, typically present later in the course of the disease, only after patients or caregivers realize that the illness is not due to a simple cold. Thus, their disease severity would be worse than that of these study participants by the time ALS-008176 could be administered. "Therefore, it may be inappropriate to directly extrapolate the results of this study to a clinical setting," Dr. DeVincenzo and his associates said.

Shared decision making cuts unneeded antibiotics

BY BIANCA NOGRADY
Frontline Medical News

Shared decision making between doctors and patients for the treatment of acute respiratory infections can achieve significant short-term reductions in antibiotic use, according to a Cochrane review published Nov. 11.

"Shared decision making is … a set of communication and evidence-based practice skills that elicits patients' expectations, clarifies any misperceptions, and discusses the best available evidence for benefits and harms of treatment," wrote Peter Coxeter of the Centre for Research in Evidence-Based Practice at Bond University, Australia.

Dr. Coxeter and his coauthors analyzed 10 published reports from nine randomized controlled trials involving more than 1,100 physicians

Shared decision making … elicits patients' expectations, clarifies any misperceptions, and discusses the best available evidence for benefits and harms of treatment.

and 492,000 patients, and found that shared decision making interventions were associated with a 39% overall reduction in antibiotic use (95% confidence interval, 0.55-0.68) within 6 weeks of the consultation, with a trend suggesting those reductions were maintained in the longer term.

The analysis also showed that this reduction did not lead to an increase in patient-initiated reconsultations or a decrease in patient satisfaction, although there were not enough data to determine the impact of these interventions on longer-term outcomes such as hospital admissions, pneumonia, or mortality (Cochrane Database Syst Rev. 2015 Nov 11. doi: 10.1002/14651858.CD010907.pub2).

Research should aim to determine which interventions provide the greatest benefit, in order to improve such programs and their use in diverse clinical settings, the authors wrote. The review was supported by the National Health and Medical Research Council (Australia). No conflicts of interest were declared.

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conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

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

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

5.12 Cardiovascular Effects Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

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

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.

Cardiac Disorders Palpitations, tachycardia.

Immune System Disorders Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

Musculoskeletal and Connective Tissue Disorders Muscle spasms.

Nervous System Disorders Tremor.

Psychiatric Disorders Nervousness.

7 DRUG INTERACTIONS

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

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

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

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

Peer support improved CV health, smoking cessation

BY AMY KARON
Frontline Medical News

A monthly peer-led support program for adults with risk factors for heart disease achieved small but significant gains in overall cardiovascular health and smoking cessation, based on results of a multicenter, randomized, controlled trial.

After 12 months, participants scored 0.75 points higher than baseline on a novel composite measure of cardiovascular health – the Fuster-BEWAT Score (FBS) – compared with controls, reported Emilia Gómez, Ph.D., at SHE Foundation, Barcelona, Dr. Juan Miguel Fernández-Alvira of Fundación Centro Nacional de Investigaciones Cardiovasculares, Madrid, and their associates.

Continued on following page

VIEW ON THE NEWS

Fifty-Fifty's approach offers innovation

The Fifty-Fifty Program offers several innovations to the field of cardiovascular prevention. First, the program did not just address one risk factor, but instead emphasized multiple aspects of cardiovascular health, including health behaviors (healthy diet and increasing physical activity) and health metrics (blood pressure and body mass index) as measured by the novel risk score, the FBS. The ability of the FBS to predict clinical outcomes has not been fully validated; but all of the included measures are intimately linked to cardiovascular health and easily reproducible in other settings, since they consist of only health behaviors and non-laboratory–based health factors.

Second, the Fifty-Fifty Program employed the widely used psychological interventions of peer support and group dynamics to yield modest yet positive results in CVH improvement at 1 year follow-up. Importantly, participants in the study selected the peer leaders. When interventions have this type of community buy-in, they are more likely to be successful. Finally, peer-based interventions are more likely to be self sustainable and scalable in the long term, and have wide applicability in diverse and resource-limited settings.

An important limitation of the Fifty-Fifty program was its attrition rate of 16%. Those who dropped out of the study tended to be younger and to have less favorable CVH profiles, which may have created selection bias and impacted the generalizability of the results.

Dr. Fatima Rodriguez is with the division of cardiovascular medicine, Stanford (Calif.) University. Dr. Robert Harrington is with the department of medicine, Stanford University. They reported no conflicts of interest.

Starting varenicline in the hospital cuts smoking

BY BRUCE JANCIN
Frontline Medical News

ORLANDO – Starting varenicline in smokers while they were hospitalized for an acute coronary syndrome resulted in substantially higher smoking abstinence rates than with placebo at all time points through 6 months of follow-up in the double-blind, randomized EVITA trial.

"The ACS population is typically older, they're long-term smokers, and they come into the hospital with a life-threatening condition. Their family is all around them. They've had angioplasty or CABG [coronary artery bypass graft] surgery. So they have pressure on them to stop smoking.

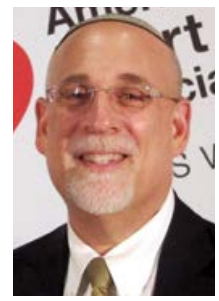
"This is a teachable moment, a window of opportunity. The public health benefit for smoking cessation in this population is huge. You can cut their risk of death and significant morbidity in half if you can get them to stop," Dr. Mark J. Eisenberg said in presenting the EVITA results at the American Heart Association scientific sessions.

EVITA (Evaluation of Varenicline in Smoking Cessation for Patients Post–Acute Coronary Syndrome) was an investigator-initiated, 40-center study involving 302 smokers hospitalized for ACS.

The study participats had smoked for an average of 36 years and were puffing 22 cigarettes per day at enrollment.

More than 90% of them had an acute MI just several days before starting on varenicline (Chantix) at 1 mg twice daily or placebo for 12 weeks.

"To our knowledge, this is the highest-risk population that's been exposed to varenicline," said Dr. Eisenberg, professor of medicine at McGill University and director of the cardiovascular health services research program at Jewish General Hospital in Montreal.



The primary study endpoint was continuous self-reported abstinence since baseline backed by biochemical confirmation in the form of an exhaled carbon monoxide level of 10 ppm or less at week 24 as well as at all the earlier follow-up visits.

The abstinence rate was 47% in the varenicline group, compared with 32% in placebo-treated controls. That placebo response rate is in line with numerous prior studies that have shown that less than one-third of smokers with ACS remain abstinent after leaving the hospital.

"Most [physicians] would say, 'All my patients stop smoking.' But in the clinic if you look in the patients' pockets, you find a pack of cigarettes. They stop smoking while they're in he hospital, but as soon as they're discharged, the relapse rate is almost immediate. Most patients are smoking the day they get out of hospital," according to Dr. Eisenberg.

In EVITA, the number-needed-to-treat with varenicline for 12 weeks in order to produce 1 extra nonsmoker at 6 months was 6.8 patients.

The secondary endpoint of at least a 50% reduction in the number of cigarettes smoked per day from baseline to 6 months was met by 67% of the varenicline group and by 56% of controls, with a number-needed-to-treat of 8.5.

No safety issues emerged in the study, although as Dr. Eisenberg noted, EVITA wasn't sufficiently powered to look at safety.

The only side effect more common in varenicline-treated patients was abnormal dreams, with a 12-week incidence of 15%, threefold higher than the rate seen in controls, a phenomenon that has been seen in other, larger varenicline studies as well.

The EVITA investigators plan to follow participants out to 12 months. "If we see someone who at 1 year post MI is still smoking, maybe it's time to go after them again, perhaps with another medication or behavioral therapy," Dr. Eisenberg said.

You can cut their risk of death and significant morbidity in half if you can get them to stop smoking.

DR. EISENBERG

There are no randomized clinical trials demonstrating that starting nicotine patches or bupropion in the hospital is effective for smoking cessation in the ACS population, according to the cardiologist.

Dr. Eisenberg predicted these study findings will change clinical practice.

In much the same way physicians now routinely start ACS patients on a statin, beta-blocker, and aspirin before they leave the hospital, physicians will capitalize on this opportunity to help ACS patients quit smoking as well, he said.

Evidence that we can start a medication in the hospital and get more people to quit smoking is game changing.

DR. GOFF

In an interview, Dr. David C. Goff, who wasn't involved in EVITA, called the trial "a game changer" in preventive cardiology.

"The use of varenicline in ACS patients before they leave the hospital is a very important step forward. [Physicains] are increasingly comfortable with the idea of starting secondary prevention medications in the hospital, and there's very little more that is important for a person with heart disease who smokes cigarettes than to help them quit smoking. It's probably the No. 1 priority.

"So evidence that we can start a medication in the hospital and get more people who smoke cigarettes to quit smoking is definitely game changing, I think," said Dr. Goff, who is professor of epidemiology and dean of the Colorado School of Public Health in Aurora.

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VITALS

Key clinical point: Varenicline, when initiated in the hospital, is effective in smokers with acute coronary syndrome.

Major finding: The number of smokers who need to be started on varenicline while hospitalized for an acute coronary syndrome in order to produce one extra nonsmoker at 6 months is 6.8.

Data source: EVITA, a double-blind, randomized multicenter trial in 302 smokers hospitalized for ACS who were prospectively followed for 6 months.

Disclosures: The EVITA study was funded by Pfizer. The presenter reported receiving a grant from the company to conduct the trial, as well as honoraria for giving continuing medical education talks on smoking cessation.

Continued from previous page

"Even though the magnitude of the impact of our intervention was modest, epidemiological data suggest that even very small changes in health behaviors and risk factors can significantly decrease the long-term risk of cardiovascular disease," the investigators wrote. They presented the findings at the American Heart Association scientific sessions and simultaneously in the Journal of the American College of Cardiology.

Peer support has been used for managing various chronic diseases, but the Fifty-Fifty Program is the first multicenter, randomized trial to assess its efficacy while also accounting for baseline health education.

The researchers designed six workshops for 543 adults aged 25-50 years who had hypertension, were overweight or obese, smoked, or exercised 150 minutes or less a week. The participants, 71% of whom were women, were then randomized to receive no further support or to attend monthly, 60- to 90-minute sessions that included activities focused on managing emotions, diet, and exercise. The 10 members of each group elected their own leaders, who then completed 3 hours of training in health promotion and leadership.

After 12 months, the intervention group scored an average of 8.84 (95% confidence interval, 8.37-9.32) on the FBS' composite measure of blood pressure, exercise, weight, diet, and tobacco use, compared with 8.17 for controls (95% CI, 7.55-8.79; $P = .016$). The intervention group also improved 0.75 points more from baseline, compared with controls (95% CI, 0.32-1.18).

In addition, support group members scored 0.24 points higher on the 1-year measure of tobacco cessation (95% CI, 0.09-0.38; $P = .003$). The groups did not otherwise significantly differ in terms of risk factors, but the intervention group outscored the control group on measures of blood pressure, exercise, and diet.

"Focusing on self control of unhealthy behaviors through peer group support can be beneficial to heterogeneous groups, without a single condition or specific CV risk factors," the researchers concluded. Follow-up results will provide insight into long-term sustainability.

The SHE Foundation and the Spanish Ministry of Health, Social Services and Equality funded the research. The researchers did not report conflicts of interest.

Sacubitril/valsartan cuts heart failure readmissions

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – The combined formulation of sacubitril and valsartan cut the rate of 30-day heart failure rehospitalizations, trimming the control rate by 38% in an analysis of data from the PARADIGM-HF trial, Dr. Scott D. Solomon reported at the American Heart Association scientific sessions.

This is an especially meaningful additional benefit for heart failure patients who take sacubitril/valsartan (Entresto) in place of enalapril or similar drugs because heart failure rehospitalizations have become a closely tracked metric for U.S. hospitals.

The sacubitril/valsartan combination received Food and Drug Administration approval last summer for treating chronic heart failure with reduced ejection fraction on the strength of results from PARADIGM-HF, which showed the two-drug combination substantially cut the rate of cardiovascular death and heart failure hospitalizations, compared with enalapril (N Engl J Med. 2014 Sep 11;371:993-1004).

The 30-day heart failure readmission rate was 10% with sacubitril/valsartan and 13% with enalap.

DR. SOLOMON

"Chronic heart failure patients treated with sacubitril/valsartan relative to enalapril are less likely to be initially hospitalized, and subsequent to discharge are less likely to return to the hospital within 30 days, thereby reducing the risk to patients and the potential financial burden to the health care system," said Dr. Solomon, professor of medicine at Harvard Medical School and director of noninvasive cardiology at Brigham and Women's Hospital in Boston.

This finding may help spur faster adoption of sacubitril/valsartan as the top drug for treating the renin-angiotensin-aldosterone system in heart failure patients, commented Dr. Adrian F. Hernandez, professor and heart failure specialist at Duke University in Durham, N.C. "The fact that you can derive an early clinical benefit" that becomes an early financial benefit should help counter the higher cost for sacubitril/valsartan, compared with generic ACE inhibitors and angiotensin-receptor blockers, he said in an interview. HAdministrators "face an issue when they can only look at long-term horizons. But data like these, with the early benefit of reduced readmissions" make it easier to justify paying a higher drug cost. Health care systems increasingly focus on treatments that can produce rapid benefits, both clinically and financially, said Dr. Hernandez, director of health services and outcomes research at Duke.

In fact, a cost-effectiveness analysis of sacubitril/valsartan treatment in PARADIGM-HF that included the hospital readmissions data showed that the combined formulation was "highly cost effective," compared

with enalapril, said Dr. Solomon, who added that he and his associates will have a full report on this in 2016.

"Not only does sacubitril/valsartan reduce mortality and hospital admissions, but it also reduced readmissions. That is very exciting. This is one of the few treatments to have this effect", commented Dr. Jennifer Thibodeau,

As we continue to see findings like these, there will be [substantial] adoption of this drug.

DR. THIBODEAU

medical director of the heart failure disease management program at the University of Texas Southwestern Medical Center in Dallas. The 38% reduction in heart failure readmissions, compared with enalapril, and the 44% reduction in number of patients with a 30-day readmission was "pretty good," she said in an interview. Plus, clinicians have already been quite excited about sacubitril/valsartan based on the primary-endpoint benefits it showed in PARADIGM-HF, "although there is always caution when a drug is brand new."

Since U.S. marketing for sacubitril/valsartan began last summer, "there has not been a big rush to adopt it," primarily out of the usual concerns about new agents. "As we continue to see findings like these [reduced readmissions], there will be [substantial] adoption of this drug. The new findings definitely add to its attraction." Dr. Thibodeau said.

The two subgroups of patients who had heart failure hospitalizations in PARADIGM-HF, the 675 patients in the sacubitril/valsartan arm and the 775 in the enalapril arm, closely matched each other for virtually all demographic and clinical parameters aside from history of atrial fibrillation, which was significantly more

The early benefit of reduced readmissions makes it easier to justify paying a higher drug cost.

DR. HERNANDEZ

common in the enalapril patients. Even though these two subgroups had not been randomized, the near uniform consistency of their profiles made this "a valid analysis," Dr. Solomon said. Overall, 20% of the PARADIGM-HF patients who had a heart failure hospitalization had a rehospitalization within 30 days.

The 30-day heart failure readmission rate was 10 among patients on sacubitril/valsartan and 13% among those on enalapril, a 38% relative risk reduction that was statistically significant. The number of patients with a heart failure readmission was 44% lower in the group on the combined formulation. After 60 days, readmissions for any cause were 23% lower in the sacubitril/valsartan arm, compared with enalapril, and the combined formulation dropped the number with any 60-day readmission by 30%, he reported.

PARADIGM-HF was sponsored by Novartis, the company marketing sacubitril/valsartan (Entresto). Dr. Solomon has been a consultant to and has received research support from Novartis. Dr. Hernandez has received honoraria and research support from Novartis. Dr. Thibodeau had no financial disclosures.

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SPRINT's results rock hypertension world

BY MITCHEL L. ZOLER
Frontline Medical News

VITALS

Key clinical point: The first full report of results from the SPRINT trial of hypertension treatment targets generated lots of opinions on their implications.

Major finding: Combined cardiovascular events occurred in 5.2% of patients treated to a target systolic blood pressure of less than 120 mm Hg and 6.8% of patients treated to a target of less than 140 mm Hg.

Data source: The multicenter, randomized trial involved 9,361 patients.

Disclosures: SPRINT received no commercial support. The study received antihypertensive drugs from Arbor and Takeda at no charge for a small percentage of enrolled patients. Dr. Pfeffer has been a consultant to more than 20 companies. Dr. Rosendorff has been a consultant to McNeil and received research funding from Eisai. Dr. Yusuf has received honoraria and research grants from Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, Bayer, and Astra Zeneca. Dr. Jones, Dr. Deedwania, and Dr. Fonarow had no disclosures.

ORLANDO – Results from the SPRINT hypertension trial had been highly anticipated ever since the study stopped early in August and the sponsoring National Heart, Lung, and Blood Institute released the topline positive result in September.

That finding was that treating systolic blood pressure to a target of less than 120 mm Hg led to statistically significant drops in a composite measure of cardiovascular endpoints as well as in all-cause death, compared with treating to the standard blood pressure target of less than 140 mm Hg.

When the much fuller report on the results finally came out in a special session at the American Heart Association scientific sessions as well as in a simultaneous publication (N Engl J Med. 2015 Nov 9. doi: 10.1056/NEJMoa1511939), the data left attendees buzzing and debating about what the results will mean for revised hypertension guidelines and for clinical practice.

[The SPRINT trial is] a major coup. Thank you, NHLBI.

DR. PFEFFER

The most prominent reactions were accolades for the trial, starting with the independent discussants that the AHA invited to comment at the session. They offered an outpouring of praise that was reminiscent of the reviews showered on a new hit movie:

Thank you for this groundbreaking study.

DR. ROSENDORFF

"A major coup. Thank you, NHLBI," declared Dr. Marc A. Pfeffer, professor of medicine at Harvard and a cardiologist at Brigham and Women's Hospital in Boston.

"Thank you for this groundbreaking study," said Dr. Clive Rosendorff, who is professor and cardiologist at Mount Sinai Hospital in New York.

"A remarkable trial. The most important blood pressure study in the last 40 years," gushed Dr. Daniel W. Jones, who is professor of medicine at the University of Mississippi, Oxford, and the director of clinical and population sciences at the Mississippi Center for Obesity Research in Jackson.

Following the huzzahs came a more substantive discussion among meeting attendees of what the results from the 9,361-patient Systolic Blood Pressure Intervention Trial will mean for revised blood pressure goals in U.S. clinical guidelines, what it might mean for defining who has hypertension, and how it might influence practice.

The most important blood pressure study in the last 40 years.

DR. JONES

Perhaps the most pressing issue for the AHA and American College of Cardiology panel that began work on a new revision of hypertension treatment guidelines earlier this year is how will the panel decide to reconcile the SPRINT results with the findings from prior studies, especially the 2010 report of results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (N Engl J Med. 2010;362[17]:1575-85.).

ACCORD, at half the size of SPRINT with 4,733 patients, had a very similar study design as SPRINT but ACCORD included only patients with diabetes while SPRINT excluded patients with diabetes.

ACCORD failed to show a significant difference in its primary composite outcome after an average of 4.7 years between patients randomized to a hypertension treatment target of less than 140 mm Hg or less than 120 mm Hg, the same goals as in SPRINT.

You can't extrapolate to the average patient the results in the highly selected, high-risk patients in SPRINT.

DR. YUSUF

ACCORD did show a statistically significant 41% relative risk reduction for stroke, also in contrast to SPRINT, which showed a much less robust and nonsignificant 11% relative risk reduction in stroke.

In his commentary on SPRINT, Dr. Jones offered several possible explanations for the divergent results. Those explanations included a possible inherent difference in vascular physiology between patients with diabetes and those with normal glycemic control; the younger patients enrolled in ACCORD (patients averaged 62 years old in ACCORD and 68 years old in SPRINT, and 28% of patients in SPRINT were at least 75 years old); the use of hydrochlorothiazide as the predominant diuretic in ACCORD versus predominant use of chlorthalidone in SPRINT; and the multiple interventions simultaneously tested in ACCORD, which also randomized patients into two arms with respect to glycemic control and into two arms of different lipid-controlling treatment.

SPRINT's results "need to be assessed in the context of ACCORD," commented Dr. Salim Yusuf in an interview.

"I think the real result is somewhere in between the results of SPRINT and ACCORD" in terms of the appropriate systolic blood pressure target.

"What we need is a balanced perspective that takes all the trials. SPRINT was a very good trial, but like all studies it should be interpreted in the context of all the other related studies, not in isolation," said Dr. Yusuf, professor and director of the Population Health Research Institute of McMaster University in Hamilton, Ont.

"Understandably, when something like SPRINT comes out there is a lot of enthusiasm. The first reaction is always 'Wow!' For patients who meet SPRINT's enrollment criteria I think we will treat to a target of less than 120 mm Hg. But the guideline writers need to discuss SPRINT and balance it," he said.

Despite his regard for SPRINT, Dr. Yusuf cited several additional concerns he has about the trial:

• Its early stoppage (SPRINT had originally been designed to run 5-6 years, but it was halted after an average treatment duration of just over 3 years).

"When you stop a trial early there is always an upward bias. The apparent treatment effect gets inflated," Dr. Yusuf said.

• The increased rate of acute kidney injury among patients randomized to the more aggressive treatment arm, a 4.1% rate, compared with a 2.5% rate in the control patients randomized to treatment to a goal of systolic pressure less than 140 mm Hg, a statistically significant difference.

SPRINT seems to say treat everyone to a blood pressure of less than 120 mm Hg, but that's not the case.

DR. DEEDWANIA

• The "highly selected, high-risk" patients enrolled into SPRINT. "You can't extrapolate the results to the average patient," Dr. Yusuf said.

Some of these concerns and cautions were shared by Dr. Prakash Deedwania, professor of medicine at the University of California, San Francisco, although overall he called the SPRINT results "very exciting."

"Superficially, SPRINT seems to say treat everyone to a blood pressure of less than 120 mm Hg, but that's not the case. The patients in SPRINT

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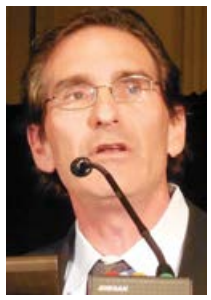
were primarily very well established patients with hypertension.

"I'd be concerned about an elderly patient with cardiovascular disease and a blood pressure of 130 mm Hg. If you reduce that to less than 120 mm Hg the diastolic pressure may also fall and that's important for coronary perfusion," Dr. Deedwania observed.



If renal function was meaningfully worsened, you would not see a reduction in all-cause mortality

DR. FONAROW

He also cited the absence, so far, of a subanalysis of what happened to patients with preexisting renal disease and the lack of data on the outcomes of patients whose systolic pressure fell to levels well below 120 mm Hg.

For others, however, the overall, statistically significant 27% reduction in overall mortality was a reassuring indicator of the safety of the aggressive treatment regimen used in SPRINT.

"If there was a meaningful worsening of renal function that harmed patients, you would not see a reduction in all-cause mortality," commented Dr. Gregg C. Fonarow, professor and associate chief of cardiology at the University of California, Los Angeles.

"We have had so many trials that couldn't dream of producing a reduction in all-cause mortality. Here we have a trial with a robust, clinically meaningful reduction in all-cause mortality that ultimately demonstrates the benefits outweigh the risks," he said in an interview.

SPRINT "is a phenomenal breakthrough. It's data we've been awaiting for 20-plus years, to now know that a lower blood pressure target is safe and absolutely essential, and where the benefits outweigh the risks," Dr. Fonarow said.

"Now implementation becomes critical. The SPRINT results are truly practice changing."

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VIEW ON THE NEWS

Dr. Jason Lazar, FCCP, comments: Despite the management of hypertension being one of the main success stories over the past century, debate rages on as to what blood pressure targets should be. Over the past several decades, the pendulum of thought has swung back and forth between more and less aggressive blood pressure control. Data from the SPRINT study indicate that lower is better. Given the high prevalence of hypertension and the degree of blood pressure elevation in such patients, tighter blood pressure control would appear to portend significant clinical benefits in terms of risk reduction of stroke to the large numbers of patients. Whether similar findings apply to cognitive decline remains unknown.

Steroids did not reduce kidney injury in CABG

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Among patients undergoing cardiac bypass surgery, perioperative use of corticosteroids did not alter the risk of acute kidney injury, results from a large randomized trial showed.

"Worldwide, over 20 million cardiac surgeries are done each year, but 4 million are complicated by acute kidney injury, and 200,000 are complicated by severe kidney injury treated with dialysis," Dr. Amit X. Garg said during a press briefing at the annual meeting of the American Society of Nephrology. "So certainly people would benefit from a therapy to prevent acute kidney injury (AKI) and improve the safety of surgery."

Dr. Garg, a nephrologist at the London Health Sciences Centre in

Continued on following page

Mixed results for mitral valve replacement vs. repair

BY TED BOSWORTH
Frontline Medical News

Patients undergoing mitral valve replacement had a lower risk of regurgitation and heart failure–related adverse events at 2 years than those undergoing valve repair, according to the results of a trial presented at the American Heart Association scientific sessions and published simultaneously in the New England Journal of Medicine.

The trial results appear to associate mitral valve replacement with clinical advantages over mitral valve repair after 2 years of follow-up.

However, replacement held no significant advantages over repair in the primary endpoint of left ventricular end-systolic volume index (LVESVI) or in overall survival, said Dr. Daniel Goldstein, who is with the department of cardiothoracic surgery at Montefiore Medical Center, New York.

In the trial conducted by the Cardiothoracic Surgical Trials Network (CTSN), 251 patients with chronic severe ischemic mitral regurgitation were randomly assigned to undergo surgical repair of the mitral valve or to receive a mitral valve replacement with a prosthetic and procedure selected at the discretion of the surgeon.

In addition to the primary endpoint of LVESVI, the two approaches were also compared for survival, regurgitation recurrence, and heart failure events.

At 2 years, the mean change from baseline in LVESVI, a measure of remodeling, did not differ significantly between the repair and replacement arms (–9.0 vs. –6.5 mL/m^2, respectively).

The rate of recurrence of moderate or severe mitral regurgitation favored replacement over repair and was significant (3.8% vs. 58.8%, respectively.

In addition, although the 2-year mortality rate was numerically lower in the repair arm relative to the replacement arm (19% vs. 23.2%, respectively), it was also not statistically different ($P = .39$).

However, the rate of recurrence of moderate or severe mitral regurgitation favored replacement over repair and was significant (3.8% vs. 58.8%, respectively; P less than .001). In addition, the rate of cardiovascular readmissions was significantly lower in the replacement group ($P = .01$).

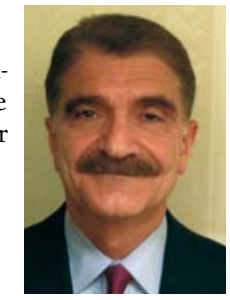
For those in the repair group, there were significant trends for more serious adverse events related to heart failure ($P = .05$) and for a lower quality of life improvement ($P = .07$) on the Minnesota Living With Heart Failure questionnaire.

There were no significant differences in rates of all serious adverse events or overall readmissions.

All of the differences between groups observed at 2 years amplify differences previously reported after 12 months (N Engl J Med. 2014 Jan 2;370[1]:23-32). For example, the difference in the rate of moderate to severe regurgitation favoring replacement over repair was already significant at that time (2.3% vs. 32.6%, respectively; P less than .001), even though the mortality rates were then, as now, numerically lower in the repair group versus the replacement group (14.3% vs. 17.6%, respectively; $P = .45$).

Dr. Goldstein reported having no financial relationships relevant to the study..

VIEW ON THE NEWS



Dr. G. Hossein Almassi, FCCP, comments: Mitral valve repair is the standard therapy for the treatment of severe mitral regurgitation. In ischemic mitral regurgitation, adverse left ventricular remodeling and the tethering of the subvalvular apparatus of the mitral valve lead to malcoaptation of leaflets and variable degrees of mitral regurgitation. As such, the standard techniques of valve repair have been fraught with early failure and recurrence of the regurgitation. In other words, treating a ventricular problem with a valvular procedure does not result in a durable and effective repair. The results of the CTSN prospective randomized trial suggest that valve replacement may be a better option than valve repair for patients with severe ischemic mitral regurgitation.

Continued from previous page

London, Ontario, Canada, noted that cardiopulmonary bypass initiates a systemic inflammatory response syndrome, "which activates complement, inflammatory cytokines, and other inflammatory mediators, which in turn increases endothelial permeability, organ damage, and increased morbidity and mortality, including acute kidney injury." Researchers are interested in corticosteroids, "because they suppress this inflammatory response. In other settings, such as acute glomerulonephritis, we successfully use corticosteroids to treat acute inflammation in the kidney," he said.

Results were similar across multiple definitions of AKI, Dr. Amit X. Garg said.

In a study known as the Steroids in caRdiac Surgery Trial (SIRS), researchers at 79 centers in 18 countries set out to investigate if methylprednisolone alters the risk of acute kidney injury in patients undergoing cardiac surgery with cardiopulmonary bypass. Between June 2007 and December 2013, 7,286 patients were randomized to intravenous methylprednisolone 250 mg at anesthetic induction and 250 mg at initiation of coronary bypass, or placebo.

AKI was defined as a 0.3 mg/dL increase or greater in postoperative serum creatinine concentration from the preoperative concentration within 14 days following surgery, or a 50% increase from the preoperative value within 14 days following surgery. Secondary outcomes included different stages of AKI and receipt of acute dialysis in the 30 days following surgery. Patients, caregivers, and researchers were blinded to the treatment allocation.

Of the 7,286 patients, 3,647 received methylprednisolone and 3,639 received placebo. The mean age of patients was 60 years, 60% were men, 26% were diabetic, and 25% of patients had combined CABG and valve surgery.

When we consider the side effect profile, the most clinically relevant outcomes, and apply the GRADE framework to the evidence, we would recommend that steroids not be used in this way, with a grade 1B recommendation.

The SIRS Investigators reported that the risk of AKI was similar among patients who received methylprednisolone and those who received placebo (40.9% vs. 39.5%, respectively; relative risk 1.03). Results were similar across multiple categorical definitions of AKI, including AKI or death (41.5% vs 40.2%; RR 1.03); AKI stage of 2 or greater (9.9% vs 9.9%; RR 1.01); AKI stage of 3 or greater (4% vs. 4.5%; RR .89), and being on acute dialysis (2.6% vs. 2.4%; RR 1.08).

"There was no benefit of steroids on the risk of AKI in those with or without preoperative chronic kidney disease," Dr. Garg said. "The result was also not different in the subpopulation of patients with AKI as defined by Kidney Disease Improving Global Outcomes."

Results from SIRS "would suggest that patients undergoing cardiac surgery with cardiopulmonary bypass should not use prophylactic steroids to prevent AKI. When we consider the side effect profile, the most clinically relevant outcomes, and apply the GRADE framework [the Grading of Recommendations Assessment, Development, and Evaluation] to the evidence, we would recommend that steroids not be used in this way, with a grade 1B recommendation."

The study was sponsored by the Population Health Research Institute in Hamilton, Ontario and the Canadian Institutes of Health Research. Dr. Garg reported having no relevant financial disclosures for this study.

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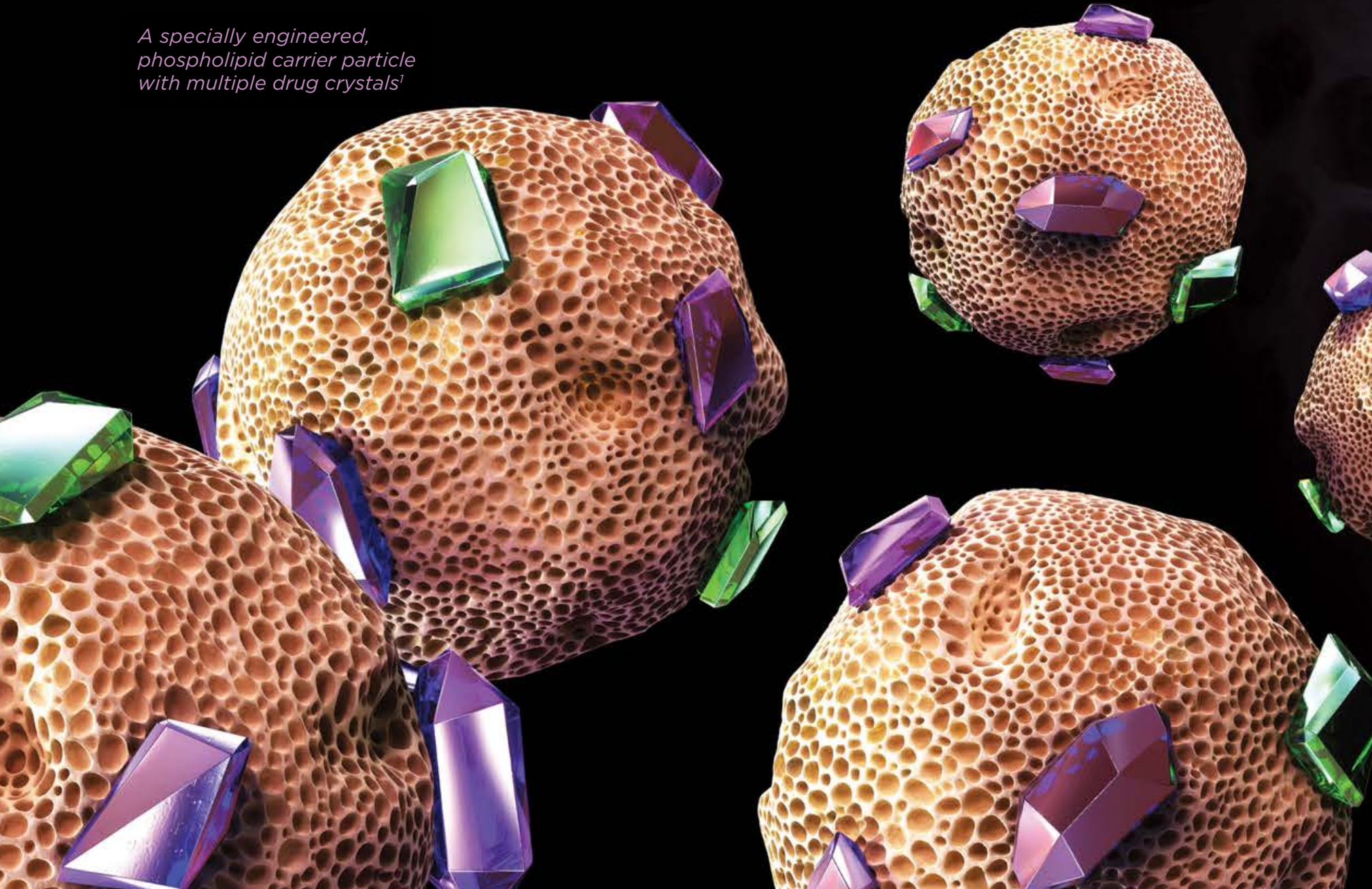
INTRODUCING

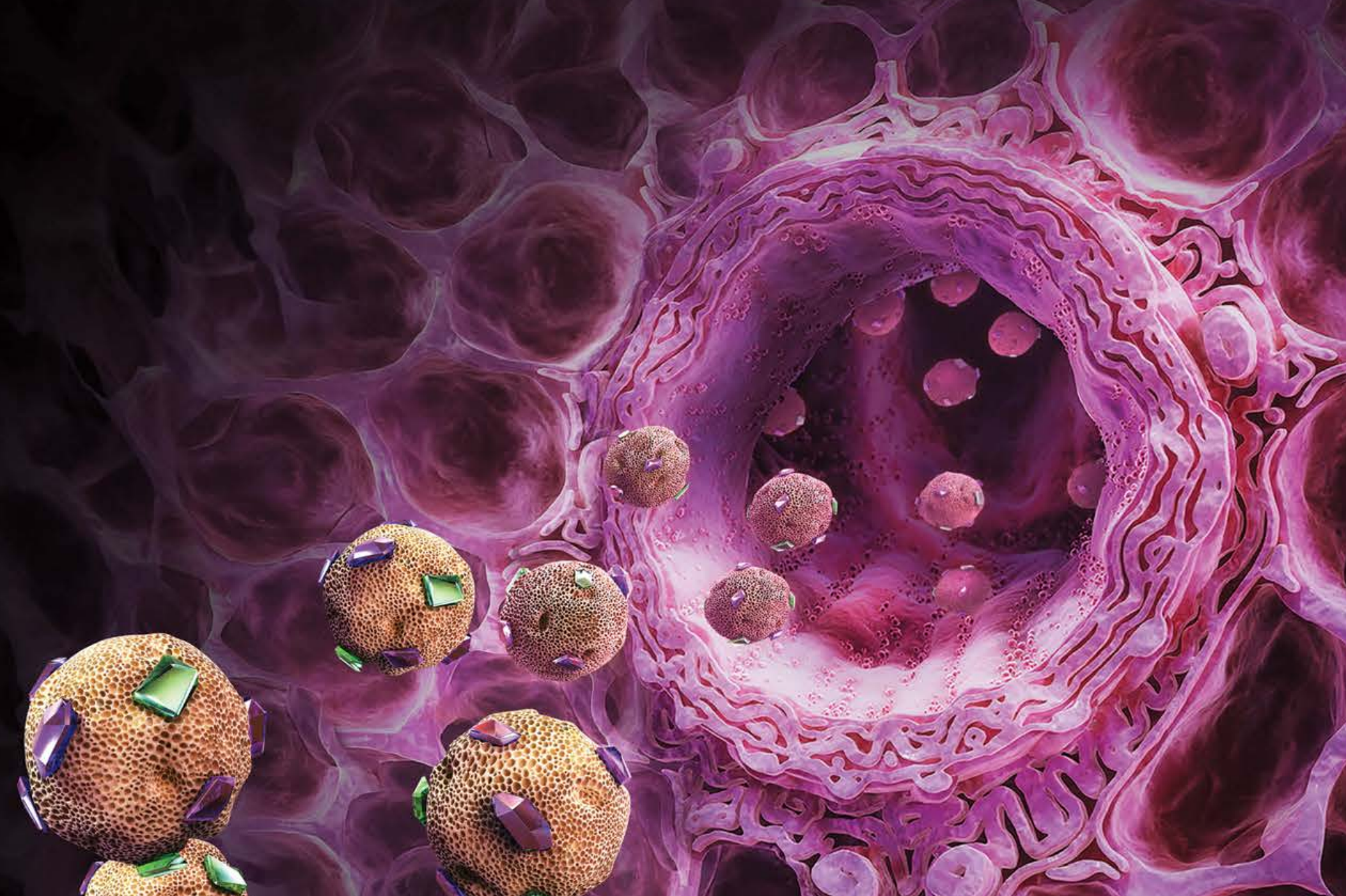
CO-SUSPENSION TECHNOLOGY

THE NEW SCIENCE OF INTELLIGENT DELIVERY IN RESPIRATORY MEDICINE

Exploring a new formulation for inhaled drug delivery



A specially engineered, phospholipid carrier particle with multiple drug crystals[1]



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Reference: 1. Vehring R, Lechuga-Ballesteros D, Joshi V, Noga B, Dwivedi SK. Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers. *Langmuir*. 2012;28(42):15015-15023.

AstraZeneca

‘Minimalist’ TAVR has short learning curve

BY RICHARD MARK KIRKNER
Frontline Medical News

As a “minimalist” approach to transcatheter aortic valve replacement – known as MA-TAVR – gains in popularity at high-volume centers, questions persist about the surgeon’s learning curve. A small series of MA-TAVR cases at Emory University in Atlanta has shown that the leaning curve may be like the TAVR approach itself: minimal.

Dr. Hanna Jensen and her associates reported on 151 consecutive patients who had MA-TAVR in the October issue of the Journal of Thoracic and Cardiovascular Surgery (J Thorac Cardiovasc Surg. 2015. doi: 10.1016/j.jtcvs.2015.07.078). They previously reported their findings at the annual meeting of the American Association for Thoracic Surgery in April in Seattle.

As experience grows, we believe that this procedure can be done with less or no ICU support, leading to a shorter hospital stay and improved resource utilization.

This study builds on an Emory study last year that reported the minimalist approach to TAVR cost about $10,000 less per patient than the standard transfemoral approach (JACC Cardiovasc Interv. 2014;7:898-904).

The operation the study authors evaluated is performed in the catheterization laboratory rather than the operating room, as in traditional TAVR. Both approaches use a femoral approach, but where traditional TAVR requires general anesthesia and transesophageal echocardiography (TEE), MA-TAVR uses local anesthesia, minimal conscious sedation, and transthoracic echocardiography (TTE).

The study authors acknowledged concerns that TTE may underestimate the severity of paravalvular leak after the procedure when compared with TEE. Their protocol relies on preoperative TTE and CT scans, or three-dimensional TEE if the case warrants it, to ensure optimal sizing of the transcatheter valve before the operation.

“If any concerns arise, our threshold is low to perform intraoperative balloon-sizing,” Dr. Jensen and her coauthors said. They also use TTE, along with a root-angiogram after valve deployment, and invasively measure the aortic regurgitation index before and after deployment.

Most study patients were high-risk surgical candidates with a median Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score of 10%. The overall major stroke rate was 3.3%, while major vascular complications occurred in 3% of patients and the greater-than-mild paravalvular leak rate was 7%.

The study retrospectively evaluated 151 consecutive patients who were divided into three groups at different time points: May 2012 to January 2013, February to August 2013, and September 2013 to July 2014. Complications were similar among all three groups, but the third group had shorter hospital stays and less time in the intensive care unit (ICU).

The first group received only the first-generation SAPIEN valve system; use of the second-generation SAPIEN XT valve increased in latter two groups. The SAPIEN XT valve is available in 23, 26, or 29 mm, but the 29-mm size was not available in the first-generation SAPIEN implant.

A subgroup analysis looked at patients who were discharged within 48 hours of the operation or more than 48 hours afterward.

The early-discharge patients had lower STS PROM scores (8.3% vs. 10.3%) and lower rates of diabetes (31% vs. 49%). They also had less need for postoperative pacemakers and less frequent rehospitalization.

“This implies that in selected MA-TAVR patients early discharge is feasible and safe, but larger studies are required to identify the optimal profile of patients who can be sent home within the first two postoperative days,” Dr. Jensen and her colleagues said.

Early in the MA-TAVR protocol all patients were sent to the ICU. As the care team gained more experience with the procedure, the protocol changed to send all patients to a regular telemetry floor after surgery unless they had vascular issues or potential need for a pacemaker.

The decreasing need for ICU “was the only indication of an institutional learning curve that was discovered, and demonstrated improved resource utilization over time,” the investigators said.

They encouraged other centers to pursue MA-TAVR. “As experience grows, we believe that this procedure can be done with less or no ICU support leading to a shorter hospital stay and improved resource utilization,” Dr. Jensen and her coauthors concluded. They called for further studies to determine the characteristics that make a patient most suitable for a short-admission MA-TAVR procedure.

Study coauthors Dr. Vasilis Babaliaros, Dr. Vinod Thourani, Amy Simone, and Patricia Keegan are research consultants with Edwards Lifesciences. The rest of the authors had no disclosures.

VIEW ON THE NEWS

Dr. G. Hossein Almassi, FCCP, comments: Transcatheter Aortic Valve Replacement (TAVR) has revolutionized the treatment of severe aortic stenosis in high-risk patients. It is, therefore, natural to see its application to lower risk patients. This has already happened in European countries. This study from Emory is a systematic approach and application of this technology to lower risk patients at a high volume TAVR center.

Hybrid revascularization: Promise, but concerns remain

BY RICHARD MARK KIRKNER
Frontline Medical News

A hybrid coronary revascularization procedure that combines off-pump left internal mammary artery (LIMA) grafting with percutaneous coronary intervention (PCI) showed good results at 1 year after surgery, but nonetheless showed a rate of adverse events that may raise questions about the procedure.

In a study published in the November issue of the Journal of Thoracic and Cardiovascular Surgery, a team of investigators from Aarhus University Hospital in Denmark reported high rates of graft patency and low rates of death and stroke with the procedure 1 year after a series of 100 operations (J Thorac Cardiovasc Surg. 2015;150:1181-6).

“The high left internal mammary artery graft patency rate and low risk of death and stroke at 1 year seem promising for the long-term outcome of this revascularization strategy,” said Dr. Ivy Susanne Modrau and colleagues.

The single-center study evaluated 1-year clinical and angiographic results of 100 consecutive trial patients with multivessel disease who had the hybrid procedure between October 2010 and February 2012.

“The rationale of hybrid coronary revascularization is to achieve the survival benefits of the LIMA to LAD (left anterior descending artery) graft with reduced invasiveness to minimize postprocedural discomfort and morbidity, in particular the risk of stroke,” Dr. Modrau and colleagues said.

The study used the LIMA to LAD graft performed off pump through a reversed J-hemisternotomy “We chose this technique because of its excellent exposure of the heart, technical ease, low risk of complicating chronic pain, and applicability in virtually all patients,” Dr. Modrau said. Eighty-

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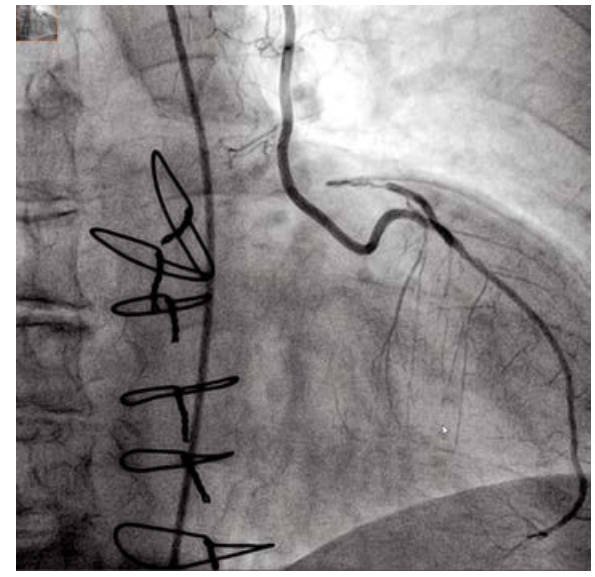

COURTESY JTCVS

The LIMA to LAD graft was performed off pump through a reversed J-hemisternotomy.

Continued from previous page

nine patients had surgery prior to PCI and 11 had PCI prior to surgery.

The primary endpoint was rate of major adverse cardiac or cerebrovascular events (MACCE), the composite of all-cause death, stroke, myocardial infarction, and repeat revascularization by PCI or coronary artery bypass grafting at 1 year. Secondary endpoints included individual components and status of stent and graft patency on angiography.

Overall, 20 patients met the 1-year primary endpoint of MACCE. One patient died, one other had a stroke, and three had heart attacks. Sixteen patients had repeat revascularization procedures, eight performed during the index hospitalization. Graft patency was 98% after 1 year.

Dr. Modrau and coauthors noted the MACCE rate of 20% "was higher than expected," and certainly higher than results in the SYNTAX study (17.8% in the PCI group and 12.4% in the coronary artery bypass grafting [CABG] group) (Euro. Intervention. 2015;10:e1-e6).

One possible reason the Danish investigators cited for higher than expected MACCE rates was that they may be attributed to the learning curve involved with LIMA grafting and the use of early angiography possibly revealing "clinically silent LIMA graft dysfunction due to technical errors."

The number of repeat revascularizations in the study was more in line with the SYNTAX study: 7% in the Aarhus University study and 6% in the SYNTAX CABG group.

However, a meta-analysis of six studies with 1,190 patients reported 1-year repeat revascularization rates of 3.8% after a hybrid procedure and 1.4% after CABG (Am Heart J. 2014;167:585-92).

Ultimately, the safety and efficacy of the hybrid revascularization approach will require long-term follow-up data and head-to-head comparison with conventional CABG and PCI in clinical trials. "Meanwhile, LIMA patency, the cornerstone of surgical revascularization, may be used as a surrogate endpoint for long-term survival after HCR," Dr. Modrau and coauthors said.

They reported having no disclosures.

VIEW ON THE NEWS

Dr. G. Hossein Almassi, FCCP, comments: CABG remains a Class 1 indication for treatment of multivessel coronary disease, and left main coronary stenosis. As compared to PCI, CABG treats the entire coronary vessel rather than the "culprit" lesion. Hybrid coronary revascularization is reasonable in patients with one or more of the following criteria (Class IIa,Level of evidence B):

a. Limitation to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI);

b. Lack of suitable conduit;

c. Unfavorable LAD artery for PCI (ie, excessive vessel tortuosity).

This small Danish study on hybrid coronary revascularization suffers from a short follow up time of only one year. The rate of repeat revascularization was also high. The data should be looked at carefully and one should wait for long-term outcomes.

Mild and moderate OSAS often resolves in children

BY DEEPAK CHITNIS
Frontline Medical News

FROM CHEST

Mild to moderate obstructive sleep apnea syndrome (OSAS) resolves spontaneously in many children in as few as 7 months, based on polysomnography results from the control arm of the Childhood Adenotonsillectomy Trial (CHAT).

Symptomatic improvement in snoring, however, was less common. Nonetheless, "watchful waiting may be a reasonable option in children with low OSAS symptom burden and, especially, little snoring, who also have low AHIs [apnea/hypopnea indexes] and do not have central obesity," markers that were most likely to be associated with resolution, wrote Dr. Ronald D. Chervin of the University of Michigan, Ann Arbor,

Continued on page 42

VIEW ON THE NEWS

Patience is rewarded

Because polysomnography is expensive, time consuming, and often unavailable, otolaryngologists will often perform an adenotonsillectomy based on a strong clinical history and parental observation in a child with snoring and chronically enlarged adenoids and tonsils. This study challenges that approach for children who have a low symptom burden, little snoring, low apnea/hypopnea indexes, and no central obesity. Admittedly, adenotonsillectomy is relatively safe, but any procedure can have complications. and all have associated costs.

Dr. Ian Nathanson, of Maitland, Fla., made his comments in an accompanying editorial (Chest. 2015;148[5]:1129-1130).

Continued from page 40

and his colleagues. "Without surgery, habitual snoring resolves in one-half to two-thirds of affected children within 1-3 years."

The study enrolled 453 children, aged 5-9, with an AHI of at least 2 events per hour of sleep, or an obstructive apnea index (OHI) of at least 1. All children were recruited from pediatric sleep clinics and otolaryngology practices. The study did not include children with severe OSAS, which was defined as having an apnea/hypopnea index of greater than 30, an obstructive apnea index greater than 20, or oxygen saturation less than 90% for at least 2% of total sleep time. None of the study participants had recurrent tonsillitis, had a BMI z-score of at least 3, or were taking medication for attention-deficit/hyperactivity disorder, the investigators reported (Chest. 2015;148[5]:1204-13).

Among 453 children randomized in CHAT, 194 in the control arm had complete follow-up, remained untreated surgically, and provided data for the current analyses. Mean AHI at baseline was 6.7 (range, 1.1-29.3), mean oxygen saturation at baseline was 88.8% (range, 59%-97%), and mean score on the Pediatric Sleep Questionnaire Sleep-Related Breath-

'Without surgery, habitual snoring resolves in one-half to two-thirds of affected children within 1-3 years.'

ing Disorder (PSQ-SRBD) scale at baseline was 0.48 (range, 0.05-0.90).

Primary endpoints based on polysomnography results at 7-month follow-up were reaching an AHI of less than 2 and an obstructive apnea index of less than 1. In addition, researchers defined "substantive resolution" of symptoms related to OSAS as a total PSQ-SRBD score of 0.33 or more at baseline that declined below 0.33 and was at least 25% below the baseline value at 7-month follow-up.

At 7 months, OSAS had spontaneously resolved by polysomnography measures in 82 of the 194 children based on achieving an AHI less than 2 and an OAI less than 1. However, symptomatic improvement was less common. Of 167 children with PSQ-SRBD scores of at least 0.33 at baseline, only 15% had scores less than 0.33 and at least a 25% reduction in PSQ-SRBD score at 7 months.

Only 12% showed both polysomnographic and symptomatic resolu-

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tion of symptoms at 7 months.

"Symptoms often matter more to patients and families than do laboratory results," the authors wrote. "In our cohort, 34 of 147 habitual snorers (23%) were no longer habitual snorers at follow-up."

The CHAT Study was supported by the National Institutes of Health.

Dr. Chervin disclosed that he is named in or has developed, patented, and copyrighted materials owned by the University of Michigan and designed to assist with assessment or treatment of sleep disorders, including the Pediatric Sleep Questionnaire Sleep-Related Breathing Disorder scale used in this study.

He also has received support for research and education from Philips Respironics and Fisher & Paykel Healthcare, and has consulted for MC3 and Zansors.

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Sleep medicine specialists issue statement on drowsy driving

BY GREGORY TWACHTMAN
Frontline Medical News

In an effort to combat drowsy driving, the American Academy of Sleep Medicine is calling for better education on the symptoms, and more research to understand the thresholds for when sleepiness while driving becomes dangerous, AASM said in a policy statement published in the Journal of Clinical Sleep Medicine (doi: 10.5664/jcsm.5200).

AASM is calling for collaboration among sleep physicians, state departments of motor vehicles and licensing, highway patrol, and the insurance industry to develop ways to reduce drowsy driving, educational material to be used in driver's education and licensing examination, drowsy driving educational insurance discount programs, and technologies that mitigate against drowsy driving.

In addition, AASM "encourages more research that better defines indicators of drowsy driving, identifies the threshold at which sleepiness while driving becomes dangerous, and provides the public with simple methods to determine when they might be too tired to drive safely."

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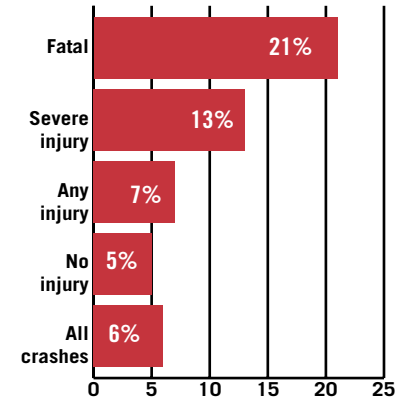
Motor vehicle crashes involving a drowsy driver, 2009-2013



FRONTLINE MEDICAL NEWS

Any injury: Any person involved treated for injury sustained in crash.

Severe injury: At least one person admitted to the hospital.

Fatal: At least one person died within 30 days as a result of injuries.

Note: Based on data for 14,268 crashes in which a vehicle was towed from the scene.

Source: AAA Foundation for Traffic Safety

Extremes of sleep linked with early signs of CVD

BY KARI OAKES
Frontline Medical News

Extremely short or extremely long sleep was associated with increased incidence of preclinical signs of cardiovascular disease in a large cross-sectional study of healthy and relatively young adults. Poor subjective sleep quality was also associated with early signs of CVD.

Dr. Chan-Won Kim of the Sungkyunkwan University in Seoul, South Korea, and his coinvestigators gathered self-reports of sleep quality and sleep duration from 47,309 healthy adults who underwent regularly scheduled physical examinations. Of those, 29,203 adults, 81% of whom were male, had measurement of coronary artery calcification (CAC); while 18,106 patients, 69% of whom were male, underwent brachial-ankle pulse wave velocity (baPWV) measurement. The patients were relatively young, with a mean age of 42 years for the CAC cohort and 46 for the baPWV cohort.

Coronary artery calcification and distal arterial stiffness are considered to be markers for preclinical CVD; by measuring these markers in a relatively young cohort, the investigators sought to avoid the many confounders that complicate the association between CVD and sleep in older patients with more comorbidities.

The study used multivariable analysis to control for factors such as smoking and alcohol use, marital status and education attainment, and physiologic variables including blood pressure, body mass index, and cholesterol.

Overall, more than 80% of subjects reported good subjective sleep quality, regardless of duration. However, women who reported poor sleep had a higher incidence of CAC, and men with poor sleep had a higher mean baPWV.

For sleep duration, Dr. Kim, Dr. Chang, and their colleagues found a U-shaped association between sleep duration and CAC and baPWV. Compared with individuals who slept 7 hours per night, individuals who reported sleeping less than 5 hours nightly had a CAC score ratio of 1.50, and an increase in baPWV of 6.7 cm/sec. At the other extreme, those who slept 9 or more hours per night had a CAC score ratio of 1.72 and an increase in baPWV of 9.6cm/sec. All these differences were statistically significant (Arterioscler Thromb Vasc Biol. 2015 Sept 10; doi: 10.1161/ATVBAHA.115.306110.).

The results help clarify that the previously known associations between sleep duration, quality, and CVD risk are not fully attributable to the comorbidities that can affect both sleep and heart health, said Dr. Kim and associates. Though they encourage further study to delineate sleep's contribution to CVD, their results "underscore the importance of adequate sleep quantity and quality, and support the need for considering subjects with extreme duration or poor subjective quality of sleep at high risk for CVD," they said.

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On post–call day, simple cognitive skills suffer

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – If you feel sleepy and out of sorts on a post–call day, compared with a normal work–day, you're not alone.

Anesthesiology faculty reported significant increases in feeling irritable, jittery, and sleepy, along with significant decreases in feeling confident, energetic, and talkative following an on-call period, according to a study presented at the annual meeting of the American Society of Anesthesiologists.

To examine the effects of partial sleep deprivation on reaction time, simple cognitive skills, and mood status, Dr. Haleh Saadat of the Nationwide Children's Hospital in Columbus, Ohio.and her associates obtained verbal consent from 21 anesthesiologists and measured reaction time, mood states, and eight subjective behavioral characteristics at two different time points: between 6:30 a.m. and 8 a.m. on a regular noncall day of work, and between 6:30 a.m. and 8 a.m. after an overnight call (a shift that runs from 3 p.m. to 7 a.m.). The behavioral characteristics included feeling alert, energetic, anxious, confident, irritable, jittery/nervous, sleepy, and talkative.

Reaction time decreased in all 21 subjects after night call, indicating worse performance ($P = .047$), while total mood disturbance was significantly higher on post–call days, relative to noncall days (P less than .001). Of the 21 anesthesiologists, 19 completed all simple cognitive task questions at both time points and reported significant increases in several of these parameters on post–call as compared with normal work days.

FRONTLINE MEDICAL NEWS

Post call, subjects felt more irritable and less confident, Dr. Saadat said.

Post–call observations found participants feeling more irritable, and less confident and energetic, more sleepy (P less than .001), more jittery ($P = .003$), and less talkative (P less than .001) than on normal work–days. "Most of our subjects using problem solving, followed by seeking social support and avoidance," Dr. Saadat noted. "People who used avoidance had greater declines in reaction time on post–call days, compared with the rest of the study participants."

"These observations require a closer look at the potential implications for patients' and professionals' safety."

The researchers reported having no financial disclosures.

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Less pneumonitis with IMRT than 3D-CRT

BY SARA FREEMAN
Frontline Medical News

SAN ANTONIO – Patients with stage III non–small-cell lung cancer undergoing chemoradiotherapy had less lung inflammation if they were treated with intensity-modulated radiation therapy (IMRT) than three-dimensional conformational radiation therapy (3D-CRT) in a secondary analysis of data from the NRG Oncology/Radiation Therapy Oncology Group (RTOG) 0617 trial.

A 44% reduction in grade 3 or higher pneumonitis cases was observed in the analysis, at 4.5% for IMRT and 8% for 3D-CRT, respectively ($P = .046$), Dr. Stephen Chun of the MD Anderson Cancer Center, Houston, reported at the annual scientific meeting of the American Society for Radiation Oncology.

RTOG 0617 was one of the largest studies to look at chemoradiation in patients with locally advanced non–small-cell lung cancer, Dr. Chun explained in an interview.

This phase III study examined whether there was any advantage of using high-dose (74-Gray) over standard dose (60-Gray) radiation therapy in combination with chemotherapy consisting of carboplatin and paclitaxel with or without additional cetuximab.

Courtesy ASTRO/Adam Donohue

A 44% reduction in grade 3 or higher pneumonitis cases was observed in the analysis, at 4.5% for IMRT and 8% for 3D-CRT, Dr. Stephen Chun said.

How the radiation therapy was delivered was left to the discretion of the treating physicians participating in the multi-institutional trial, and so the aim of the secondary analysis was to see if there was any difference in outcomes between patients who received IMRT versus those who received 3D-CRT.

"Our main hypothesis was that by using highly complex modulated beam arrangements, we would improve oncologic outcomes, whether that be toxicity or tumor control; we looked at all sorts of outcomes," Dr. Chun said.

"We defined severe or grade 3+ pneumonitis as that requiring high steroids, oxygen, hospital admission, a ventilator, or death," he said. "So we were really dealing with the most serious types of pneumonitis."

Among the 482 patients studied in the analysis, 47% had received IMRT, and 53% had received 3D-RT.

During his presentation, Dr. Chun noted that the "deck was stacked against IMRT" at baseline, with significantly more patients with stage IIIB (39% vs. 30%) and smaller mean planned target volumes (PTV, 427 mL vs. 486 mL) and a lower PTV/lung ratio (0.13 vs. 0.15) in the IMRT group versus the 3D-RT group.

Despite having less favorable tumors at the outset of the study, patients in the IMRT arm did just as well as those in the conventional radiotherapy group in terms of local tumor control. At 2 years, local control was 31% and 37% ($P = .50$), respectively.

There was no statistical difference in 2-year overall (53% vs. 49%, $P = .597$), progression-free (25% vs. 27%, $P = .595$), or distant metastasis-free survival (46% vs. 50%, $P = .66$).

IMRT was associated with more consolidative chemotherapy (37% vs. 29%, P less than .05), and significantly lower doses of radiation were delivered to the patients' hearts, which may confer survival advantage and further toxicity benefits in the future with longer follow-up, Dr. Chun suggested.

The potential ramifications of the pneumonitis finding are currently such that they could drastically decrease medical and associated hospitalization costs, he added.

"For the past decade or so, IMRT has been accepted for disease sites like the head and neck, the prostate, the brain, and other sites because of potential toxicity benefits.

"With what we are seeing here, we believe that these findings support more routine use of IMRT for this population and a similar leap in lung cancer," Dr. Chun said.

Is Skip N2 Metastasis Its Own Category?

BY RICHARD MARK KIRKNER
Frontline Medical News

So-called "skip metastasis" of lung cancer to the lymph nodes – when the cancer "skips" over the N1 bronchopulmonary or hilar stage to N2 ipsilateral mediastinal metastasis – may be associated with distinct histological characteristics that can further help understand its association with longer survival and better prognosis in advanced resectable lung adenocarcinoma, according to a small study from China.

Researchers at Fudan (Shanghai) University Cancer Center published their findings online ahead of print for the October issue of the Journal of Thoracic and Cardiovascular Surgery (2015 July 6 [doi: 10.1016/j.jtcvs.2015.03.067]). In all, they enrolled 177 patients with N2 adenocarcinoma, 45 (25%) of whom had skip N2 metastasis.

They reported that patients with skip metastasis had considerably better 5-year recurrence-free survival rates of 37% vs. 5.7% and better overall survival rates of 61% vs. 32% when compared with those with non-skip involvement.

"There are distinct differences in clinicopathological features and prognosis in patients with or without skip N2 metastasis," Dr. Haiquan Chen and his colleagues said. "Considering the results of our study, subclassifications of mediastinal lymph nodes metastases would have potential clinical significance for patients with lung adenocarcinoma."

Dr. Chen and his colleagues sought to identify specific histological features that characterized the association between skip N2 metastasis and adenocarcinoma subtypes and prognosis. "Skip N2 patients have more cases that are acinar adenocarcinoma subtype, well differentiated and located in the right lung than [do] non-skip patients," they said.

In fact, they found the predictive value of skip N2 was more significant in patients with right-lung disease, with 5-year recurrence-free survival of 37% vs. 0% and overall survival of 57% vs. 28% in non–right-lung lesions. Tumor size of 3 cm or smaller in skip N2 was associated with significantly improved survival rates – 43% vs. 6.7% recurrence-free survival and 75% vs. 28% for overall survival, compared with patients with larger tumors.

The skip N2 lung adenocarcinoma patients had "remarkably lower incidence" of vascular invasion of the lymph nodes, Dr. Chen and his coauthors wrote. Skip N2 patients also had lower, but not statistically significant, rates of pleural invasion. The Fudan University researchers also reported that the incidence of non-skip N2 metastasis was "significantly high" in patients with papillary-predominant subtype.

"Considering our results, skip N2 should not be recognized as [a] predictor for better survival in all lung adenocarcinoma cases, but in [a] more specific group of patients," Dr. Chen and his coauthors said.

A multivariate analysis confirmed the predictive significance of skip N2 for recurrence-free survival, but not so much for overall survival. Single N2 metastasis was also an independent predictor for better recurrence-free and overall survival.

The study was funded by the Key Construction Program of the National "985" Project, Ministry of Science and Technology of China; the National Natural Science Foundation of China; the Science and Technology Commission of Shanghai Municipality; and Shanghai Hospital Development Center. The authors had no disclosures.

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

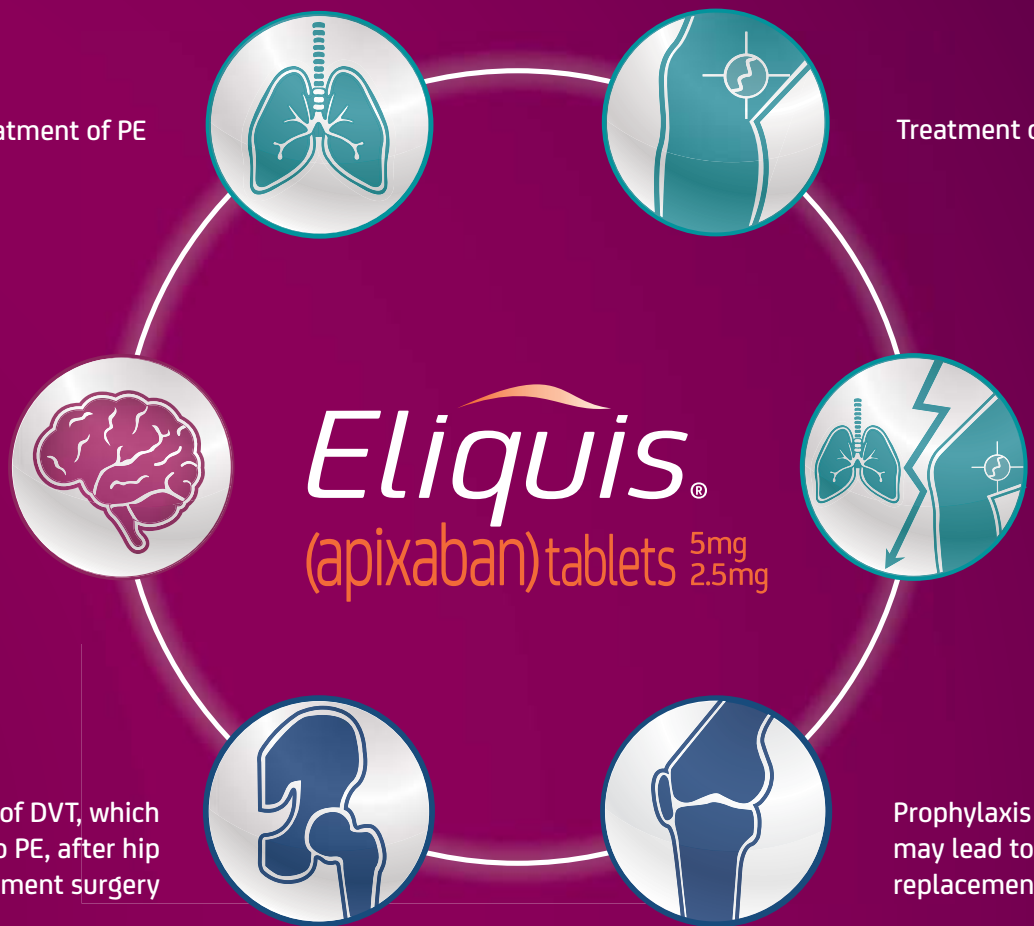
DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

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

Bristol-Myers Squibb Pfizer

Approved for 6 indications



Learn more about ELIQUIS for the treatment of DVT/PE and access reprints of our clinical studies.

hcp.eliquis.com

NVAF=nonvalvular atrial fibrillation; DVT=deep vein thrombosis; PE=pulmonary embolism.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

DRUG INTERACTIONS (CONT'D)

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

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

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

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS
(B) SPINAL/EPIDURAL HEMATOMA

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except nonvalvular atrial fibrillation patients who meet the criteria for dosage adjustment *[see Dosage and Administration (2.1) in full Prescribing Information]*. Patients with ESRD (CrCl <15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction *[see Warnings and Precautions]*. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

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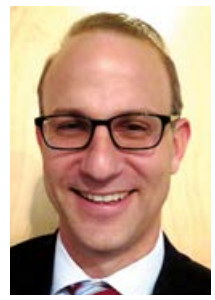
Actionable mutations are highly prevalent in young

BY SUSAN LONDON
Frontline Medical News

DENVER – Genomic testing in young patients with lung cancer is critical, as the majority have adenocarcinomas harboring driver alterations that can be targeted with drugs available today, suggested a trio of cohort studies presented at a conference sponsored by the International Association for the Study of Lung Cancer.

More than three-fourths of patients aged 40 years or younger with adenocarcinoma were found to have driver alterations in genes such as those for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (ROS1), investigators reported in a session and related press conference.

"Lung cancer under 40 is a group of patients enriched for actionable mutations," commented invited discussant Dr. Benjamin Levy, medical director of the thoracic oncology program for the Mount Sinai Health System in New York. "If there was ever a clinical circumstance in which next-generation sequencing should be performed routinely outside a clinical trial, it's for these patients under 40."



Lung cancer under 40 is a group of patients enriched for actionable mutations.

DR. LEVY

Of note, in two of the three studies, the majority of patients had some history of smoking, "suggesting that this lung cancer in patients under 40 is not necessarily a nonsmoking disease," he said.

New study design expands enrollment options

In the first study, a team led by Dr. Barbara J. Gitlitz, associate professor of clinical medicine at the University of Southern California in Los Angeles, analyzed data from the Genomics of Young Lung Cancer Study, the first to prospectively assess clinical characteristics and genomic alterations of this population.

The study is open to patients younger than 40 years at diagnosis. All are tested for alterations of EGFR, BRAF, HER2, KRAS, ALK, ROS1, and RET, and those negative for alterations in these genes have additional testing.

"One interesting point of our study is that people can enter either through coming to a [brick and mortar] site that has IRB approval or through a website (https://www.openmednet.org/site/alcmi-goyl) where people can remotely consent anywhere in the world and participate in our clinical trial," Dr. Gitlitz noted.

Most patients, 76%, had an actionable mutation for which they are on targeted therapy, Dr. Gitlitz said.

VITALS

Key clinical point: The majority of young patients with lung cancer have mutations for which targeted therapies are available.

Major finding: Actionable mutations were found in more than 76% of patients with stage IV adenocarcinoma and in 82% of patients with any-stage adenocarcinoma. Sizable proportions of patients had a smoking history.

Data source: Three cohort studies in 68 patients younger than 40 years, 67 patients aged 40 or younger, and 20 patients aged 45 or younger at lung cancer diagnosis.

Disclosures: Dr. Gitlitz reported that she is on the speakers bureaus of Genentech and Eli Lilly. Dr. Tanaka reported that he had no relevant conflicts of interest. Dr. Ma reported that he had no relevant conflicts of interest.

In fact, of the 68 patients enrolled in the first year, 44% did so through the website, including some from as far away as Australia, Norway, and Turkey. The patients ranged in age from 16 to 39 years at diagnosis (median, 35 years), and 52% were female. They tended to be never-smokers, Dr. Gitlitz reported.

Fifty of the patients had stage IV adenocarcinoma at diagnosis. In this group, 76% were found to have known actionable driver alterations – most commonly in ALK (44%), EGFR (26%), or ROS1 (6%). The prevalence was higher among women than men (95% vs 74%), "so there might be a different genomic spectrum of females to males," she said.

Another 14% had other driver mutations identified, most of which also were targetable. Of note, this group included a young man found to have a previously unknown EGFR kinase domain duplication who had a response to afatinib (Cancer Discov. 2015 Aug. 18. doi: 10.1158/2159-8290.CD-15-0654). "So a new, actionable EGFR mutation has been discovered through looking at young-emergent lung cancer," noted Dr. Gitlitz.

"We hypothesized that this cohort may be a special population enriched for driver mutations, but we have far exceeded our statistical expectations, with the majority having an actionable mutation for which they are on targeted therapy, greater than 76%," she said. "A website allowing for virtual consenting so that patients can participate remotely and use social networking to share trial information is a novel, feasible way to conduct research across continents."

"We will continue accrual for at least another year, and my plea at this international congress is that we would very much love more international participation," she concluded. "Ultimately, we plan a follow-up study, Epidemiology of Young Lung Cancer, to build upon our unique web-based, patient-engaged trial design."

Dr. Levy, the discussant, commented, "This study should be lauded … for taking the additional steps to look at both somatic and germline mutations via whole-exome next-generation sequencing, and also pushing the envelope for those who have no matching mutation in evaluating relevant alterations via next-generation sequencing and cell-free DNA."

He also commended the novel web-based recruitment and consenting design, saying, "We have to put this in the context that only 5% of all lung cancer patients go on clinical trials. Anything we can do that's novel or outside the box, as done here, is a welcome change."

ALK translocations predominate

In the second study, Dr. Kosuke Tanaka of the department of thoracic oncology at Aichi Cancer Center Hospital in Nagoya, Japan, performed retrospective genomic screening of 67 consecutive patients who received a diagnosis of lung adenocarcinoma when aged 40 years or younger.

All patients had evaluation for EGFR and KRAS mutations, and most had evaluation for ALK translocations. Those negative for all three had additional testing.

The patients had a median age of 36 years, 60% were female, and 68% had stage IV disease, Dr. Tanaka reported. The majority, 61%, were former or current smokers.

Early-emerging adenocarcinoma has a high risk of driver oncogenes, Dr. Kosuke Tanaka said.

Overall, 82% of the patients had targetable alterations of driver oncogenes. The most common were ALK translocation (seen in 45%) and EGFR mutation (27%); KRAS mutation was uncommon (3%). Among 15 patients known to be negative for all of these, analyses identified HER2 mutations in three and RET mutations in two.

Driver mutations were more common among patients who had no or only a light smoking history, compared with peers who smoked (89% vs. 72%, $P = .069$). ALK translocation was more common in patients with stage IV disease (58% vs. 18%, $P = .002$).

"Early-emerging adenocarcinoma has a very high possibility of having some targetable driver oncogenes," Dr. Tanaka concluded. "Among younger populations, examination of all known oncogenes, including minor ones, is strongly recommended."

Continued on following page

Continued from previous page

Data finger genes involved in cell adhesion

In the third study, investigators performed genomic analysis in 20 patients from the Cleveland Clinic who underwent surgery for non–small-cell lung cancer (NSCLC) that was diagnosed at age 45 years or younger.

Genes involved in cell adhesion and EMT showed a sevenfold enrichment in mutation frequency.

DR. MA

Overall, 60% were women and 65% had smoked at some time, reported lead author Dr. Patrick C. Ma of the Mary Babb Randolph Cancer Center at West Virginia University, Morgantown, and the Sun Yat-sen University Cancer Center's State Key Laboratory of Oncology in South China and the Collaborative Innovation Center for Cancer Medicine, Guangzhou, China.

Some 55% of patients had adenocarcinomas, and 20% had stage IV disease. Of note, 25% had a history of some other type of cancer and 60% had a first-degree relative with a cancer diagnosis.

The somatic mutation rate was much higher in ever-smokers than never-smokers (3.47 vs. 0.76 per megabase). The former value "is a relatively high mutational burden, standing shoulder to shoulder with melanoma and bladder cancer," Dr. Ma said.

Mutations of key driver genes such as TP53 and KRAS were seen exclusively in smokers, but EGFR mutations were more often seen in never-smokers.

Genes involved in cell adhesion and epithelial-mesenchymal transition (EMT) showed a sevenfold enrichment in mutation frequency in the cohort, compared with that seen in the lung cancer data set of the Cancer Genome Atlas.

Dr. Gitlitz disclosed that she is on the speakers bureaus of Genentech and Eli Lilly. Dr. Tanaka and Dr. Ma disclosed that they had no relevant conflicts of interest.

VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: Three cohort studies involving patients less than 45 years old with adenocarcinoma of the lung found that 82% (76% stage IV) had genetic mutations that could alter treatment plans. ALK, EGFR, KRAS, and ROS1 are just a few of the mutations tested for. Some have targeted therapy available, and molecular testing is crucial and should be performed on all patients diagnosed with adenocarcinoma. Individualized treatment plans can have significant effects on patient outcomes. Interestingly, the majority of the patients were female, and a large number had a smoking history. This emphasizes the importance of preventive measures. At every office visit, asking about smoking history and offering tobacco cessation therapies to all patients who continue to smoke are vital.

Surgery, dose-escalated CRT yield similar outcomes

BY JENNIFER SHEPPHIRD
Frontline Medical News

After induction chemotherapy and concurrent chemoradiotherapy, patients with non–small cell lung cancer (NSCLC) who underwent surgery versus dose-escalated chemoradiotherapy had similar 5-year overall survival rates.

With a median follow-up of 78 months, the 5-year overall survival for the surgery arm was 44% compared with 40% for the chemoradiotherapy arm, and progression-free survival (PFS) rates were 32% vs. 35%, respectively. In addition, the study showed no significant improvement for the surgery group in median overall survival or median PFS.

Although the results did not demonstrate a benefit for surgery versus chemoradiotherapy, the 5-year overall survival data for all randomly

assigned patients, "are among the best reported so far from prospective trials with definitive chemoradiotherapy," wrote Dr. Wilfried Eberhardt, of the department of medical oncology, University Hospital Essen, Germany, and colleagues.

"Both trimodality treatment that includes surgery and bimodality treatment without surgery but with a definitive chemoradiotherapy boost lead to excellent long-term [overall survival] and PFS," the researchers wrote (J Clin Oncol 2015 Oct 26. doi:10.1200/JCO.2015.62.6812).

The multicenter phase III trial enrolled 246 patients with NSCLC stage IIIA-UICC6 (n = 75) or IIIB-UICC6 (n = 171) from 2004 to 2013. Overall, 161 patients completed induction therapy with three cycles of cisplatin and paclitaxel and concurrent chemoradiotherapy with 45 Gy, hyperfractionated-accelerated radiotherapy.

Patients who had complete, partial, or minor responses after the third cycle were assigned to surgery (n = 81) or chemoradiotherapy (n = 80).

Dr. Eberhardt reported having financial relationships with Eli Lilly, Boehringer Ingelheim, Pfizer, Novartis, Roche, and several other pharmaceutical companies.

Several of his coauthors reported ties to industry sources.

FDA approves pembrolizumab for advanced NSCLC

BY LAURA NIKOLAIDES
Frontline Medical News

The Food and Drug Administration has granted accelerated approval for pembrolizumab to treat patients with metastatic non–small cell lung cancer (NSCLC) who have disease that has progressed after other treatments and tumors that express PD-L1.

FDA NEWS

The anti–PD-L1 drug is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test.

Pembrolizumab was approved to treat patients with advanced melanoma in 2014. The effectiveness of the immunotherapy for treating advanced NSCLC was demonstrated among 61 patients enrolled within a larger multicenter, open-label,

BRIEF SUMMARY

ANORO® ELLIPTA®
(umeclidinium and vilanterol inhalation powder)
FOR ORAL INHALATION USE
The following is a brief summary only; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

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

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

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*

The anti–PD-L1 drug is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test.

multipart study, according to a statement issued by the FDA. These patients had advanced NSCLC that progressed following platinum-based chemotherapy or, if appropriate, targeted therapy for certain genetic mutations (ALK or EGFR), and they each had PD-L1–positive tumors based on the results of the 22C3 pharmDx diagnostic test.

The overall response rate was 41%, and the effect lasted between 2.1 and 9.1 months, the FDA said.

The most common side effects in 550 patients with advanced NSCLC included fatigue, decreased appetite, dyspnea, and cough. Severe immune-mediated side effects occurred involving the lungs, colon, and hormone-producing glands.

Pembrolizumab is marketed as Keytruda by Merck & Co., and the PD-L1 IHC 22C3 pharmDx diagnostic test is marketed by Dako North America Inc.

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On Twitter @NikolaidesLaura

• Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
• Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

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

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

Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

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

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

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

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

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

ANORO ELLIPTA: It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be

Hunger hormone mimic anamorelin treats cachexia

BY NEIL OSTERWEIL
Frontline Medical News

DENVER – Anamorelin, an investigational compound that mimics the action of the so-called "hunger hormone" ghrelin, was effective at helping patients with cachexia gain weight, but fell short when it came to improving hand-grip strength, results of two clinical trials showed.

Among patients with advanced non–small cell lung cancer (NSCLC) and cachexia enrolled in two randomized trials, those who took anamorelin daily over 12 weeks gained about 1 kg of lean body mass, compared with patients on placebo, who had further losses of lean body mass.

"Weight loss and loss of appetite are dominant symptoms in lung cancer patients, especially advanced lung cancer patients. About 70% experience this problem, and it's something we hear in the clinic every day, said Dr. Philip Bonomi from Rush University Medical Center in Chicago.

He discussed the ROMANA 1 and ROMANA 2 trials at a briefing at a world conference on lung cancer sponsored by the International Association for the Study of Lung Cancer.

Weight loss and loss of appetite are dominant symptoms; about 70% experience this problem.

DR. BONOMI

Cachexia, defined as a loss of 5% or more of body weight over 6 months or a body mass index below 20 kg/m^2, is associated with poor clinical outcomes, including worse functional status, decreased quality of life, and shorter survival.

Anamorelin is a selective ghrelin receptor agonist that mimics the hunger-inducing and anabolic effects of the natural hormone.

In the ROMANA 1 and ROMANA 2 trials, 979 patients with unresectable stage III or IV NSCLC and cachexia were randomly assigned on a 2:1 basis to anamorelin 100 mg/day or placebo for 12 weeks. For the coprimary endpoint of change in lean body mass, patients assigned to anamorelin in ROMANA 1 (323 patients) had a median gain of 1.1 kg over 12 weeks, compared with a loss of 0.44 kg among 161 patients who received placebo (*P* less than .001)

In ROMANA 2, the 330 patients assigned to anamorelin gained a median of 0.75 kg, while the 165 assigned to placebo lost a median of 0.96 kg (*P* less than .001). But for the other coprimary endpoint of improvement in hand-grip strength, there were no significant between-group differences.

For the secondary endpoint of change in anorexia/cachexia in the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire, patients who received anamorelin in each trial had significantly greater mean change from baseline in scores (4.12 vs. 1.92 for placebo in ROMANA 1; *P* = .0004: and 3.48 vs. 1.34 in ROMANA 2; *P* = .0016).

Over 40% who ask for a prescription drug get it

BY RICHARD FRANKI
Frontline Medical News

About 28% of patients surveyed say that they have talked to a physician about a prescription drug they saw advertised, and 44% of those patients report that they were given the drug they asked about, according to a recent Kaiser Family Foundation Health Tracking Poll.

About 54% say that their physicians recommended behavior or lifestyle changes after being asked about a drug the patient had seen advertised, while 49% of patients say that the physician recommended a different prescription drug and 39% say that the physician recommended an over-the-counter drug, Kaiser reported.

About 28% of patients surveyed say that they have talked to a physician about a prescription drug they saw advertised.

The results were similar to those seen in a Health Tracking Poll conducted in March of 2008, when 32% of patients had talked with their physicians about a drug they had seen advertised. Of those patients, 57% had physicians who recommended lifestyle or behavior changes, 54% recommended a different prescription drug, 44% recommended the drug the patient asked about, and 30% recommended an OTC drug.

The 2015 poll was conducted by phone among a nationally representative sample of 1,203 adults living in the United States.

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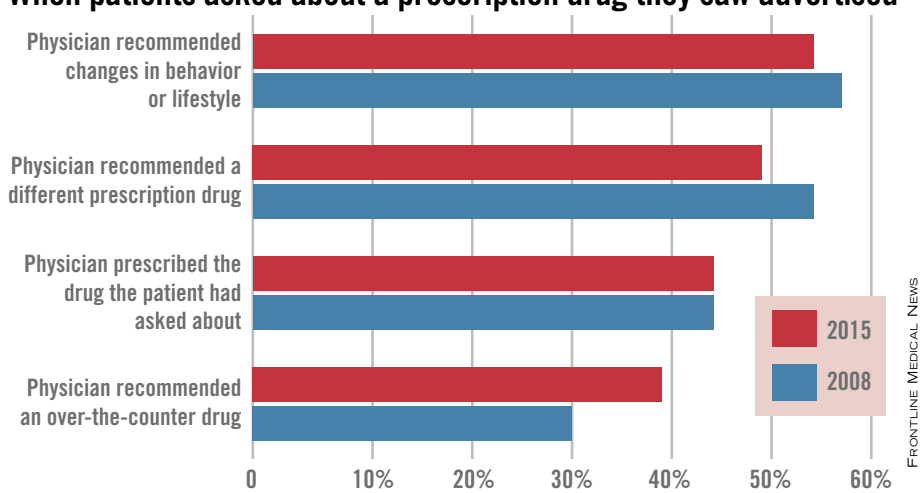
When patients asked about a prescription drug they saw advertised



Note: The poll was conducted Oct. 14-20, 2015, among 1,203 adults.

Source: Kaiser Family Foundation Health Tracking Poll

VIEW ON THE NEWS

Dr. Michael E. Nelson, FCCP, comments: This information should make one pause and wonder who is the captain of the ship. The American Medical Assso-ciation recently called for a ban on direct-to-consumer advertising from prescription drug and medical device companies. A recent market survey by Kantar Media reported that $4.5 billion was spent on drug advertising last year.

Obviously, drug advertising is effective. Dr. Benjamin Rush (1746-1813) provided advice that should be heeded today: "Do not condemn, or oppose unnecessarily, the simple prescriptions of your patients. Yield to them in matters of little consequence but maintain an inflexible authority over matters that are essential to life."

Today, this might include prescription drugs and medical devices.

CMS delays Stage 3 meaningful use until 2018

BY GREGORY TWACHTMAN
Frontline Medical News

Doctors will have 1 more year – until Jan. 1, 2018 – to comply with Stage 3 meaningful use requirements for electronic health records (EHRs), the Centers for Medicare & Medicaid Services announced.

In its long-awaited final rule, CMS also announced simplifications to the program designed to align meaningful use with other incentive programs and shift the overall focus of the programs to make them tools for improving overall health.

The announced changes "will ease the reporting burden for providers, increase simplicity and flexibility, support interoperability and information exchange, and improve patient outcomes," CMS Acting Principal Deputy Administrator and Chief Medical Officer Patrick Conway noted during a conference call with the media.

The final rule reduces the number of objectives from about 20 to 8 to allow doctors to find the measures that are most relevant to their practice. Measures also are better aligned, so that a single measure can allow providers to earn credit across multiple incentive programs.

CMS also explained in a separate fact sheet that it was removing many of the "check box" process measures and enhancing the focus on aspects of patient care, such as clinical decision support, e-prescribing, and information exchange.

The agency also finalized a 90-day reporting period in 2015 for all providers currently active in the meaningful use program. Given that the rule was finalized with fewer than 90 days left in the year, Dr. Conway provided additional clarity regarding the flexibility physicians will have to meet those requirements.

Those using an electronic health record on Oct. 1, 2015, "actually will not report until the end of February, and if we need to extend that time frame, we would look at that at the end of February 2016," he said. "So, they still have almost 5 months before the reporting actually occurs."

Dr. Conway added that even if a provider launched an EHR system after Oct. 1, "the thresholds for the program are not 100%. So, even if they were to deploy it tomorrow [and] use it successfully through the end of the year, they could then report that performance in 2016 and avoid a penalty."

Providers also can use the exemption process if there have been implementation issues, which CMS reviews on a case-by-case basis.

Stage 2 concerns linger

There was concern that the changes did not go far enough, particularly as they relate to modifications of Stage 2 meaningful use.

"Many of the requirements for Stage 2 proved unattainable," American College of Cardiology President Kim Allan Williams Sr. said in a statement. "Large numbers of providers either haven't met them or, after trying and failing, have given up. That is why it is vital that CMS consider participation data from the current stage to see what is working and what isn't before outlining an upcoming stage."

By 2018, all providers will have to meet Stage 3 meaningful use requirements, because the earlier stages will no longer be available to help new entrants transition into the program. However, if a provider chooses to adopt the 2018 requirements a year early, they will have only a 90-day reporting requirement.

What about MACRA?

Even with the extended time line, CMS is drawing criticism for progressing with Stage 3.

"We still have some concerns about how the program is going," Ms. Laura C. Wooster, vice president of public policy at the American Osteopathic Association, said in an interview. One is the current meaningful use time line's intersection with the start of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) reforms, which will replace the Medicare Sustainable Growth Rate payment system.

"Stage 3 begins voluntarily in 2017 and then is required for all physicians in 2018. MACRA begins in 2019, and electronic health record reporting will still be part of the Merit-Based Incentive Payment System."

She expressed concern that physicians are going to have to make changes for Stage 3 meaningful use in 2018, only to have to make more changes for MACRA a year later.

VIEW ON THE NEWS

Dr. Michael E. Nelson, FCCP, comments: While any news of a delay in the burdensome "Meaningful Use" program is welcome, more welcome would be for CMS to mandate that software and hardware vendors ensure interoperability. In addition, there should be seamless collection of data that would verify meaningful use without having to mine it from one's system. Even more important would be the identification of the parts of the program that actually result in a positive effect in patient outcomes. Until that time, the program will only be "meaningless" for patients and a potential way for CMS to cut costs by penalizing physicians' incomes.

The American Medical Association expressed similar concerns.

"We hope the decision by CMS to leave Stage 3 open to additional comment will allow for further improvements in the program and promote technological innovation that supports patient care," AMA President Steven Stack said in a statement.

Given the changes that will come as a result of MACRA, CMS is taking comments on the final rule to help inform future policy on how it and MACRA will align.

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UnitedHealth warns it may exit marketplace exchanges

BY JULIE APPLEBY
Kaiser Health News

UnitedHealthGroup has laid out a litany of reasons as to why it might stop selling individual health insurance through federal and state markets in 2017 – a move some see as an effort to compel the Obama administration to ease regulations and make good on promised payments.

Those problems, including low participation by healthy people, have led to financial losses, according to UnitedHealth. If not addressed, similar issues could affect other insurers, causing more to exit the market in the coming years, some Wall Street analysts and policy experts said.

The insurer said it would cut its earnings forecast and projected hundreds of millions in losses stemming from the policies it sells through the health law's marketplaces.

Stephen Hemsley, UnitedHealth chief executive officer, said too many healthy people dropped coverage and noted slower than expected enrollment. A major factor, he added, was far higher costs for those who signed up for 2015 coverage under special exemptions after the general open-enrollment period ended. Those exemptions included, for example, people who lost their insurance, moved, or suffered a hardship, such as an eviction or had their utilities turned off. United said it did not see a similar increase in costs for people who bought policies from private brokers or websites instead of the government marketplaces after open enrollment, suggesting the reason was partly that the company's eligibility assessments were more thorough.

The firm did not say it would halt sales in 2017 but warned that it would strongly consider doing so based on what happens in the next few months.

While seen as a serious challenge to the health care law, United's decision alone doesn't mark the death knell for the exchanges. In remarks to analysts and press reports, Aetna and Kaiser Permanente re-affirmed their commitment to selling through the marketplaces. But insurers, including Humana, Aetna, and some of the large Blue Cross Blue Shield plans, were losing money or barely breaking even on their marketplace business, according to earnings reports.

"If there are no changes, all the large publicly traded companies will end up leaving," said Ana Gupte, analyst with Leerink Partners. "But I would be very surprised if [the Department of Health & Human Services] doesn't do something to accommodate their issues."

Those options would be limited to what the agency could do without congressional action, many analysts said. Still, that could include relaxing some regulations or reconsidering some of the exemptions that allow people to sign up after the open-enrollment period.

Former insurance executive and consultant Robert Laszewski said the administration needs to relax the rules to give insurers more flexibility to design plans that would attract healthier people. He said the costs – including deductibles and premiums – were too high for many people, particularly those with few medical needs.

Considering treatment options for your pulmonary arterial hypertension (PAH) patients?

REVATIO® (sildenafil)— is now available as an oral suspension treatment for PAH

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No dose adjustment required for renal impaired.

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

Indication

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

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

Consider REVATIO oral suspension for your appropriate PAH patients.
To learn more about REVATIO, please visit REVATIOHCP.com.

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

Revatio® sildenafil
20 mg tablets

RVU751722-02

June 2015

Revatio®
sildenafil
20 mg tablets

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

INDICATION AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

Rx only Rev. June 2015

Higher spending, fewer malpractice claims

BY ALICIA GALLEGOS
Frontline Medical News

Greater than average spending was associated with reduced risk of incurring a malpractice claim across all physician specialties in a study of almost 25,000 doctors published Nov. 4 in the BMJ. The finding is consistent with widespread beliefs that higher resource use – sometimes defined as defensive medicine – limits the risk of litigation.

Dr. Anupam B. Jena of Harvard Medical School, Boston, and colleagues compared data from the Florida Agency for Health Care Administration on all acute care hospital discharges from 2000 to 2009 with data from the Florida Office of Insurance Regulation on all closed malpractice claims against Florida physicians during the same period. The data included 24,637 physicians (pediatricians, family physicians, general surgeons, obstetrician-gynecologists, and some subspecialists), more than 18 million hospital admissions, and 4,342 malpractice claims (BMJ 2015;351:h5516. doi: 10.1136/bmj.h5516). They looked at total hospital charges associated with patients treated by a given physician in a given year, averaged across all patients treated by that physician in that year, and adjusted for patient personal and clinical characteristics.

Across all specialties, higher average spending per year was associated with a lower probability of an alleged malpractice incident in the subsequent year. For internists, mean risk-adjusted spending per physician ranged from $19,725 for each hospital admission in the bottom fifth of physician years to $39,379 in the top fifth. The probability for an alleged malpractice claim ranged from 1.5% in the bottom spending fifth to 0.3% in the top spending fifth. Similarly, for ob.gyns., the probability of experiencing an alleged malpractice incident ranged from 1.9% in the bottom fifth of spending to 0.4% in the top fifth. Ob.gyns. on the low end of resource utilization spent a risk-adjusted mean of $8,653, while ob.gyns. on the high end spent $18,162.

Dr. Jena and colleagues also studied more than 1.5 million deliveries performed by 1,625 obstetricians; 15% were cesarean deliveries. In total, 496 malpractice claims were filed against these obstetricians. Ob.gyns. with higher cesarean rates per year were less likely to face a malpractice claim. The probability of being sued ranged from 5.7% in the bottom fifth of cesarean delivery rates to 2.7% in the top fifth.

Higher average spending per year was associated with a lower probability of an alleged malpractice incident in the subsequent year.

Authors note that if higher spending is motivated by concerns about malpractice, then the spending would be considered "defensively motivated. However, that spending may not be wasteful if it is associated with fewer errors and therefore lower malpractice claims. More study is needed to compare the costs of additional resource use and the value of reduced errors to learn whether such defensively motivated care is socially wasteful or reflects socially beneficial deterrence."

The study was supported by the National Institutes of Health.

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On Twitter @legal_med

VIEW ON THE NEWS

Understanding defensive medicine

It may be tempting for doctors to view the results of the study by Dr. Jena and colleagues as a means to justify additional tests and procedures to mitigate the risk of a malpractice claim. We would suggest that they should view the study results as a contribution to our understanding of the risk of such claims. We need to better understand defensive medicine, how to define it, how to measure it, and how its practice impacts patients and doctors.

Dr. Tara F. Bishop and Dr. Michael Pesko are with the department of health care policy and research at Weill Cornell Medical College in New York. Their comments were taken from an editorial accompanying Dr. Jena's study (BMJ 2015;351:h5786. doi: 10.1136/bmj.h5786).

CHEST announces Dr. Barbara Phillips as its 78th President

The American College of Chest Physicians (CHEST) has announced Dr. Barbara Phillips as its new President, effective November 1. At CHEST 2015 in Montréal, the appointments of Dr. Gerard Silvestri as President-Elect and Dr. John Studdard as President-Designate were confirmed, and Dr. Curtis Sessler, who completed his term as President and became Immediate Past President of CHEST was honored.

Barbara Phillips, MD, MSPH, FCCP, is a Professor of Pulmonary, Critical Care, and Sleep Medicine in the Department of Internal Medicine, and Medical Director of the Sleep Laboratory at the University of Kentucky College of Medicine. She is board-certified in internal medicine, pulmonary medicine, and sleep medicine. After joining CHEST as an affiliate member in 1982, Dr. Phillips advanced to Fellow in 1983. She became a member of the Sleep Medicine NetWork and CHEST Governor of Kentucky. She has chaired the Sleep Institute and is Editor of *CHEST SEEK Sleep Medicine* (Second, Third, and Fourth Editions). Dr. Phillips also served for 8 years as a Regent-at-Large for the American College of Chest Physicians. Besides her work with CHEST, Dr. Phillips chaired the National Sleep Foundation and has served on the boards of the American Lung Association, the American Academy of Sleep Medicine, and the American Board of Sleep Medicine. Dr. Phillips received a Sleep Academic Award from the National Institutes of Health and was presented with the College Medalist Award at CHEST 2013. Dr. Phillips' research interests include the effects of sleep apnea on performance and outcomes, genetic risk factors for sleep apnea, nonpharmacologic treatment of sleep apnea, and sleep in aging.


DR. PHILLIPS

Gerard Silvestri, MD, FCCP, is the Hillenbrand Professor of Thoracic Oncology and Vice-Chair of Medicine for Faculty Development at the Medical University of South Carolina. He completed his fellowship training in pulmonary and critical care at Dartmouth. He has an advanced degree in the evaluative clinical sciences, also from Dartmouth. He is a lung cancer and interventional pulmonologist with an interest in health services research, lung cancer screening, nodule evaluation and management, and staging of lung cancer. After becoming a Fellow of the American College of Chest Physicians in 1998, Dr. Silvestri became active with the NetWorks, serving on the Steering Committees of the Thoracic Oncology and the Interventional Chest/Diagnostic Procedures NetWorks, eventually chairing the Thoracic Oncology NetWork. Dr. Silvestri has also served on the Nominating Committee, the CHEST Scientific Program Committee, the CHEST Foundation Development Committee, as Treasurer and Trustee on the foundation's Board of Trustees, and as a Regent-at-Large for the American College of Chest Physicians for 3 years. At CHEST 2012, Dr. Silvestri was awarded the Pasquale Ciaglia Memorial Lecture in Interventional Medicine, and at CHEST 2014, he received the Edward C. Rosenow III, MD, Master FCCP/Master Teacher Honor Lecture. Dr. Silvestri has authored more than 200 scientific articles, book chapters, and editorials, and he currently serves on the editorial board of the journal *CHEST*.


DR. SILVESTRI

John Studdard, MD, FCCP, is a pulmonary and critical care physician in private practice with Jackson Pulmonary Associates in Jackson, Mississippi. Dr. Studdard completed his fellowship training at the Mayo Graduate School of Medicine. He has served in numerous CHEST leadership roles, including President and Chair of the CHEST Foundation, the philanthropic arm of CHEST; chair of the Government Relations Committee; member of the Marketing Committee; and Ex Officio member of the Diversity Committee, Scientific Program Committee, and Financial Oversight Committee. Dr. Studdard's dedication to reducing the number of patients he treats for tobacco-related diseases, and his leadership qualities led him to serve as representative for CHEST in the negotiations with the tobacco industry leading to the Attorneys General Master Settlement Agreement of 1998. More recently, in his roles with the CHEST Foundation, Dr. Studdard served as a vice chair of the Beyond Our Walls capital campaign, the CHEST Foundation Nominating Committee, and several foundation work groups.


DR. STUDDARD

Curtis N. Sessler MD, FCCP, is the Orhan Muren Distinguished Professor of Medicine at Virginia Commonwealth University (VCU) Health System in the Division of Pulmonary and Critical Care Medicine, where he is Director of the Center for Adult Critical Care and Medical Director of Critical Care and the Medical Respiratory ICU. Dr. Sessler is an enthusiastic clinician and educator who has received teaching awards at VCU, including the School of Medicine Educational Innovation Award. His research interests include ICU sedation, mechanical ventilation, and infection prevention, authoring more than 300 articles, book chapters, books, and abstracts. He has served on a variety of multisociety task forces addressing research, training competency, workforce shortage, and ICU burnout. He is Past President of the Virginia Thoracic Society and has served as Chair of the Pulmonary and Allergy Drug Advisory Committee of the US FDA. An active member of CHEST, he has served on the Board of Regents and as Chair of the Critical Care Section, Chair of the Council of Sections, Chair of the Critical Care Institute, Program Chair for the 2003 CHEST annual meeting, and an Ex Officio member of the CHEST Foundation Board of Trustees. He received the Roger C. Bone Memorial Lecture award in 2010. He is a member of the editorial board of *CHEST*, Editor in Chief of *CHEST SEEK Critical Care Medicine*, and is co-section editor for *Contemporary Reviews in Critical Care Medicine* (in *CHEST*).


DR. SESSLER

From the EVP/CEO: A Time to Look Back...and Forward

BY PAUL A. MARKOWSKI, CAE

It's December—the end of the calendar year and a time of reflection. When I look back on the goals we set for CHEST in 2015, I'm enthusiastic by what I see. We concentrated our efforts around the five main goals from our strategic plan to focus our work. There are many noteworthy accomplishments in each, but I'll highlight just a few.

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

We held a very successful annual meeting in Montréal with more than 7,000 total attendees. Throughout the year, we hosted 19 live learning simulation courses in our Innovation, Simulation, and Training Center, reaching over 900 learners. With a full line of courses scheduled for 2016, we're on track to continue providing quality education next year. People have already begun registering. Check out the calendar at chestnet.org/live-learning.

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

We released eight guidelines and consensus statements in 2015. (Visit journal.publications.chestnet.org/ss/guidelines.aspx for the complete list.) And, following our model to publish updates to topics as new evidence is evaluated, we released seven chapter updates to *Diagnosis and Management of Cough: Evidence-Based Clinical Practice Guidelines*.

MR. MARKOWSKI

Beginning January 2016, Elsevier, a world-leading provider of scientific products and services, will publish the journal *CHEST*, allowing us to deliver research to a larger audience and attract higher profile clinical research from around the world. I'm looking forward to seeing the impact of this new partnership.

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

We continue to host international education events around the world. In 2015, we offered "Best of CHEST" courses in Argentina and Beijing, a board review course in Turkey, simulation training at ERS in Amsterdam, four GAIN Europe courses, and sent CHEST faculty to international education events around the globe. Through disease awareness campaigns, the CHEST Foundation is reaching both patients and clinicians. This past year, the foundation promoted the importance of understanding COPD with both English and Spanish resources. In addition, the foundation teamed up with the Foundation for Sarcoidosis Research to launch "Sarcoidosis: Seek Answers. Inspire Results" and built awareness of lung health and lung cancer at major sporting events.

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

Our greatest asset is our membership. In May 2015, we updated our membership model to reflect emerging, team-based health-care models and opened membership to the entire chest medicine team. Team-based care is consistent with how health care is practiced, and it's the way to keep advancing patient care. Under our new model, we've gained 90% of US chest medicine fellows-in-training as members and have maintained a 90% membership retention rate.

Another asset, our journal *CHEST*, continues to be respected around the world. The *CHEST* Impact Factor rose again to 7.483. *CHEST* now ranks fifth of 54 journals in the Respiratory Medicine category and second of 27 in the Critical Care category. We continue using our social media outlets to serve as thought leaders in chest medicine. Over the past year, our Twitter followers grew to more than 10,000, and our Facebook fans topped 90,000. These numbers indicate those with interest in chest medicine are taking note and engaging with us.

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

I'm happy to report we had positive financial performances for CHEST, the CHEST Foundation, and CHEST Enterprises. We

Continued on following page

Societies join NAMDRC, CHEST on regulatory push; Respiratory Compromise Institute announces two projects

BY PHIL PORTE, NAMDRC EXECUTIVE DIRECTOR

NAMDRC and CHEST, along with the ATS and AARC, have submitted a series of recommendations to CMS to address an archaic, outdated Decision Memo from 2001 that stipulates that patients who receive home mechanical ventilation must have an artificial airway AND must succumb to death if the ventilator is removed. Even though the Decision Memo clearly signals that contractors have discretion in applying the rule, all the DME MACs have pushed forward with it in an attempt to control the growing use of noninvasive home mechanical ventilation, usually billed under HCPCS code E0464.

There are several moving pieces to this issue, and finding consensus was a challenge. While everyone agreed with the problems that have apparently triggered a review by the Office of the Inspector General, finding specific solutions to guide CMS took several months of collaborative work. Because CMS rejects all textbook definitions of mechanical ventilators, as well as FDA classifications, our approach was to explain that the presence of respiratory failure, by well accepted standards of care, includes use of a mechanical ventilator. Therefore, by defining "respiratory failure" and accepting the principle of mechanical ventilation as integral to treatment, a revised policy can now be created by CMS that reflects 2015 standards of care. Importantly, the societies also emphasized that chronic respiratory failure is not always a 24/7 medical phenomena; rather, it can occur nocturnally, intermittently, or progress into a 24/7 reality. In all of these examples, mechanical ventilation is warranted as long as respiratory failure is documented.


MR. PORTE

Tangential but integral to this issue is the barrier to bilevel devices, called respiratory-assist devices (RADs) by CMS. Because the rules for access to these devices are currently so problematic, physicians understandably make the shift to ordering NIV because that is the only option available for treatment for the patient. Therefore, integral to the recommendations related to home mechanical ventilation, the societies made a series of recommendations for improvement in RAD policies, as well. These recommendations are available on the NAMDRC website at www.namdrc.org.

Respiratory Compromise Institute: The Institute is currently pursuing two specific research endeavors, and the RFP for the large, meta-analysis is open for review at both the NAMDRC website www.namdrc.org and the Institute website, www.respiratorycompromise.org. The meta-analysis is a challenge because any literature search will reveal virtually nothing with the specific term "respiratory compromise" because of its newness. The challenge, therefore, is to conduct a broad search that encompasses all the key variables in the downward cascade from respiratory insufficiency to respiratory failure to respiratory arrest. That includes literature focusing on appropriate monitoring, treatment, therapies, outcomes, length of stay, etc. The Institute hopes to award the contract at the next meeting of its Clinical Advisory Committee, scheduled for March 1.

The second project focuses on Medicare data mining of hospital inpatient records. Beginning with a focus on records where respiratory failure is not present upon admission or within the first 24 hours following admission but present in the medical record, the data mining then expands outward to focus on the services provided, the length of stay, monitoring and therapies instituted, etc. A team of physician researchers are working with the data mining company to focus the research on specific ICD-9 codes (ICD-10 records will not appear in available data until late 2016/early 2017), CPT codes, and HCPCS codes. Hopefully, we will be able to begin with an initial 1 year snapshot, expanding to a multiyear longitudinal review to determine what trends, if any, exist. The data will then be sent to the physician researchers for analysis, and several papers will be generated as a result of those analyses.

While everyone agreed with the problems that have apparently triggered a review by the Office of the Inspector General, finding specific solutions to guide CMS took several months of collaborative work.

NAMDRC Annual Meeting: The NAMDRC Annual Educational Conference is scheduled for March 3-5, 2016, in Palm Springs, California, at the Omni Rancho Las Palmas Resort. The entire program and registration information are available on the NAMDRC website. **Registration for the conference is complimentary for new members who join NAMDRC after May 1, 2015, a value of $400.** Physicians who want to take advantage of this special offer must contact the NAMDRC Executive Office at 703/752-4359.

Continued from previous page

controlled key expenses throughout the year while achieving the highest-ever revenue on the CHEST Annual Meeting, attracting higher royalties and advertising revenue, and more to improve margins. Moving into 2016, we're financially stable because of our many valued assets.

CHEST accomplished much more during 2015, 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 Dr. Curt Sessler, FCCP, and it represents a culmination of the work of our leaders and members. CHEST has a proud history of dedicated members committed to advancing chest medicine and patient care.

Your contributions continue to make our organization a success, and I look forward to beginning another outstanding year in 2016.

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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Join a Leading Healthcare System in South Florida

Memorial Healthcare System is seeking a critical care physician, dedicated to night shifts, to join the critical care team. Successful candidates will demonstrate excellent clinical skills, a broad knowledge base in critical care and dedication to providing high quality, evidence-based care. Applicants must be BE/BC in critical care medicine. Previous experience in managing cardiac surgery patients is a plus but not a requirement. Physician(s) would have exposure to all aspects of the care of cardiac surgery patients, including mechanical devices, advanced heart failure patients, ECMO and transplant.

- 12-hour in-house shifts (7 pm–7 am); no responsibilities outside of in-house shifts
- Approximately 15 shifts per month (more if desired)
- Highly competitive salary differential for the nocturnist position

This is a full-time employed position within the multispecialty Memorial Physician Group. The position offers competitive benefits and a compensation package that is commensurate with training and experience. Professional malpractice and medical liability are covered under sovereign immunity.

About Memorial Healthcare System

Memorial Healthcare System is the third-largest public healthcare system in the United States. A national leader in quality care and patient satisfaction, Memorial has ranked 11 times since 2008 on nationally recognized lists of great places to work – in Modern Healthcare magazine, Florida Trend magazine and Becker's Hospital Review, just to name a few.

Memorial's facilities include its flagship, Memorial Regional Hospital, one of the largest in Florida; Memorial Regional Hospital South; Joe DiMaggio Children's Hospital, the only freestanding children's hospital in Broward and Palm Beach counties; Memorial Hospital West; Memorial Hospital Miramar; Memorial Hospital Pembroke; and Memorial Manor, a US News five-star-rated nursing home.

Memorial's work environment has been rated by employees and physicians alike as an open-door, inclusive culture that is committed to safety, transparency and, above all, outstanding service to patients and families.

memorialphysician.com

mhsemp039

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Chest Physician assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.

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PROFESSIONAL OPPORTUNITIES

MOUNT NITTANY HEALTH

Mount Nittany Health Pulmonologist Opportunity

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

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

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

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

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

WISCONSIN

MINISTRY HEALTH CARE

PULMONOLOGY /CRITICAL CARE OPPORTUNITY UPPER MIDWEST

Ministry Health Care is actively seeking a BC/BE Pulmonology/ Critical Care physician for a growing program at our 110-bed tertiary referral center in Weston, WI. This is an excellent opportunity to join a financially sound, physician-led organization, treat a broad scope of cases and play a significant role in the growth and success of our program.
• Call is 1:4
• 12+ ICU bed coverage with significant support from Hospitalist team, Anesthesia and E-ICU
• EBUS and EUS on site; would support any procedures you were interested in
• Strong, established referral network
• Digitally advanced facility consistently named one of the nation's "Most Wired" hospitals

You'll enjoy an excellent quality oflife in the Wausau/Weston area. The community is vibrant, safe and affordable and offers a full complement of metropolitan amenities complete with a downhill ski resort and a regional airport.

CONTACT: BRENDA CHAMBERS (715) 342-6579
mmgrecruitment@ministryhealth.org
www.ministryhealth.org

PRESBYTERIAN

PULMONARY / CRITICAL CARE PHYSICIAN

Presbyterian Healthcare Services (PHS) is seeking a Pulmonary/Critical Care trained physician to join our established group.

The physician will consist of 75% Critical Care and 25% Pulmonary.

PHS is a non-profit integrated health-care system that employs over 600 providers and includes a healthplan.

Benefits include medical, dental, vision, 403(b) plus match, CME, malpractice coverage (tail insurance included), competitive salary, sign on bonus and relocation assistance.

For more information, please contact:
Kelly Herrera
505-923-5662
kherrera@phs.org

Memorial Healthcare System

Critical Care Medicine Employment Opportunity

Join a Leading Healthcare System in South Florida

Memorial Healthcare System is seeking an Intensivist, dedicated to night shifts, to join the critical care team. Successful candidates will demonstrate excellent clinical skills, a broad knowledge base and dedication to providing high quality, evidence-based patient care. Applicants must be BE/BC in critical care medicine. Currently, the critical care program includes 28 full-time intensivists and six critical care ARNPs. The successful candidate will integrate into the existing operational structure, joining the team of eight dedicated full-time nocturnists.

• 12-hour in-house shifts (7 pm – 7 am); no responsibilities outside of in-house shifts
• Approximately 12 – 14 shifts per month (more if desired)
• Highly competitive salary differential for the nocturnist position

This is a full-time employed position within the multispecialty Memorial Physician Group. The position offers competitive benefits and a compensation package that is commensurate with training and experience. Professional malpractice and medical liability are covered under sovereign immunity.

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WANTED

Pulmonary/Critical Care Physician. Pulmonary Consultants P.C. located in Phoenix Arizona is a Six-Doctor Pulmonary/ Critical group seeking additional Physician due to practice growth. Diverse Hospital/office practice encompassing pulmonary, critical care medicine. Competitive salary/excellent benefits. Please send your CV via fax to 480 218-5706 or email to **aliciaga@PCofMesa.com** cell 480-466-2612

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Join us at CHEST World Congress 2016

April 15 – 17, 2016

Shanghai, China, will set a perfect backdrop for CHEST World Congress 2016. This unique, modern city will keep you moving and thinking, as we make sure you're informed on the latest updates and innovations in chest medicine.

CHEST, in collaboration with the Chinese Thoracic Society, will host this clinical event, featuring simulation-based education, case- and problem-based sessions, and evidence-based medicine for clinical respirologists, intensive care physicians, and specialists in sleep medicine.

On Friday, April 15, we'll offer postgraduate courses for an intensive learning experience. With additional registration, you can choose from the following topics:

- Advanced Mechanical Ventilation
- Clinical Pulmonary Medicine: A Case-Based Review
- Lung Cancer Education Program: A Multidisciplinary Team-Bbased Approach
- Thoracic Ultrasonography for the Pulmonary and Critical Care Consultant

We'll also enhance your skills in a hands-on clinical environment within our CHEST Simulation Center. Work with expert faculty to sharpen your skills and apply your knowledge using real equipment and simulators. With additional registration, you'll choose from the following topics:

- Ultrasonography for the Assessment of Cardiopulmonary Failure
- Bronchoscopy Procedures: EBUS-TBNA, Radial EBUS, and Endobronchial Blockers
- Mechanical Ventilation: Techniques to Optimize Care of the Critically Ill Patient
- Home-Based Sleep Apnea Testing
- Advanced Positive Airway Pressure Devices and Downloads
- Pulmonary Function Testing: A Case-Based, Hands-On, Guidelines-Driven Practicum

When you have some free time, be sure to explore Shanghai. You will be immersed in a wonderful Chinese culture, complete with flavorful, authentic food; exquisite, local architecture and gardens; and a native language with beautifully written characters.

Learn more and register today at chestworldcongress2016.org/.

This Month in *CHEST* Editor's Picks

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

Pulmonologists' Reported Use of Guidelines and Shared Decision-making in Evaluation of Pulmonary Nodules: A Qualitative Study. *By Dr. R. Soylemez Wiener et al.*

Primary Care Providers and a System Problem: A Qualitative Study of Clinicians Caring for Patients With Incidental Pulmonary Nodules. *By Dr. S. E. Golden et al.*

Management of Pulmonary Nodules by Community Pulmonologists: A Multicenter Observational Study. *By Dr. N. T. Tanner et al.*

Lung-Dominant Connective Tissue Disease: Clinical, Radiologic, and Histologic Features. *By Dr. N. Omote et al.*

The Use of a Fully Automated Automatic Adaptive Servoventilation Algorithm in the Acute and Long-term Treatment of Central Sleep Apnea. *By Dr. S. Javaheri et al.*

CLASSIFIEDS

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PROFESSIONAL OPPORTUNITIES

PQRS reporting: Do you understand your risk?

Do you understand your PQRS financial risk?

Successful reporting doesn't just satisfy 2015 reporting requirements but will also help you to avoid fast approaching PQRS and Value-Based Modifier penalties.

Value Modifier Penalty for 2015 PQRS Nonreporters

- Groups with 2-9 Eligible Professionals (EPs) and solo practitioners: automatic -2.0% of Medicare Physician Fee Schedule (MPFS) downward adjustment
- Groups with 10+ EPs: Automatic -4.0% of MPFS downward adjustment

Quality-Tiering for Successful 2015 PQRS Reporters

- Groups with 2-9 EPs and solo practitioners: Upward or neutral value modifier adjustment only based on quality-tiering (+0.0% to +2.0x of MPFS)
- Groups with 10+ EPs: Upward, neutral, or downward value modifier adjustment based on quality-tiering (up to -4.0% to or +4.0x of MPFS)
- Eligible professionals have several options to participate in annual PQRS reporting to avoid PQRS and VBM automatic penalties, including Measures Groups, Individual Measures, and Group Practice Reporting Option (GPRO) reporting for practices reporting through the GPRO.

Don't know where to begin? The *PQRSwizard*, a CHEST-affiliated product, can help.

The *PQRSwizard* is a fast, convenient, and cost-effective online tool to help collect and report quality measure data for the CMS PQRS incentive payment program.

Similar to online tax preparation software, the *PQRSwizard* helps guide you through a few easy steps to help rapidly collect, validate, report, and submit the results to CMS for payment.

❖❖❖❖

Learn more about PQRSwizard during a live demo on December 7 at 2:00 PM ET or on January 19 at 12:00 PM ET. CECity's PQRS experts will provide a guided tour of reporting using the PQRSwizard.

Register for the webinar by going to aquire.pqrswizard.com and clicking on "View webcasts."

Physician group size	Reporting year	Year of financial impact	Providers/groups that DON'T successfully report PQRS	Providers/groups that DO successfully report PQRS	
				PQRS	Value-based modifier adjustment
1-9	2015	2017	–4% (includes PQRS & VBM penalties)	No penalty	Neutral (0%) Upward (up to 2%)
10+	2015	2017	–6% (includes PQRS & VBM penalties)	No penalty	Negative (up to –4%) Neutral (0%) Upward (up to 4%)

Table 1. Summary of financial risk for the 2015 PQRS and VBM programs by practice size.

ABIM continues to offer MOC benefits for newly certified Internal Medicine physicians and fellows

BY DR. KEVIN M. CHAN, FCCP, DR. SERPIL C. ERZURUM, FCCP, AND DR. PETER H.S. SPORN, FCCP,
for the ABIM Pulmonary Disease Board

If you are an American Board of Internal Medicine (ABIM) Board-Certified physician newly certified in Internal Medicine, or a fellow who has completed an accredited fellowship year, ABIM recognizes the work that goes into those efforts with fee waivers, credits, and MOC points.

When ABIM updated its MOC program in January 2014, the program was designed to provide continuous learning opportunities for doctors and to help physicians, their colleagues, and their patients know that they were staying current in knowledge and practice throughout their careers.

Recognizing that those who have just completed training and those engaged in fellowship are just beginning their careers or are embedded in learning environments, ABIM wants to recognize this work as part of MOC and, thus, not burden these individuals with additional MOC costs or activities.

For those newly certified in Internal Medicine:

• Passing the Internal Medicine exam earns a waiver that covers the MOC program fee for the first calendar year after earning the certification.

• A diplomate will need to enroll in MOC but will not owe any fees through the subsequent calendar year ending December 31.

For those in ACGME-accredited fellowship training:

• For each year of successful ACGME-accredited fellowship training*, fellows earn:
  • a full year's MOC fee credit and
  • 20 MOC points (10 in medical knowledge and 10 in practice assessment)

• The MOC fee credit, earned at the end of the academic year, will be applied to the following calendar year as long as the fee credit is claimed by logging into the Physician Login, clicking on "Enroll in MOC," and applying the credit on the payment screen. The fee credit is earned when the fellowship program director submits an evaluation via ABIM's online clinical competence evaluation system (FasTrack®) following a year of successfully completed accredited fellowship training.

It's important to note that the fee credit is not automatically applied to a diplomate's account; rather, every year a credit is earned, it must be claimed when enrolling in MOC via the Physician Login.

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Passing the Internal Medicine exam earns a waiver that covers the MOC program fee for the first calendar year after earning the certification.

Fellows and recent graduates are encouraged to confirm with their program director that evaluations have been submitted (via (ABIM's online clinical competence evaluation system) by September after the training year was completed (Most often training years end in June, but this may vary for some academic years at some institutions).

Please note - fellows and recent graduates (within 5 years of completing an initial certification examination in Internal Medicine or a subspecialty) will remain certified whether or not they choose to enroll in MOC.

However, if they participate in an unaccredited training year either before or after accredited training years, they may need to pay an MOC program fee for that year in order to be reported as participating in MOC, since fee credits are granted for the calendar year after successful completion of accredited training years (most academic years end in June).

Unaccredited years may include:

• year(s) spent working as a hospitalist between residency and fellowship,

• research years that are unaccredited, and

• a year as a chief resident, usually occurring immediately following residency before starting fellowship.

However, as noted above, if fellows do not enroll in MOC and pay the MOC program fee for the calendar year after the unaccredited training year, **they will remain certified** as long as they are meeting all other programmatic requirements, but will be reported as not participating in MOC.

Fellows will be reported as participating in MOC as soon as they enroll in the MOC program by either paying the MOC program fee or claiming the fee credit earned through fellowship training.

Going forward, as they successfully complete accredited training years, fellows will receive the fee credit that can be applied to the MOC program fee due each subsequent calendar year.

*Fellowship years in ABIM subspecialties completed in 2014 and after are eligible if accredited by the Accreditation Council for Graduate Medical Education (ACGME), the Royal College of Physicians and Surgeons of Canada, or the Professional Corporation of Physicians of Quebec.

Currently, only accredited years are tracked by ABIM in its online clinical competence evaluation system, and, therefore, only the accredited years can be verified reliably across all programs for satisfactory completion.

If in doubt, fellows should contact their program directors to verify whether their training is accredited.

We encourage you to visit and subscribe to the Transforming ABIM blog (http://transforming.abim.blog) to learn more about ABIM's ongoing discussions regarding certification and MOC, as well as upcoming opportunities to provide input.

To learn more about your specific requirements and deadlines, or to check your certification status, log into www.abim.org to view your MOC Status Report.

We look forward to sharing updates as we work to ensure the relevancy of MOC to pulmonary disease physicians.

NEW - Earn CME AND MOC at CHEST live learning courses

Effective September 30, the American Board of Internal Medicine (ABIM) in collaboration with the Accreditation Council for Continuing Medical Education (ACCME) implemented a process for providers like CHEST to deliver educational activities that offer both MOC (Maintenance of Certification) points and CME (Continuing Medical Education) credits.

This will increase the number of MOC offerings available to CHEST members and minimize the time, effort, and resources needed for members to earn MOC and CME.

As a result of this development, live learning courses offered at the CHEST Innovation, Simulation, and Training Center are now eligible for Maintenance of Certification (MOC).

CHEST will submit your MOC points directly to the ABIM (minimum performance scores required).

MOC points will correspond to the number of *AMA PRA Category 1 Credits*™ offered and claimed for the course.

More About MOC (http://www.chestnet.org/Education/Advanced-Clinical-Training/MOC-PIMs)

Live Learning Courses (chestnet.org/live-learning)

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