Suicide is a concern in lung cancer patients

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – U.S. patients diagnosed with lung cancer have had the highest suicide rates among patients diagnosed with any of the other most common, non-skin cancers, and they also had a substantially higher suicide risk, compared with the general U.S. adult population, based on U.S. national data collected during 1973-2013.

Although U.S. lung cancer patients showed a “steep” decline in suicide rates starting in about 1985 that then accelerated beginning in the mid-1990s, as recently as 2010-2013 the rate was roughly twice as high in lung cancer patients when compared with the general U.S. adult population. The rate of lung cancer patients taking their lives was also significantly above the suicide rates among patients with breast, colorectal, or prostate cancer, Mohamed Rahouma, MD, reported at an international conference of the American Thoracic Society.

Dr. Rahouma speculated that the high suicide rate among lung cancer patients reflected the low progression-free survival rate often seen with the disease, especially several decades ago. He also hypothesized that the reductions in lung cancer–associated suicides that began some 30 years ago may be explained by the introduction

See Suicide • page 4
HELP PRESERVE MORE LUNG FUNCTION

Reduce lung function decline with Esbriet®

Clinical trials included patients with IPF with a range of clinical characteristics, demographics, and select comorbidities.1

BROAD PATIENT POPULATION

DEMONSTRATED EFFICACY

In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF.1–4

IPF = idiopathic pulmonary fibrosis.

*Baseline characteristics (including clinical characteristics, demographics, and select comorbidities) were well balanced across treatment groups, with 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624).1,2

1 The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624). In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide (%DLCO) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.2 In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DLCO ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DLCO ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.1 Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.2,3 Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).1,4 No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.2,4

1 In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).7

2 Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

3 The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.2

4 Dosage modifications may be necessary in some cases.

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. In some cases, 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 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 dosing reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.
NOW APPROVED
in Tablets

ESTABLISHED
SAFETY AND
TOLERABILITY

The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials.

COMMITTED
TO PATIENTS

Genentech offers a breadth of patient support and assistance services to help your patients with IPF.

WORLDWIDE
PATIENT
EXPERIENCE

More than 31,000 patients have taken pirfenidone worldwide.

Adverse reactions: The most common adverse reactions (≥10%) are 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 (e.g., 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.

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 (CLcr, 50–80 mL/min), moderate (CLcr, 30–50 mL/min), or severe (CLcr, 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 diseases 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.

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

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

Men, widowed had high rates

Suicide from page 1

of improved diagnostic methods such as lung CT scans, that led to earlier diagnoses and some improvements in mid-term prognosis. Earlier diagnosis has “given some hope” to lung cancer patients, said Dr. Rahouma, a cardiothoracic surgeon and researcher at Cornell University, New York, in an interview. However, he also stressed that identification of lung cancer patients at especially high suicide risk was important to allow “proper psychological assessment, support, and counseling to reduce [suicide] rates.” Lung cancer patients with the highest rates included men, widowed individuals, septuagenarians, and Asians, his analysis showed. Standardized mortality ratios (SMRs) for suicide of these highest-risk subgroups were near or exceeding 10 times higher than the suicide rates of comparable demographic groups among the general U.S. adult population, according to Dr. Rahouma and his associates.

The overall SMR for all lung cancer patients during the entire four decades

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ESBRIET 2403 mg/day (N = 623)</th>
<th>Placebo (N = 624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Rash</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>24%</td>
<td>15%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26%</td>
<td>19%</td>
</tr>
<tr>
<td>Headache</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastro-esophageal Reflux Disease</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Adverse reactions occurring in >5% to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (19% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), nausea (6% vs. 4%), dyspepsia (6% vs. 2%), orthostatic hypotension (5% vs. 4%).

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) by CYP1A2 with minor contributions from other CYP isoforms including CYP2C9, CYP3A, and CYP2D6. Strong CYP1A2 inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enacrin) is not recommended because it significantly increases exposure to ESBRIET (see Clinical Pharmacology section 12.3 in full Prescribing Information). Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during
studied, compared with the overall U.S. adult population, was 4. Even during the period 2005-2013, when suicide among lung cancer patients had fallen to its lowest level, the SMR for this group was still more than 2.

The investigators used data collected by the U.S. Surveillance Epidemiology and End Results (SEER) Program cancer database maintained by the National Cancer Institute. For suicide rates among the general U.S. population they used data from the National Vital Statistics Reports produced by the Centers for Disease Control and Prevention. The SEER database included entries for more than 3.6 million U.S. cancer patients during 1973-2013, of whom 6,611 patients had committed suicide, an overall SMR of 1.6.

When the researchers drilled down the SMRs for individual cancer types they found that, while the SMR for lung cancer patients throughout the period studied was just above 4, the SMRs for breast and colorectal cancer patients were both 1.4 and 1.2 for patients with prostate cancer. This analysis adjusted for patients’ age, sex, race, and year of diagnosis, Dr. Rahouma reported.

The time from diagnosis to suicide was also strikingly quicker among lung cancer patients, at an average of 8 months, compared with average delays from diagnosis to suicide of 40-60 months for patients with breast, colorectal, or prostate cancer. Dr. Rahouma’s time-trend analysis showed that the SMRs for these three other cancer types held more or less steady within the range of 1-2 throughout the 4 decades examined, and by 2010-2013 the three SMRs all were at or just above 1.

Lung cancer was the only malignancy in this group that showed a wide range in SMR over time, with the peak some 30-40 years ago. Among the lung cancer patient subgroups that showed the highest SMRs for suicide during the entire period studied, men had a SMR of 9, Asians had a SMR of nearly 14, those with a deceased spouse had a SMR for suicide of almost 12, and septuagenarians had a SMR of 12, said Dr. Rahouma. The impact of these risk factors was greatest during the first 8 months following lung cancer diagnosis. After 8 months, the strength of the risk factors diminished, with the SMRs within each risk category dropping by roughly half.

The highest-risk subgroups that the analysis identified should especially be referred for psychiatric support, Dr. Rahouma concluded. “These data will change our practice” at Cornell, he predicted.

Dr. Rahouma had no disclosures.

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ed findings of the same study. After multivariate adjustment, including controlling for change in body mass index over time, both mild and moderate OSA were significantly associated with increased odds for developing hypertension, compared with controls without OSA (odds ratios, 4.36 and 3.46, respectively).

The researchers found their test for an age interaction was also significant, indicating that younger adults with nonsevere OSA were at increased risk of hypertension, while those over 60 years of age were not.

“Given the stronger association of sleep apnea with metabolic abnormalities in this age group, emphasis should be placed on yearly monitoring of indices of metabolic symptoms and lifestyle interventions, such as weight control, healthy diet, regular exercise, and stress management.”

Moderate OSA was significantly associated with an almost threefold increased odds for developing diabetes after adjusting for a range of baseline and follow-up variables (OR, 2.78), but mild OSA was not associated with incident diabetes (OR, 0.47).

Both studies utilized data from the Penn State Adult Cohort, a random general population sample of 1,741 adults who underwent an overnight polysomnography sleep study and had a detailed medical history interview at baseline. Mild and moderate OSA were defined as an apnea hypopnea index from 5 to 14.9 and from 15 to 29.9, respectively. The presence of hypertension or diabetes at baseline and follow-up was defined by a self-report of receiving treatment for or having a physician diagnosis of either condition.

The age range of the studied population was wide (20-84 years), with a mean age of about 47 years. The incidence of diabetes was 10.2% at follow-up, while hypertension was found in 34.2% of patients. Dr. Vgontzas said the percentage of patients with hypertension was roughly what he had expected for this population.

“Our conclusion is that the younger a person is, the stronger is the need for detection and treatment of sleep apnea,” said Dr. Vgontzas.

The study was supported by National Institutes of Health grants. Dr. Vgontzas reported no conflicts of interest.

Moderate OSA ups diabetes risk

OSA from page 1

VIEW ON THE NEWS

David A. Schulman, MD, FCCP, comments: This study suggests that mild sleep apnea may increase the risk of incident hypertension, a finding that we have long suspected, but struggled to show in prior data sets. That noted, there are some oddities in the data that will require further investigation once the full manuscript is published, including the lack of a dose-response relationship between sleep apnea and hypertension (the odds ratio for moderate OSA and incident hypertension is lower than that for mild OSA), and the seemingly protective effect of mild OSA on the development of diabetes (though we do not know if this was statistically significant). Until we get a more comprehensive look at the numbers, it seems prudent to continue to advise patients with mild sleep apnea to seek treatment based upon the likelihood of symptomatic benefit, and not oversell the possible cardiovascular risks of untreated mild OSA.

IN THIS ISSUE

CHEST Physician is Online

CHEST Physician is available on the Web at chestphysician.org

Vera A. De Palo, MD, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.
Algorithm had moderate sensitivity

Septic shock from page 1

and a specificity of 98%, reported Dr. Giannini, a researcher in the Center for Evidence-Based Practice at the University of Pennsylvania in Philadelphia.

Analysis also showed a positive likelihood ratio of 13 for severe sepsis or septic shock actually occurring following an alert generated by the computer program, a level indicating a “very strong” ability to predict sepsis, she said.

Dr. Giannini and her associates developed the prediction program using a technique called “computational machine learning,” an alternative to standard logistic regression modeling that is better suited to analyzing large data sets and can better integrate outlier data points.

They took EHR data for all non-ICU, non-ED inpatients at three Philadelphia hospitals during a 3-year period during 2011-2014 and had the program focus particularly on EHR data gleaned from the nearly 1,000 patients who developed severe sepsis or septic shock during the 12 hours preceding the start of these sepsis events.

The analysis identified patients having developed severe sepsis or shock if they had a blood draw positive for infection at the same time as having a blood lactate level above 2.2 mmol/L or a systolic blood pressure below 90 mm Hg.

To create the algorithm, Dr. Giannini said, the machine-learning device compared the EHR entries for patients who developed severe sepsis or septic shock with EHR data from patients who did not, a process that involved hundreds of thousands of data points. This identified 587 individual types of relevant EHR data entries and ranked them from most important to least important. Important, novel determinants of impending severe sepsis identified this way included anion gap, blood urea nitrogen, and platelet count. The development process also confirmed an important role for many classic markers of septic shock, such as respiration rate, heart rate, and temperature.

The researchers designed the algorithm to have a moderate level of sensitivity to avoid “alert fatigue” from generating too many alarms for impending severe sepsis. Their goal was for clinicians to receive no more than about 10 alerts per day for each hospital.

“We are satisfied with the sensitivity. We felt it was better to have too few alerts rather than overwhelm clinicians. About 10 alerts a day is reasonable,” Dr. Giannini explained. During initial 2015 testing, the system generated a daily average of 11 alerts.

Development of this algorithm is tremendously important and exciting. It is an example of how researchers can use big data to predict patient outcomes and use that information to help deliver better patient care, noted Michelle N. Gong, MD, professor of medicine and chief of research in critical care at Albert Einstein College of Medicine and Montefiore Medical Center in New York, in an interview. The algorithm’s performance so far is laudable and extremely promising, and has great potential to help deliver better care to patients when they need it, but it requires further validation.

Dr. Gong noted that she had no relevant financial conflicts of interest regarding this study.

This project is extremely promising, noted Dr. Michelle N. Gong.

NIH releases COPD National Action Plan

BY KATIE WAGNER LENNON

WASHINGTON – The National Heart, Lung, and Blood Institute of the National Institutes of Health recently released its first COPD National Action Plan, a five-point initiative to reduce the burden of chronic obstructive pulmonary disease and increase research into prevention and treatment.

Some of the plan’s supporters described its evolution and why they thought its implementation was important at an international conference of the American Thoracic Society that occurred May 19-24.

Today, we are here to announce for the first time a COPD National Action Plan, which has been developed with input from the entire COPD community,” said James Kiley, PhD, director of the division of lung diseases at NHLBI, during a press conference on May 22, at the meeting. “It provides goals and objectives everyone in the nation affected by and interested in COPD can work toward to help reduce the burden of this disease. Each goal is designed to address a different aspect of the disease and the part of the community with the capacity to address it.”

The plan’s five goals are:

• Empower people with COPD, their families, and caregivers to recognize and reduce the burden of COPD.

• Improve the prevention, diagnosis, treatment, and management of COPD by increasing the quality of care delivered across the health care continuum.

• Collect, analyze, report, and disseminate COPD-related public health data that drive change and track progress.

• Increase and sustain research to better understand the prevention, pathogenesis, diagnosis, treatment, and management of COPD.

• Translate national policy, educational, and program recommendations into research and public health care actions.

“Chronic obstructive pulmonary disease is the third-leading cause of death in this country; it’s just behind heart disease and cancer,” Dr. Kiley noted. “What’s really disappointing and discouraging is it’s the only cause of death in this country where the numbers are not declining.”

COPD “got the attention of Congress a number of years ago,” he added. “They encouraged the National Institutes of Health to work with the community stakeholders and other federal agencies to develop a national action plan to respond to the growing burden of this disease.”

COPD’s stakeholder community, the federal government, and other partners worked together to develop a set of core goals that the National Action Plan would address, Dr. Kiley continued. “It was meant to obtain the broadest amount of input possible so that we could get it right from the start.”

Another of the plan’s advocates, MeiLan Han, MD, medical director of the women’s respiratory health program at the University of Michigan, Ann Arbor, illustrated the need to increase and sustain COPD research related to the disease.

“We face some serious barriers to being able to provide adequate care for patients,” said Dr. Han, who served as a panelist at the press conference. Those barriers include lack of access to providers who are knowledgeable about COPD, as well as lack of access to affordable and conveniently located pulmonary rehabilitation and education materials.

From a research standpoint, Dr. Han added, medicine still doesn’t know enough about the disease. “We certainly have good treatments, but we need better treatments,” she said.

The National Action Plan and information about how to get involved are available at copd.nih.gov.
Take a different path

*INDICATIONS

- Adempas (riociguat) tablets is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

† Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanooids. Studies establishing effectiveness included predominantly patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

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

IMPORTANT SAFETY INFORMATION

**WARNING: EMBRYO-FETAL TOXICITY**

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

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

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

CONTRAINDICATIONS

- Adempas is contraindicated in:
  - Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
  - Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
  - Concomitant administration with specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.
  - Patients with Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP).

WARNINGS AND PRECAUTIONS

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

- Exercise capacity, as measured by 6MWD in PAH and CTEPH
- WHO Functional Class in PAH and CTEPH
- Hemodynamics: PVR and NT-proBNP in PAH and CTEPH
- Delayed time to clinical worsening in PAH

Learn more or contact a representative at adempas-us.com

WARNINGS AND PRECAUTIONS (continued)

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program. Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

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

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

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

Warnings and Precautions (continued)

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

Most Common Adverse Reactions

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

For important risk and use information, please see the brief summary of the full Prescribing Information, including Boxed Warning, on the following pages.
ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

1 INDICATIONS AND USAGE
   1.1 Chronic-Thromboembolic Pulmonary Hypertension
   Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].
   1.2 Pulmonary Arterial Hypertension
   Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

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

3 ADVERSE REACTIONS
   3.1 Headache
   Headache was the most commonly reported treatment-emergent adverse reaction in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1) [see Clinical Trials Experience (14.1, 14.2)].

6.1 Clinical Trials Experience
   Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1).

5.3 Hypotension
   Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

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

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

6 ADVERSE REACTIONS
   The following serious adverse reactions are discussed elsewhere in the labeling:
   • Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
   • Hypotension [see Warnings and Precautions (5.3)]
   • Bleeding [see Warnings and Precautions (5.4)]

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

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2% for Adempas and 5.1% for placebo (pooled data).

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Adempas % (n=490)</th>
<th>Placebo % (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Dyspepsia and Gastritis</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

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

7 DRUG INTERACTIONS
   7.1 Pharmacodynamic Interactions with Adempas
   Nitrites: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension [see Contraindications (4.2) and Clinical Pharmacology (12.2)].

   PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadafinil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.

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

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7 DRUG INTERACTIONS
   7.1 Pharmacodynamic Interactions with Adempas
   Nitrites: Co-administration of Adempas with nitrate or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension [see Contraindications (4.2) and Clinical Pharmacology (12.2)].
7.2 Pharmacokinetic Interactions with Adempas
Smoking: Plasma concentrations in smokers are reduced by 50% to 60%
compared to nonsmokers. Based on pharmacokinetic modeling, for patients
who are smokers, doses higher than 2.5 mg three times a day may be
considered in order to match exposure seen in nonsmoking patients. Safety
and effectiveness of Adempas doses higher than 2.5 mg three times a day
have not been established. A dose reduction should be considered in
patients who stop smoking [see Dosage and Administration (2.4) and Clinical
Pharmacology (12.3)].

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

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

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category X
Risk Summary
Adempas may cause fetal harm when administered to a pregnant woman
and is contraindicated during pregnancy. Adempas was teratogenic and
embryotoxic in rats at doses with exposures to unbound drug that were
approximately 8 times and 2 times, respectively, the human exposure.
In rabbits, riociguat led to abortions at 4 times the human exposure and
total fertility toxicity with exposures approximately 13 times the human exposure.
If Adempas is used in pregnancy, or if the patient becomes pregnant while
taking this drug, apprise the patient of the potential hazard to the fetus [see
Boxed Warning and Contraindications (4.1)].

Animal Data
In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout
organogenesis, an increased rate of cardiac ventricular-septal defect was
observed at the highest dose tested. The highest dose produced evidence of
maternal toxicity (reduced body weight). Post-implantation loss was statistically
significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at
the lowest dose in which no adverse effects were observed is approximately
0.4 times that in humans at the maximally recommended human dose (MRHD) of
2.5 mg three times a day based on area under the time-concentration curve
(AUC) for unbound drug in rat and humans. Plasma exposure at the highest
dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD
while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in
humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an
increase in spontaneous abortions was observed starting at the mid-dose of
1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day.
Plasma exposures at these doses were 4 times and 13 times, respectively, the
human exposure at the MRHD.

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

8.4 Pediatric Use
Safety and effectiveness of Adempas in pediatric patients have not been established [see Nonclinical Toxicology (13.2)].

8.5 Geriatric Use
Of the total number of subjects in clinical studies of Adempas, 23% were 65
and over, and 6% were 75 and over [see Clinical Studies (14)]. No overall
differences in safety or effectiveness were observed between these subjects
and younger subjects, and other reported clinical experience has not identified
differences in responses between the elderly and younger patients, but greater
sensitivity of some older individuals cannot be ruled out.

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

8.6 Females and Males of Reproductive Potential
Pregnancy Testing: Female patients of reproductive potential must have a
negative pregnancy test prior to starting treatment with Adempas, monthly
during treatment, and one month after discontinuation of treatment with
Adempas. Advise patients to contact their healthcare provider if they become
pregnant or suspect they may be pregnant. Counsel patients on the risks to the
fetus [see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)].

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

8.7 Renal Impairment
Safety and efficacy have not been demonstrated in patients with creatinine
clearance <15 mL/min or on dialysis [see Clinical Pharmacology (12.3)].

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

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

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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

Adempas REMS Program
For female patients, Adempas is available only through a restricted program
called the Adempas REMS Program [see Warnings and Precautions (5.2)].
Male patients are not enrolled in the Adempas REMS Program.

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

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

Other Risks Associated with Adempas
• Inform patients of the contraindication of Adempas with nitrates or nitric
oxide donors or PDE-5 inhibitors.
• Advise patients about the potential risks/signs of hemoptysis and to report
any potential signs of hemoptysis to their physicians.
• Instruct patients on the dosing, titration, and maintenance of Adempas.
• Advise patients regarding activities that may impact the pharmacology of
Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and
smoking). Instruct patients to report all current medications and new
medications to their physician.
• Advise patients that antacids should not be taken within 1 hour of taking
Adempas.
• Inform patients that Adempas can cause dizziness, which can affect the
ability to drive and use machines [see Adverse Reactions (6.1)]. Advise
patients to be aware of how they react to Adempas before driving or
operating machinery, and if needed, consult their physician. Patients should
consult their physicians if dizziness gets worse with Adempas.

Manufactured for: Bayer Healthcare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

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6/19/17 12:52 PM
Noninvasive therapy cut COPD readmissions

BY ELI ZIMMERMAN
Frontline Medical News

WASHINGTON – The addition of noninvasive ventilation to home oxygen therapy regimens correlated with increased time to readmission or death among patients with exacerbated chronic obstructive pulmonary diseases (COPD), according to a study presented at an international conference of the American Thoracic Society.

Among 116 patients observed with COPD, the 57 patients given home oxygen and noninvasive ventilation reported an average time to readmission of 4.3 months, compared with 1.4 months among the 59 patients given only home oxygen, according to Patrick B. Murphy, PhD, of St. Thomas’s Hospital, London (JAMA. 2017 May 21. doi: 10.1001/jama.2017.4451), who presented this research on the same day it was published in JAMA.

Intervention patients also reported a decrease in annual COPD exacerbations, with an average 3.8 per year compared with 5.1 per year among patients in the control group.

In 2013, the reported readmission rate of patients with hypercapnia was one in five, according to Dr. Murphy and his coinvestigators.

Dr. Murphy said the findings are encouraging for patients with COPD suffering from exacerbations from the disease.

“Patients with established chronic respiratory failure secondary to COPD have poor outcomes with limited treatment options available,” the investigators noted. “The results of the current trial are reassuring, suggesting that home noninvasive ventilation added to home oxygen therapy in this population improved the overall clinical outcome without adding to the health burden of the patient.”

In this 12-month, phase III, multicenter, randomized clinical trial, the average age of the patients was 67 years, and the average body mass index was 21.6 mg/k2. The patients had an average partial pressure of carbon dioxide level of 59, indicating persistent hypercapnia.

The investigators gave those in the intervention group one of three noninvasive home ventilators – nasal, oronasal, or total face mask – to use for a minimum of 6 hours nightly. Patients in both groups received 15 hours of oxygen therapy daily.

Doctors gathered data from patients after 6 weeks, 3 months, 6 months, and 12 months. After 12 months, risk of readmission or death in the intervention group was 63.4%, while those in the oxygen-only group reported a risk of 80.4%. Despite a 17% risk reduction, a similar number of patients died during the experiment in both groups: five in the noninvasive intervention group and four in the control group, according to the investigators.

At the end of the trial, 16 patients (28%) in the intervention group and 19 (32%) in the control group died.

The researchers asserted that these deaths do not take away from the success of the treatment, as the focus of the study was to find a way to reduce readmissions, not necessarily mortality.

“The driver of the clinical improvement in the home oxygen therapy plus home noninvasive ventilation group was readmission avoidance with no significant difference in mortality,” they wrote. “This study has major clinical relevance because readmission avoidance is beneficial to the patient in terms of preservation of lung function and health-related quality of life, as well as providing a direct and indirect cost saving.”

The study was limited by the lack of a double-blind design; however, investigators said that a sham device may have made patients respiratory failure worse.

The researchers reported financial support from ResMed, Philips Respironics, and B&D Electromedical.

Noninvasive therapy cut COPD readmissions

Online pulmonary rehab improved walk test scores

BY ELI ZIMMERMAN
Frontline Medical News

WASHINGTON – An online pulmonary rehabilitation program for patients with chronic obstructive pulmonary disease (COPD) was not inferior to an in-person program, according to study findings presented at an international conference of the American Thoracic Society.

In a walking test conducted after all patients completed a 7-week program, participants in the online program, on average, increased their 6MWT (6-minute walking test) score by 23.8 m (P = .098) from baseline; this amount of improvement is much greater than the noninferiority threshold for this study. COPD assessment, hospital anxiety, respiratory function, and modified medical research council dyspnea scores of patients who participated in the online program were also not inferior to the scores of patients who participated in the in-person program.

If found to be a viable option, online options for COPD patients could be useful for treatment in those who would otherwise not have access to in-person rehabilitation sessions, said Tom Wilkinson, MD, PhD, of the University of Southhampton (England), in his presentation.

“The challenges for patients with COPD are quite real; there are factors which are limiting the access of treatments … in the way of geography of where our patients live,” said Dr. Wilkinson. “[Also] some patients may be housebound or have social anxiety but would benefit from using programs more regularly.”

The study’s 90 participants were assigned to participate either in an online program designed as an in-home guide for pulmonary rehabilitation or in pulmonary rehabilitation sessions at a local facility, after a baseline 6-minute walking test, according to Dr. Wilkinson.

The average age of patients participating in the face-to-face program was 71 years, while the average age for the online group was 69 years. Both groups were predominantly male and former smokers.

Investigators designed the online program to mimic face-to-face sessions by integrating advice on exercises, and information about a patient’s condition, into the program. While the online program included five sessions per week of either exercise or education, the program for patients in the control group involved two facility sessions per week. The online program also offered a service hotline and digital literacy program.

An online application could be a helpful supplement for facilities that do not have the resources to hire additional workers or do not have the proper facility to conduct these sessions, Dr. Wilkinson noted.

This study was funded by a grant awarded through the U.K. small business research initiative.

The researchers asserted that these deaths do not take away from the success of the treatment, as the focus of the study was to find a way to reduce readmissions, not necessarily mortality.

“Increasing hospital-free and exacerbation-free days helps to improve that quality of life. The authors report that the addition of noninvasive ventilation therapy increased the time to readmission due to COPD exacerbation. This adds another tool to the armamentarium to help improve outcomes for our COPD patients.”

Online pulmonary rehab improved walk test scores

View on the News

Vera A. De Palo, MD, FCCP
MBA, comments: A goal for any patient with a chronic disease is the best possible quality of life. Increasing hospital-free and exacerbation-free days helps to improve that quality of life. The authors report that the addition of noninvasive ventilation therapy increased the time to readmission due to COPD exacerbation. This adds another tool to the armamentarium to help improve outcomes for our COPD patients.

Online pulmonary rehab improved walk test scores

View on the News

Eric Gartman, MD, FCCP, comments: The functional improvement and other gains of pulmonary rehab are well established, but, unfortunately, too few of our patients are willing or able to participate in a formal program (for many reasons). Having viable alternatives outside of a facility-based program would prove extremely beneficial for all involved in the care of chronic pulmonary patients. Further research into these technolo-
New chest x-ray assessment reflects ARDS severity

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON—A new way to semiquantitatively score chest x-rays that takes into account lung density and consolidation may be a useful adjunct to current methods for assessing severity of acute respiratory distress syndrome.

The score, known as the Radiographic Assessment of Lung Edema (RALE) score, showed good correlations with lung edema, the severity of acute respiratory distress syndrome (ARDS), and response to fluid management resulting in reduced pulmonary edema, Melissa A. Warren, MD, said at an international conference of the American Thoracic Society.

“The chest x-ray may be an untapped resource for detecting ARDS severity and prognosis,” said Dr. Warren, a pulmonologist at Vanderbilt University, Nashville, Tenn. “Currently, no noninvasive and accurate measurement exists to quantify pulmonary edema.”

The RALE score that Dr. Warren and her associates devised rates a patient’s chest x-ray for two parameters: consolidation, which is based on the extent of alveolar opacity in each of the four lung quadrants (left upper, left lower, right upper, and right lower), and a density score that is based on the density of alveolar opacity in each quadrant.

The consolidation score for each quadrant is rated on a 0-4 scale with 0 corresponding to no opacity, 1 for 1%-24% opacity, 2 for 25%-49% opacity, 3 for 50%-75% opacity, and 4 for more than 75%. The density score is rated on a scale of 1-3 with 1 for hazy opacity, 2 for moderate opacity, and 3 for dense opacity. The score for each quadrant is obtained by multiplying the extent score by the density score. A patient’s total RALE score sums the scores from all four quadrants.

The researchers ran three tests of the clinical relevance of this scoring system. First, they used it to score chest x-rays of 72 preprocurement lungs donated for transplant but unable to be used for that purpose, and compared the scores with the extent of lung edema measured by the actual weight of each explanted lung. This showed high correlation between the scores and the amount of edema, Dr. Warren reported. Next they assessed

Continued on page 18

OVER 10,000 IPF PATIENTS HAVE BEEN TREATED WITH OFEV WORLDWIDE¹²

SLOW THE PATH OF IPF PROGRESSION

OFEV (nintedanib) has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials²

INDICATION AND USAGE
OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS
Hepatic Impairment

• OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dosage (100 mg twice daily). Consider treatment interruption or discontinuation for management of adverse reactions.

Please see additional Important Safety Information and brief summary for OFEV on the following pages.

FVC, forced vital capacity.
Hyperinflammatory ARDS responds to simvastatin

BY MITCHEL L. ZOLER

WASHINGON – Acute respiratory distress syndrome (ARDS) appears to exist in at least two major forms, and one of these, the hyperinflammatory form, seemed responsive to simvastatin in a post-hoc analysis of trial data. The other version of ARDS is a hypoinflammatory form, which occurred in 70% of ARDS patients in most of the analyses that have been done. Researchers classified the 540 ARDS patients enrolled in a 2014 study of simvastatin as either hyperinflammatory or hypoinflammatory. Separating out the hyperinflammatory patients created a subclass that responded to simvastatin, with a 13% absolute reduction in mortality during follow-up, compared with no response among patients in the

OFEV has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials*

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted annual rate of decline in FVC, mL/year</th>
<th>Relative reduction in FVC decline</th>
<th>P-value</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>INPULSIS®-1 (Study 2)</td>
<td>-115 mL/year</td>
<td>52%</td>
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<td>INPULSIS®-2 (Study 3)</td>
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<td>TOMORROW (Study 1)</td>
<td>-191 mL/year</td>
<td>68%</td>
<td>&lt;.001</td>
<td>(95% CI=27, 235)</td>
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<td>Placebo (n=83)</td>
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Cl, confidence interval.

The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.1,2

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT’D)

Elevated Liver Enzymes
• OFEV (nintedanib) was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN.
• Conduct liver function tests prior to treatment, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Monitor for adverse reactions and consider dosage modifications, interruption, or discontinuation as necessary for liver enzyme elevations.

Gastrointestinal Disorders

Diarrhea
• Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and <1% in placebo patients, respectively.
• Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and anti-diarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

Nausea and Vomiting
• Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
• If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

Embryofetal Toxicity: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to starting OFEV.
hypo-inflammatory group, Carolyn S. Calfee, MD, said at an international conference of the American Thoracic Society.

“Hyper-inflammatory patients treated with simvastatin may have improved outcomes, compared with hypo-inflammatory patients treated with placebo,” said Dr. Calfee, a pulmonologist at the University of California, San Francisco. The finding raises the possibility that simvastatin, as well as other statins, may be an effective treatment for selected patients with ARDS, but proving this requires new prospective, randomized trials in hyper-inflammatory patients, Dr. Calfee said in a video interview available on mdedge.com/chestphysician. Currently, the tests Dr. Calfee uses to distinguish hyper-inflammatory and hypo-inflammatory ARDS patients take about 6-8 hours to complete. A critical next step would be the development of a “practical, rapid, bedside assay” to ease identification of hyper-inflammatory ARDS patients, she said.

“Hypo-inflammatory patients also merit study, she added. Although hyper-inflammatory patients have significantly worse mortality rates, the hypo-inflammatory subclass includes about 70% of ARDS patients, “so we

Continued on following page

3 out of every 10 patients on OFEV showed an improvement (≤0% decline) in lung function in the INPULSIS® trials

![Graph showing lung function improvement with OFEV vs. placebo](chart.png)

- More patients had improved lung function with OFEV than with placebo in the INPULSIS® trials

**INPULSIS®-1**

<table>
<thead>
<tr>
<th>% change</th>
<th>Relative increase</th>
<th>Absolute difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFEV</td>
<td>-67%</td>
<td>-12%</td>
</tr>
<tr>
<td>Placebo</td>
<td>-30%</td>
<td>-18%</td>
</tr>
</tbody>
</table>

**LESS THAN ONE-THIRD OF PATIENTS ON OFEV HAD A MEANINGFUL DECLINE IN LUNG FUNCTION IN THE INPULSIS® TRIALS**

**INPULSIS®-1,6-8**

<table>
<thead>
<tr>
<th>% change</th>
<th>Relative decrease</th>
<th>Absolute difference</th>
</tr>
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<tbody>
<tr>
<td>OFEV</td>
<td>-33%</td>
<td>-14%</td>
</tr>
<tr>
<td>Placebo</td>
<td>-29%</td>
<td>-43%</td>
</tr>
</tbody>
</table>

According to American Thoracic Society (ATS) guidelines, ≥10% FVC decline is an established measure of IPF disease progression and a surrogate marker in mortality6,7,9

In INPULSIS® trials, there was not a statistically significant difference in all-cause mortality for OFEV compared with placebo.3

**IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT’D)**

**Arterial Thromboembolic Events:** Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Please see additional Important Safety Information and brief summary for OFEV on the following pages.
Continued from previous page

need to better understand how to potentially treat this group."

Dr. Calfee and her associates first reported finding the two ARDS subclasses, what they also call subphenotypes or endotypes, in two separate cohorts of ARDS patients in a 2014 report (Lancet Resp Med. 2014 Aug;2(8):611-20). Then, they confirmed the finding in a third ARDS cohort in a 2017 report (Amer J Resp Crit Care Med. 2017 Feb 1;195[3]:331-8). These reports have documented other characteristics of the hyperinflammatory ARDS subclass: hypotension, metabolic acidosis, more frequent treatment with vasopressors, and a higher prevalence of sepsis and shock. Concurrent with the 2017 report, an editorial hailed the finding as “the dawn of personalized medicine for ARDS” (Amer J Resp Crit Care Med. 2017 Feb 1;195[3]:280-1).

To build on this, Dr. Calfee and her associates applied their method for identifying ARDS subclasses to a different cohort of 540 patients enrolled in the The HARP (Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction) study, a multicenter UK and Irish study designed to test the efficacy of daily simvastatin treat-

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**OFEV is only available through participating specialty pharmacies**

TO GET YOUR APPROPRIATE PATIENTS WITH IPF STARTED ON OFEV:

CONDUCT liver function tests (ALT, AST, and bilirubin) prior to initiating treatment with OFEV (nintedanib)

COMPLETE the OFEV Prescription Form—available at www.OFEVhcp.com—and fax it to one of the participating specialty pharmacies

OFFER enrollment in OPEN DOORS™, a patient support program for patients receiving OFEV

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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONT’D)**

**Risk of Bleeding:** OFEV may increase the risk of bleeding. Bleeding events were reported in 10% of OFEV versus 7% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

**Gastrointestinal Perforation:** OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus in 0% placebo patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

**ADVERSE REACTIONS**

- Adverse reactions reported in ≥5% of OFEV patients included diarrhea, nausea, abdominal pain, liver enzyme elevations, vomiting, decreased appetite, weight decreased, headache, and hypertension

- The most frequent serious adverse reactions reported in OFEV patients were bronchitis and myocardial infarction. The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

**DRUG INTERACTIONS**

- P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

- Anticoagulants: Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

**USE IN SPECIFIC POPULATIONS**

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.

- **Reproductive Potential:** OFEV may reduce fertility in females of reproductive potential.

- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

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Please see accompanying brief summary of Prescribing Information, including Patient Information.

References:
OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information, including Patient Information

INDICATIONS AND USAGE: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSAGE AND ADMINISTRATION: See Warnings and Precautions. Recommended Dosage: The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole without liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 500 mg. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily approximately 12 hours apart taken with food.}

Dose Modification Due to Adverse Reactions: In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. Treatment with OFEV may be resumed at the full dosage (150 mg twice daily) or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinuation of treatment with OFEV (see Warnings and Precautions and Adverse Reactions). Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reinitiated at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) (see Warnings and Precautions and Adverse Reactions). Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs of severe liver damage. In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption, or discontinuation for management of adverse reactions.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Hepatic Impairment: Treatment with OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment (see Use in Specific Populations). Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV (see Dosing and Administration). Elevated Liver Enzymes: In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (84%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority of patients with bilirubin elevations had <2 times ULN (see Use in Specific Populations). Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV and monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dose modifications or interruption may be necessary for liver enzyme elevations.

Gastrointestinal Disorders: Diarrhea: Diarrhea was the most frequent adverse reaction (>5% and ≥5% more frequent in the OFEV group than in the placebo group). In clinical trials, 41% of patients treated with OFEV reported diarrhea compared to 23% of placebo-treated patients. Diarrhea was dose related and more common in the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV and placebo, respectively (see Adverse Reactions). In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV and placebo. Nausea may have led to discontinuation of OFEV in 1% of patients and 1.8% of placebo-treated patients. Nausea was reported in 4% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively (see Adverse Reactions). In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, consideration should be given to discontinuation of OFEV (see Warnings and Precautions and Adverse Reactions). In most patients, these events were of mild to moderate intensity. OFEV has not been studied in patients with active peptic ulcer disease, and patients with upper gastrointestinal disorders requiring frequent dose reduction or discontinuation of therapy with OFEV. Concomitant use of drugs that affect gastric emptying such as prokinetic agents or drugs that cause gastric hypermotility may increase the risk of gastrointestinal perforation in patients with IPF treated with OFEV.

In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (80%). The most frequent serious adverse reactions reported in patients treated with OFEV were more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse reactions leading to death in patients treated with OFEV were more than placebo, were pneumonia (0.7% vs. 0.0%), lung cancer (5 cases of lung cancer), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.9% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 11% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (6%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OFEV, n=723</th>
<th>Placebo, n=508</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>62%</td>
<td>18%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver enzyme elevation a</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Abnormal hepatic enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal perforation b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting that persists despite symptomatic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation of therapy due to adverse reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal perforation b</td>
<td></td>
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</tr>
<tr>
<td>Discontinuation of therapy due to adverse reactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1% vs. 0.6%).

DRUG INTERACTIONS: P-glycoprotein (P-gp) and P-gp Inhibitors and Inducers: OFEV is a substrate of P-gp and, to a minor extent, CYP3A4. Co-administration with oral doses of P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure (AUC and Cmax) by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require dose reduction, discontinuation of therapy with OFEV. Concomitant use of drugs that affect gastric emptying such as prokinetic agents or drugs that cause gastric hypermotility may increase the risk of gastrointestinal perforation in patients with IPF treated with OFEV. Concomitant use of drugs that affect gastric emptying such as prokinetic agents or drugs that cause gastric hypermotility may increase the risk of gastrointestinal perforation in patients with IPF treated with OFEV.
Continued from previous page

in this case including 188 (35%) of the cohort, and a hypoinflammatory subclass with 352 (65%) patients. The next step was to see what impact simvastatin treatment had in each of the two patient subclasses. They focused the analysis on a secondary outcome use of P-gp and OMP34 inducers (e.g., camptothecin, phenyltoin, and St. John’s work) with OFEV should be avoided as these drugs may decrease exposure to nil-
tedanib. Antiangiopaties: Nintedanib is a VEGF inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary (see Warnings and Precautions).

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenicity: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman and may reduce fertility in females of reproductive potential (see Use in Specific Populations). Counsel patients on pregnancy prevention and planning. Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV (see Dosage and Administration, Warnings and Precautions and Use in Specific Populations). Contraception: Advise females of reproductive potential 65 about becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use effective contraception during treatment, and for at least 3 months after the last dose of OFEV. Infertility: Based on animal data, OFEV may reduce fertility in females of reproductive potential.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Geriatric Use: Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 or over; while 16.3% were 75 or over. In a phase 3 study, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment: Nintedanib is extensively eliminated via biliary/enteral excretion (>90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily (see Dosage and Administration). Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients (see Dosage and Administration). Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended (see Warnings and Precautions).

Renal Impairment: Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not recommended. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<20 ml/min) GFR) and end-stage renal disease. Smoking: Smoking was associated with decreased exposure to OFEV which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV to avoid smoking-related effects. OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (thrombophlebitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

PATIENT COUNSELING INFORMATION: Advise the patient to notify the FDA-approved patient labeling (Patient Information). [see Expire and Do Not Expiry]: Advise patients that they will need to undergo liver function test-
ing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleeding or bruising more-

The RALE score as a marker of ARDS by retrospectively calculating the scores of 174 patients with baseline chest x-rays enrolled in the Fluids and Catheters Treatment Trial (FACTT) (N Engl J Med. 2006;354:24;2564-73). This analysis showed that patients with the highest RALE scores had significantly worse survival during 90-day follow-up, compared with the patients with the lowest scores. Finally, the researchers assessed how the RALE score changed in response to either the liberal or conservative fluid management approaches tested in FACTT. This showed that at baseline the average RALE scores were similar among 92 patients randomized to the liberal fluid management treatment arm and 82 patients assigned to the conservative fluid management arm. But after 3 days of treatment, patients in the conservative arm showed a roughly one-third reduction in their average RALE score, while patients in the liberal fluid arm showed virtually no change in their score. A conservative fluid management strategy favorably impacted the RALE score, reflecting a decrease in pulmonary edema,” Dr. Warren concluded.

Continued from page 13

Dr. Melissa A. Warren

the RALE score as a marker of ARDS by retrospectively calculating the scores of 174 patients with baseline chest x-rays enrolled in the Fluids and Catheters Treatment Trial (FACTT)
Rest dyspnea dims as heart failure treatment target

BY MITCHEL L. ZOLER
Frontline Medical News

PARIS – During the most recent pharmaceutical generation, drug development for heart failure largely focused on acute heart failure, and specifically on patients with rest dyspnea as the primary manifestation of their acute heart failure decompensation events.

That has now changed, agreed heart failure experts as they debated the unorth of sobering results from two neutral trials that failed to show a midterm mortality benefit in patients hospitalized for acute heart failure who underwent aggressive management of their congestion using 2 days of intravenous treatment with either of two potent vasodilating drugs. Results first reported in November 2016 failed to show a survival benefit from ulitide in the 2,100-patient TRUE-AHF (Ef ficacy and Safety of Ulitide for the Treatment of Acute Decompensated Heart Failure) trial (N Engl J Med. 2017 May 18;376[20]:1956-64). And results reported at a meeting of the Heart Failure Association of the European Society of Cardiology failed to show a survival benefit from serelaxin in more than 6,300 acute heart failure patients in the RELAX-AHF-2 (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF) trial.

The failure of a 2-1 day infusion of serelaxin to produce a significant reduction in cardiovascular death in RELAX-AHF-2 was especially surprising because the predecessor trial, RELAX-AHF, which randomized only 1,160 patients and used a surrogate endpoint of dyspnea improvement, had shown significant benefit that hinted more clinically meaningful benefits might also result from serelaxin treatment (Lancet. 2013 Jan 5;381[9860]:29-39). The disappointing serelaxin and ulitide results also culminate a series of studies using several different agents or procedures to treat acute decompensated heart failure patients that all failed to produce a reduction in deaths.

The neutral results from TRUE-AHF and RELAX-AHF-2 “mark the start of a new era. We need to rethink and fine-tune our strategies,” commented Frank Ruschitzka, MD, president of the Heart Failure Association, as he shared his take-home message from the meeting at the end of the closing session.

“This is a sea change; make no mistake. We will need a more targeted, selective approach. It was always a daunting proposition to believe that short-term infusion could have an effect 6 months later. We were misled by the analogy [of acute heart failure] to acute coronary syndrome,” said Dr. Ruschitzka, professor of medicine at the University of Zürich.

The right time to intervene
Meeting attendees offered several hypotheses to explain why the acute ulitide and serelaxin trials both failed to show a mortality benefit, with timing of treatment the most common denominator.

Acute heart failure “is an event, not a disease,” declared Milton Packer, MD, lead investigator of TRUE-AHF, during a session devoted to vasodilator treatment of acute heart failure. Acute heart failure decompensations “are fluctuations in a chronic disease. It doesn’t matter what you do during the episode – it matters what you do between acute episodes. We focus all our attention on which vasodilator and which dose of Lasix [furosemide], but we send patients home on inadequate chronic therapy. It doesn’t matter what you do to the dyspnea, the shortness of breath will get better. Do we need a new drug that makes dyspnea go away an hour sooner and doesn’t cost a fortune?

What really matters is what patients do between acute episodes and how to prevent them,” said Dr. Packer, distinguished scholar in cardiovascular science at Baylor University Medical Center in Dallas.

Dr. Packer strongly urged clinicians to put heart failure patients on the full regimen of guideline-directed drugs and at full dosages, a step he thinks would go a long way toward preventing a majority of decompensation episodes. “Chronic heart failure treatment has improved dramatically, but implementation is abysmal,” he said.

Acute decompensation is the wrong time to target intervention, agreed G. Michael Felker, MD, professor of medicine at Duke University in Durham, N.C. “We study patients at the time of their hospitalization. As we get more and more neutral studies, many are now thinking that this may not be the best time for intervention. An untapped opportunity is a few weeks before hospitalization, because acute heart failure patients get sick over weeks, not hours.” The time to treat is in the “early, predecompensation period. That is an important time to target as we develop new drugs,” he said in an interview.

Of course, at this phase of their disease heart failure patients are usually at home, which more or less demands that the treatments they take are oral or at least delivered by subcutaneous injection.

“We’ve had a mismatch of candidate drugs, which have mostly been IV fusions, with a clinical setting where an IV infusion is challenging to use.”

“We are killing good drugs by the way we’re testing them,” commented Javed Butler, MD, who moaned the ignominious outcome of serelaxin in treatment in RELAX-AHF-2.

“The available data show it makes no sense to treat for just 2 days. We should take true worsening heart failure patients, those who are truly failing standard treatment, and look at new chronic oral therapies to try on them.” Oral drugs similar to serelaxin and ulitide could be used chronically, suggested Dr. Butler, professor of medicine and chief of cardiology at Stony Brook (N.Y.) School of Medicine.

Wrong patients with the wrong presentation
Perhaps just as big a flaw of the acute heart failure trials has been their target patient population, patients with rest dyspnea at the time of admission. “Why do we think that dyspnea is a clinically relevant symptom for acute heart failure?” Dr. Packer asked.

It’s not because it’s the most prevalent, according to new findings reported at the meeting by John G.F. Cleland, MD, professor of cardiology at Imperial College, London.

Dr. Cleland and his associates analyzed data on 116,752 hospitalizations for acute heart failure in England and Wales during April 2007–March 2013, a database that included more than 90% of hospitals for these regions.

“We found that a large proportion of admitted patients did not have breathlessness at rest as their primary reason for seeking hospitalization. For about half the patients, moderate or severe peripheral edema was the main problem,” he reported. Roughly a third of patients had rest dyspnea as their main symptom.

An unadjusted analysis also showed a stronger link between peripheral edema and the rate of mortality during a median follow-up of about a year following hospitalization, compared with rest dyspnea. Compared with the lowest-risk subgroup, the patients with severe peripheral edema (18% of the population) had more than twice the mortality. In contrast, the patients with the most severe rest dyspnea and no evidence at all of peripheral edema, just 6% of the population, had a 50% higher mortality rate than the lowest-risk patients.

“It’s peripheral edema rather than breathlessness that is the important determinant of length of stay and prognosis. The disastrous neutral trials for acute heart failure have all targeted the breathless subset of patients. Maybe a reason for the failures has been that they’ve been treating a problem that does not exist. The trials have looked at the wrong patients,” Dr. Cleland said.

“We’ve told the wrong story to industry” about the importance of rest dyspnea to acute heart failure patients. “When we say acute heart failure, we mean an ambulance and oxygen and the emergency department and rapid IV treatment. That’s
Continued from previous page

breathlessness. Patients with peripheral edema usually get driven in and walk from the car to a wheelchair and they wait 4 hours to be seen. I think that, following the TRUE-AHF and RELAX-AHF-2 results, we’ll see a radical change.”

But just because the focus should be on peripheral edema rather than dyspnea, that doesn’t mean better drugs aren’t needed, Dr. Cleland added.

“We need better treatments to deal with congestion. Once a patient is congested, we are not very good at getting rid of it. We depend on diuretics, which we don’t use properly. Ultimately I’d like to see agents as adjuncts to diuretics, to produce better kidney function.” But treatments for breathlessness are decent as they now exist: furosemide plus oxygen. When a simple, cheap drug works 80% of the time, it is really hard to improve on that.” The real unmet needs for treating acute decompensated heart failure are patients with rest dyspnea who don’t respond to conventional treatment, and especially patients with gross peripheral edema plus low blood pressure and renal dysfunction for whom no good treatments have been developed, Dr. Cleland said. Another flaw in the patient selection criteria for the acute heart failure studies has been the focus on patients with elevated blood pressures, noted Dr. Felker.

The TRUE-AHF trial was sponsored by Cardiorentis. RELAX-AHF-2 was sponsored by Novartis. Dr. Ruschitzka has been a speaker on behalf of Novartis, and has been a speaker for or consultant to several companies for whom no good treatments have been developed, Dr. Felker. The TRUE-AHF and received fees from Cardiorentis for his participation. Dr. Packer is a consultant to and stockholder in Cardiorentis and has been a consultant to several other companies. Dr. Felker has been a consultant to Novartis and several other companies and was a coinvestigator on TRUE-AHF and RELAX-AHF-2. Dr. Butler has been a consultant to several companies. Dr. Cleland has received research support from several companies, including Novartis, and has done consulting work for companies.

Dr. FELKER

“Treatment options for patients with catecholamine-resistant vasodilatory shock are limited, and the treatments that are available are often associated with side effects,” said Dr. Khanna and his colleagues.

Angiotensin II may improve vasopressors’ efficacy

**BY ELI ZIMMERMAN**

Frontline Medical News

WASHINGTON – Adding angiotensin II to available vasopressor therapies correlated with significantly improved arterial pressure in patients with catecholamine-resistant vasodilatory shock and less adverse effects, according to a study presented at the recent international conference of the American Thoracic Society.

In a double-blind, controlled, phase III study, 70% of 163 patients given angiotensin II reached arterial pressure of at least 75 mm HG or improved by at least 10 mm HG 3 hours later, compared with 23.4% of the 138 patients given a placebo (P less than .001).

Those in the angiotensin II group also saw a mean pressure increase of 12.5 mm HG in the first 3 hours after initiating treatment, compared with 2.9 mm HG in the placebo group (P less than .001), according to Ashish Khanna, MD, FCCP, of the Cleveland Clinic, and his fellow researchers (N Engl J Med. 2017 May 21. doi: 10.1056/NEJMoa1704154).

Current vasopressor therapies for vasodilatory patients are associated with dangerous side effects and a 30-day mortality rate of more than 50%, which is a major concern for patients who do not have many options to begin with, the researchers noted.

“Treatment options for patients with catecholamine-resistant vasodilatory shock are limited, and the treatments that are available are often associated with side effects,” said Dr. Khanna and his colleagues.

The researchers added the naturally occurring peptide hormone angiotensin II to vasodilatory patients’ treatment regimen in order to “more closely [mimic] natural physiologic responses to shock, which include increased secretion of catecholamines, vasopressin, and RAAS hormones.”

To test the efficacy of angiotensin II, researchers gathered patients with a median age of 64 years and a mean arterial pressure of 66.3 mm HG.

Sepsis was the predominant cause of shock for 80.7% of the study’s participants.

Patients were injected with either 20 ug/kg of body weight per minute of angiotensin II or an equivalent dose of a placebo until mean arterial pressure reached 75 mm Hg. After 3 hours and 15 minutes of treatment, the dosages were adjusted to keep pressure between 65 and 75 mm Hg for the next 48 hours.

Among patients in the angiotensin II group, 67% of patients were able to decrease angiotensin II and vasopressor doses within 30 minutes of injection, according to researchers.

When researchers measured improvement using the cardiovascular Sequential Organ Failure Assessment, patients in the angiotensin II group saw an average decrease of 1.75 points, compared with 1.28 points in patients in the placebo group (P = .01) 48 hours after treatment.

The Sequential Organ Failure Assessment is scaled from 0-4, with higher scores indicating more severe organ failure.

As for adverse effects, serious events occurred in 60.7% of the angiotensin II patients, compared with in 67.1% of those in the placebo group.

At the 28-day mark, 75 angiotensin II patients (46.0%) died, compared with 85 patients (53.8%) of the placebo group.

This study was limited by the sample size, “so the possibility of clinically important side effects attributable to angiotensin II therapy cannot be excluded,” the researchers warned.

Also, the follow-up timeline of 28 days, may not have given researchers enough time to uncover the full extent of positive and negative long-term effects associated with angiotensin II.

This study was supported by La Jolla Pharmaceutical, from which multiple researchers reported receiving financial support in the form of personal fees and grants. Two of the researchers reported having patents related to administering angiotensin II and additional patents pending.
COPD helps fuel heart failure readmissions

BY MITCHEL L. ZOLER
Frontline Medical News

PARIS – Patients hospitalized for heart failure increasingly present with a growing number of noncardiovascular comorbidities, according to registry data from more than 300 U.S. hospitals.

During the decade of 2005-2014, the percentage of patients hospitalized for heart failure diagnosed with three or more noncardiovascular comorbidities (NCCs) jumped from about 17% of these patients in 2005 to about 28% in 2015, Abhinav Sharma, MD, said at a meeting held by the Heart Failure Association of the European Society of Cardiology. This increase occurred as the percentages of hospitalized heart failure patients with none or one NCC showed clear decreases.

This time trend suggests that clinicians should be on the lookout for NCCs in patients admitted for heart failure, and that "strategies to address the growing burden of noncardiovascular comorbidities may be a way to improve outcomes," said Dr. Sharma, a cardiologist at Duke University in Durham, N.C.

U.S. patients hospitalized for heart failure “appear to now be sicker and more medically complex. Probably, a large number of the noncardiovascular comorbidities are not being recognized when the focus is on treating the patient’s heart failure,” he said in an interview. “If we can identify the noncardiovascular comorbidities and target appropriate treatment, it may potentially decrease the risk of readmissions.”

He included five NCCs in his analysis: chronic obstructive pulmonary disease (COPD), anemia, diabetes, chronic kidney disease, and obesity.

His analysis showed that a higher rate of readmissions, as well as increased mortality both in hospital and during the 30 days following discharge, are outcomes that all connect with increased numbers of NCCs. Patients with three or more NCCs at the time of their heart failure admission were about 50% more likely to have an index hospitalization of at least 4 days, compared with patients with no NCC.

All five of the NCCs included in his analysis showed increased prevalence rates from 2005 to 2014 in the patients he studied. The biggest jump occurred in the prevalence of COPD, which rose from about 27% in 2005 to about 35% in 2014. His study used data collected in the Get With the Guidelines–Heart Failure Registry, which began in 2005, and included just under 208,000 total patients.

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OSA in pregnancy linked to congenital anomalies

BY DEBRA L. BECK
Frontline Medical News

BOSTON – Newborns exposed to obstructive sleep apnea (OSA) in utero are at a higher risk of being diagnosed with congenital anomalies, according to a new study presented at the annual meeting of the Associated Professional Sleep Societies. Researchers’ analyses of data from more than 1.4 million births during 2010-2014, circulatory, musculoskeletal, and central nervous systems were among the types of anomalies they saw in the 17.3% of babies born to mothers who had OSA during pregnancy. These babies were also more likely to require intensive care at birth, compared with those born to mothers who had not been diagnosed with OSA. While more than 17% of babies born to mothers with OSA had con-
genital anomalies, 10.6% of the newborns of mothers without an OSA diagnosis had the same types of health issues (P less than .001). This finding was significant after a multivariate analysis that adjusted for potential confounding variables including maternal obesity or diabetes (odd ratio, 1.26; P less than .05). The highest risk was for musculoskeletal anomalies, with a significant 89% increase in risk seen after the adjustment.

Additionally, the investigators found that the 0.1% of women who had been diagnosed with OSA were 2.76 times more likely to have babies that required some kind of resuscitative effort at birth. Specifically, 0.5% of the newborns of the mothers with OSA required resuscitation, compared with 0.1% of the other group’s babies. The newborns of women with OSA were also 2.25 times more likely to have a longer hospital stay.

Mothers with OSA were older and more likely to be non-Hispanic black and have a diagnosis of obesity, tobacco use, and drug use but not alcohol use. We do not know that the prevalence of sleep apnea is causing these outcomes, said abstract presenter and principal investigator Ghada Bourjeily, MD, FCCP, of Brown University and Miriam Hospital, both in Providence, R.I., in an interview.

“We know that women who have sleep apnea often also have other morbidities, so we don’t know what might have contributed to the congenital outcomes,” said Dr. Bourjeily. “We also don’t know if treating sleep apnea can reverse or prevent birth complications or even maternal complications, like preeclampsia or gestational diabetes.”

Ongoing studies are looking at maternal continuous positive airway pressure therapy use and neonatal outcomes, but “they are nothing to write home about yet,” she said.

“This is an underdiagnosed condition and it’s probably undercoded too, but we know from another study that the prevalence of OSA in the first trimester in an all-comers population that was screened for the condition is 4%,” said Dr. Bourjeily. “If another 3% of (the study participants) actually had OSA, then all of these findings are potentially underestimated.”

The majority of OSA in pregnant women that has been identified in prospective studies is mild and not necessarily something that most physicians would treat, she noted. “In our study, the ones who were diagnosed were those who were likely to want to sleep more, which is probably why they came to their doctors and complained of sleepiness or loud snoring,” she said.

The researchers also determined that the newborns of mothers with sleep apnea were more likely to be admitted to an intensive care unit (25.3% vs. 8.1%) or a special care nursery (34.9% vs. 13.6%).

A diagnosis of OSA was established when a diagnosis code for OSA was present on the delivery discharge record. Maternal and infant outcomes were collected for ICD-9 and procedural codes.

Dr. Bourjeily received research equipment support from Respironics.
BY DEBRA L. BECK  
Frontline Medical News

BOSTON – Showing patients videos of themselves having apneic episodes may convince them to use continuous positive airway pressure (CPAP), suggests the first results of an ongoing randomized clinical trial.

The investigators based their research project design on a previous pilot study that showed improved adherence to CPAP in patients who were shown videos of themselves sleeping while participating in a sleep study. Mark S. Aloia, PhD, said in a presentation at the annual meeting of the Associated Professional Sleep Societies.

In the new study, patients who had been recently diagnosed with sleep apnea were randomly assigned to participate in one of the three treatment groups. All three groups received sleep apnea and CPAP education prior to the use of CPAP. One group also watched videos of themselves sleeping, snoring, and gasping for air, and another group watched videos of a stranger sleeping and having apneic events.

In this study’s preliminary findings for 24 patients, those who were shown brief videos of themselves sleeping used their prescribed CPAP treatment for a mean of 6.5 hours per night across a 99-day time period. In contrast, those who watched a video of a stranger sleeping had a mean CPAP use of 4.1 hours, and those who received standard CPAP education used their devices a mean of 3.5 hours per night.

After adjustment for age, educational level, and baseline sleep apnea severity, those who watched videos of themselves still used their CPAP devices more than 2 hours per night longer than did patients in each of the groups receiving the other two interventions (P < .02).

Both video interventions involved watching 30 minutes of sleep footage shown to each patient once before starting CPAP therapy. CPAP adherence was measured by downloaded data from PAP devices over the first 90 days of use.

The average age of the patients was 50 years, and they had moderate or severe sleep apnea, with mean apnea hypopnea indices ranging from 26.5 to 33.3 in the three study arms. The majority of patients had body mass indexes over 30.

“Many times we think that, if our patient just knew what we know, he or she would use CPAP more, but there is evidence that doctors don't take their medications any more than patients do, so it is not just a matter of education, it is a little bit deeper than that and it has to be personalized,” said Dr. Aloia.

**Adherence to CPAP treatment is often poor, with many patients failing to use the device for even 4 hours per night, said Dr. Aloia, a psychologist at National Jewish Health in Denver. Many patients prescribed CPAP for obstructive sleep apnea will undergo an educational component that may include watching a video of someone with OSA sleeping and having apneic events, he added. They often have "dramatic responses" to these videos, but then fail to positively change their own behavior.

"Many times we think that, if our patient just knew what we know, he or she would use CPAP more, but there is evidence that doctors don't take their medications any more than patients do, so it is not just a matter of education, it is a little bit deeper than that and it has to be personalized," he said.

"The use of a personalized video isn't my problem; it just bothers my bed partner." "I'm sleepy because I'm overweight and I don't exercise enough; it's not a disease." Showing the video brings it home, which is likely why patients were more adherent to therapy thereafter. In this case, a picture isn't just worth a thousand words; it is also equal to about 2 additional hours of high-quality sleep each night.

**Personalized snoring video boosts CPAP adherence**

**VIEW ON THE NEWS**

David A. Schulman, MD, FCCP, comments: This interesting study suggests a robust improvement in CPAP adherence for patients shown a video of themselves having apneic events, compared with standard CPAP education alone. Perhaps this is not surprising; maybe a disease isn’t “real” until each patient can see its manifestations on himself or herself. "Snoring

**Most arrhythmia clinic patients have undetected OSA**

**VIEW ON THE NEWS**

Dr. Shapiro noted that “high scores suggestive of daytime sleepiness, fatigue, or insomnia did not particularly predict the presence of OSA in patients with arrhythmia.” He concluded that, “with a hit rate of 85%, just about every patient with an arrhythmia should have a sleep study.”

Dr. Shapiro informed attendees at the annual meeting of the Professional Sleep Societies that he was presenting in place of his student and the abstract’s first author, Dr. Asmaa M. Abumuamar, MD, who was denied a visa to attend the meeting. Dr. Abumuamar is from the Toronto Western Research Institute, University of Toronto.

Dr. Shapiro reported that Dr. Abumuamar has no conflicts of interest. Dr. Shapiro reported that he is an investor in the company that supplied the home sleep testing apparatus.
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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 12-16 week term trials, and included predominate 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.

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 5%, 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.

REVATIO is available in the following dosage forms:

- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)

The REVATIO Family

Available in OS, tablet, and injection forms.

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

DOSEAGE 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 60 mL of water and pour 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 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 adapter into the neck of the bottle. The adapter 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 nitrates, 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 about 1 year and causes of death were typical of PAH. Use of PDE5, 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 not known in patients with bleeding disorders or those experiencing 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 PDE5 inhibitors, 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 PDE5 inhibitors, including REVATIO.

Diarrhea
The incidence of diarrhea was 4% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 4%, placebo 4%) patients. Diarrhea is not known in patients with bleeding disorders or those experiencing 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 PDE5 inhibitors, 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 PDE5 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 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 trial (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)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo, % (n=70)</th>
<th>REVATIO 20 mg three times a day, % (n=69)</th>
<th>Placebo-Subtracted, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Erhyma</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia exacerbated</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Gastroitis</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and not 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 1.3% 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 hemorrhage were reported in patients in hypertension 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 use of sildenafil without sexual activity. Others were reported to have occurred within 6 hours after 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.

Drug Interactions
Nitrites
Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ritonavir and other Potent CYP3A4 Inhibitors
Concomitant use of REVATIO with ritonavir and other potent CYP3A4 inhibitors is not recommended.
Other drugs that reduce blood pressure  
Alpha blockers. In drug-drug interaction  
studies, sildenafil (25 mg, 50, 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 adverse experiences in patients who experienced excessive  
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/m² 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/m² 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 ≤ 27% in > 95% of patients). 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  
developing PAH and in the test group. 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, of which 37 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  
hapatological impairment (CLcr ≥ 30 mL/min).  

Patients with Renal Impairment  
No dose adjustment is required (including severe  
renal 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  

BOSTON – Remote monitoring of  
continuous positive airway pressure (CPAP) use with feedback messaging  
to patients improves adherence but  
only when patients opt to receive  
continual feedback on their usage,  
according to a study.  

Dennis Hwang, MD, medical di-  
rector of Kaiser Permanente Fontana  
(Calif.) Medical Center and his col- 
leagues designed the four-arm Tele- 
OSA study to evaluate the impact of  
two automated telemedicine interven- 
tions: an obstructive sleep apnea  
(OSA) education program (provided  
by Emmi Solutions) and a CPAP  
remote monitoring system with au- 
tomated patient feedback (U-Sleep, 
ResMed). Dr. Hwang, who is also  
cochair of sleep medicine at South- 
ern California Permanente Medical  
Group, presented his findings at the  
annual meeting of the Associated  
Professional Sleep Societies.  

A total of 1,455 patients with OSA  
were randomized to usual care, usual  
care + tele-education, usual care +  
telemonitoring, or usual care + both  
tele-education and telemonitoring.  
The tele-education provided OSA  
and CPAP web-based education, offered  
patients a personalized invitation via  
email, was interactive, allowed for  
repeat viewing, and tracked patient  
viewing status. The telemonitoring  
system used automated algorithms  
to process the uploaded CPAP data.  
If the patient met certain thresholds,  
such as no CPAP-data for 2 consecu- 
tive days or CPAP usage greater than  
4 hours for 3 consecutive nights, a  
message was automatically sent ei- 
ther by text, email, or phone to the  
patient.  

CPAP adherence was compared at  
3 months and 1 year for patients in  
all four groups. Dr. Hwang reported  
findings from 556 patients who com- 
pleted 1-year follow-up.  

At 90 days, patients assigned to  
either of the telemonitoring arms  
had significantly higher CPAP us- 
age than those who did not receive  
telemonitoring.  

However, at 3 months when the  
study protocol called for the auto- 
mated messaging to be turned off,  
CPAP adherence dropped off. By 8  
months, adherence in patients using  
the telemonitoring system was no  
different from that in those who nev- 
er received the automated messag- 
ing. That would have been the end  
of the story, except that there was a  
glitch in the system.  

“Perhaps serendipitously, we had  
a group of patients, about one-third,  
for whom we inadvertently did not  
turn off the messaging,” explained  
Dr. Hwang. “In these patients who  
continued to receive feedback, CPAP  
usage remained elevated throughout  
the course of the year and, at 12  
months, was significantly higher than  
in the patients who were not receiv- 
ing any kind of messaging,” Dr. Hwang said.  

“Perhaps serendipitously, we  
had a group of patients,  
about one-third, for whom we  
inaudiently did not turn off the  
messaging. In these patients  
(CPAP usage) was significantly  
higher than in the patients who  
were not receiving any kind of  
messaging,” Dr. Hwang said.

Dr. Dennis Hwang  

Dr. Dennis Hwang received support from  
the American Sleep Medicine Foun- 
Antibiotic monotherapy fails 25% of CAP patients

BY ELI ZIMMERMAN
Frontline Medical News

WASHINGTON – A substantial failure rate of antibiotic monotherapy was found in patients with community-acquired pneumonia (CAP), according to a presentation given at an international conference of the American Thoracic Society.

In a study of 413,801 patient records with confirmed CAP, an average of 25% of patients reported treatment failure, according to James A. McKinnell, MD, an infectious disease specialist at LA BioMed and an assistant professor at the University of California, Los Angeles.

Adult outpatient records with a diagnosis of CAP and a prescription for antibiotics were gathered from the period of 2012-2015, with treatment failure defined as a refill or change in the medication prescribed, a visit to the emergency department, or a hospitalization, according to Dr. McKinnell and the other investigators. When broken down, the failure rates in patients given beta-lactams (25.7%), macrolides (22.9%), tetracycline (22.5%), and fluoroquinolones (20.8%) were all found to increase when patients’ Charlson Comorbidity Index (CCI) score increased (odds ratio, 1.16 [1.13-1.20], for CCI = 1, OR, 1.22 [1.18-1.26], for CCI = 2, OR, 1.44 [1.39-1.49], for CCI greater than or equal to 3).

These medications have been shown to be effective through the usual array of controlled tests. While these trials do confirm overall efficacy, they are not always accurate in predicting how they will affect individual patients, Dr. McKinnell noted.

“I want to know the best drug for my patient, (and) unfortunately randomized clinical trials are not completely generalizable,” Dr. McKinnell said during his presentation.

“Pathogen distribution and resistance is different in a clinical trial compared to the patients we see, and there’s a measuring bias, so there’s a lot of limitations when just using clinical trials.”

When analyzing failure endpoints, the investigators found 79%, 73.4%, 80.8%, and 64% of patients switched their antibiotics while taking beta-lactams, macrolides, tetracycline, or fluoroquinolones, respectively. The investigators interpreted this as a sign that patient treatment plans must be better fitted for their personal circumstances.

This is where the idea of “big data” would apply; using large-scale, “real-world” data of current and previous CAP patients could be instrumental to test the benefits and limitations of certain treatment options on patients with certain comorbidities, according to Dr. McKinnell and his fellow investigators.

“When breaking down comorbidities among patients, the investigators found that many of the comorbid conditions had a ‘significant predictor value’ of treatment failure, according to Dr. McKinnell.

Investigators were not surprised that hemiplegia or paraplegia, which increased the odds of antibiotic failure by 33%, were independent factors; however, comorbidities such as peptic ulcer disease (OR, 1.15) was less expected, Dr. McKinnell noted.

As for the mortality rate of patients 18 years of age and older with treatment failure, 18.1% (10,087) died (P < .0001), with an even higher mortality rate of 24.3% (3,299) among those at least 65 years of age, he said.

If big data studies could decrease the number of treatment failures, the implications would be significant in decreasing the number of mortality, the investigators noted.

“Prescribers should be aware of those CAP patients most at risk for poor outcomes and consider these factors to guide a comprehensive treatment plan,” said Dr. McKinnell.

Cempra Pharmaceuticals funded the study. The researchers did not report any conflicts of interest during their presentation.

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On Twitter @eaztweets
Days with MRSA bacteremia ups complications risk

BY CATHERINE COOPER NELLIST
Frontline Medical News

Every additional day of methicillin-resistant Staphylococcus aureus (MRSA) bacteremia in hospitalized children was associated with a 50% increased risk of developing a complication, according to a study performed in three hospitals in the United States.

The researchers aimed to determine the epidemiology, clinical outcomes, and risk factors for treatment failure in pediatric MRSA bacteremia.

In the 174 hospitalized children (all were younger than 19 years) with MRSA bacteremia, 78% of infections were community onset. The primary sources of infection were osteomyelitis (31%), catheter-related bloodstream infections (22%), and skin and soft-tissue infections (16%); endocarditis occurred in only 2%. The median duration of MRSA bacteremia was 2 days; only 10% lasted beyond 7 days.

“This finding is in contrast to the epidemiology of MRSA bacteremia in adults, in whom bacteremia is more frequently attributed to catheter-related infections (31%-36%), endovascular infections (13%-15%), or an unknown source (15%-20%), and the durations of MRSA bacteremia are typically more prolonged (median duration of bacteremia is 8-9 days),” wrote Rana F. Hamdy, MD, of Children’s National Health System, Washington, and her associates.

“Differences in the epidemiology of MRSA bacteremia between children and adults emphasize the need for dedicated pediatric studies to better understand the clinical characteristics and outcomes specific to children,” the researchers noted.

Musculoskeletal infections and endovascular infections were linked with treatment failure, possibly reflecting “the relatively higher burden of bacteria and/or decreased drug penetration into bone and endovascular infection sites,” the investigators said.

Catheter-related infections were tied to reduced odds of treatment failure, “these episodes being localized to the catheter and therefore potentially less-invasive S. aureus infections.”

Mortality among these children with MRSA bacteremia was low, at 2%, but “nearly one-quarter of all patients experienced complications,” the study authors said (Pediatrics. 2017 May 5. doi: 10.1542/peds.2017-0183).

There was progression of infection in 7% of cases, and hematogenous complications or sequelae occurred in 23%. Twenty percent of children developed septic emboli or another metastatic focus of infection.

“This association between the duration of bacteremia and the development of complications has been previously reported among adults with S. aureus bacteremia,” Dr. Hamdy noted, “and provides important epidemiologic data that could inform decisions relating to the timing of additional imaging, such as echocardiograms, to identify metastatic foci.”

The National Institutes of Health funded the study.
Mycobacteria subset plagues pulmonary patients

BY HEIDI SPLETE
Frontline Medical News
FROM CHEST

Nontuberculous mycobacteria accounts for an increasing percentage of pulmonary disease, and nonsurgical treatment alone has not shown effectiveness, according to data from a meta-analysis of 24 studies and 1,224 patients. The study results were published online in Chest.

Data on therapeutic successes in cases of nontuberculosis mycobacteria (NTM)-related pulmonary disease are limited, in particular for those species not related to the Mycobacterium avium complex (non-MAC), wrote Roland Diel, MD, of University Medical Hospital Schleswig-Holstein (Germany) and his colleagues.

In particular, non-MAC species Mycobacterium xenopi (MX), Mycobacterium abscessus, Mycobacterium malmoense,
and Mycobacterium kansasii (MK) were addressed in the studies, which included 16 retrospective chart reviews, 5 randomized trials, and 3 prospective, nonrandomized studies (Chest. 2017. doi: 10.1016/j.chest.2017.04.166).

Treatment success was measured by rates of sputum culture conversion (SCC).

Overall, the average proportion of SCC for patients with M. abscessus was 41% after subtraction for post-treatment relapses, but reached 70% for subspecies M. massiliense in macrolide-containing treatments. The average proportion of SCC was 80% for patients with M. kansasii, 32% for those with MX, and 54% for those with M. malmoense.

Treatment success ranged from 9% to 73% for M. xenopi patients, but all-cause mortality was 69%. Of note, a 100% success rate was noted in M. kansasii patients using a three-drug TB regimen of isoniazid, rifampicin, and ethambutol, or with a combination of ethambutol, rifampicin, and clarithromycin, the researchers noted.

The percentage of SCC in 55 patients with lung resection and either MX or M. abscessus was considered high at 76%.

Dr. Diel reported receiving lecturing and/or consulting fees from Insmed and Riemser.
Study IDs infant pertussis cases that are ICU bound

BY BRUCE JANCIN

MADRID – Infants hospitalized for pertussis are more likely to develop severe disease requiring pediatric ICU admission if they are experiencing apnea, are unvaccinated against pertussis, or are less than 2 months old, Maria Arranz, MD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

“The presence of these parameters on admission should warn us of possible severe disease,” said Dr. Arranz of Gregorio Maranon Hospital in Madrid. Also, infants with severe pertussis develop significantly higher peak levels of leukocytes, lymphocytes, and neutrophils during their hospital stay, although not necessarily on admission, she added.

Dr. Arranz presented a retrospective observational study of 101...
children under 1 year of age who were hospitalized for pertussis at the Madrid tertiary center prior to the hospital’s 2016 shift to a strategy of maternal immunization during pregnancy as a means of preventing pertussis in infancy. Thirteen percent of the children required admission to the pediatric ICU and thus by definition had severe disease. Half of infants in the study were not vaccinated against pertussis. That proved to be a powerful risk factor for severe disease requiring ICU stay. Only 8% of children with severe pertussis were vaccinated, compared with a 48% vaccination rate among those who avoided the ICU.

Apneic pauses were noted in 67% of the severe disease group, compared with 28% of the infants who didn’t need the ICU. The pertussis patients admitted to the pediatric ICU averaged 1 month of age, compared with 2 months in the nonsevere group. The maximum leukocyte, lymphocyte, and neutrophil counts during the hospital stay of the severe disease group averaged 23,600 cells/mm³, 18,000/mm³, and 5,000/mm³, respectively, significantly greater than the 15,300, 10,700, and 3,900 cells/mm³ in infants who did not require the ICU.

### Prescribing Information

**Symbicort (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol**

The daily prednisone dose by 2.5 mg on a weekly basis during therapy with Symbicort. Long term (mean forced expiratory volume in 1 second [FEV1] or morning peak expiratory flow) data were collected between two Symbicort Budesonide 2.5mg/60mcg inhalers, which are not contained in the Symbicort label. This study assessed the efficacy and safety of inhaled corticosteroids, including budesonide, as a component of Symbicort. Therefore, dose monitoring is recommended in patients with a change in vision or with history of increased intracocular pressure, glaucoma, and/or cataracts.

Effects of treatment with Symbicort 100/4.5, Symbicort 400/5, foradila 4.5 mg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophtalmic examinations were conducted every 24 weeks, 26 weeks, and 28 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum (≥2) during the randomization period. Changes in posterior subcapsular scores of ≥1.7 from baseline to treatment maximum occurred in 11 patients (9%) in the Symbicort 160/4.5 group, 4 patients (8%) in the Symbicort 400/5 group, 5 patients (4%) in the formoterol group, and 4 patients (5%) in the placebo group.

**Leukopenia and Neutropenia**

Beta-adrenergic agonist medications may produce significant leukopenia in some patients, possibly through intrathoracic shrinkage, which has the potential to produce adverse cardiovascular effects. [See Clinical Pharmacology (12.2)] in the Full Prescribing Information]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with Symbicort at recommended doses.

**Drug Interactions**

Long-acting beta-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in Symbicort, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see Warnings and Precautions (5.1) in the Full Prescribing Information].

Systemic and inhaled corticosteroid use may result in the following:

- **Coadministration with other corticosteroids**
  - Coadministration with other corticosteroids may increase glucocorticoid effects.

- **Coadministration with other immunosuppressants**
  - Coadministration with other immunosuppressants may increase corticosteroid effects.

- **Coadministration with other agents**
  - Coadministration with other agents may increase corticosteroid effects.

**Precautions**

**Cardiovascular and Central Nervous System Effects**

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and inanition. [See Overdosage (10) in the Full Prescribing Information]. Therefore, Symbicort, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

**Reduction in Bone Mineral Density**

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, toba in use, advanced age, poor nutrition, or chronice use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have factors for decreased bone mineral content, monitoring and treatment of BMD should be considered in these patients. The decrease in BMD observed in osteoporosis was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline of -2.1% for hip BMD were observed in the Symbicort group and then Symbicort and periodontally by dental examination. If significant reductions in BMD on treatment with Symbicort and Symbicort is still considered medically important for that patient’s COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

**Effects of treatment with Symbicort 160/4.5, Symbicort 400/5, formoterol 4.5 mg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study.**

**Adverse Reactions**

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

**Clinical Trials Experience in Asthma**

**Adult and Adolescent Patients 12 Years of Age and Older**

The overall safety data in adults and adolescents are based on active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2023 females and 1341 males) with asthma of varying severity were treated with Symbicort 400/5 or 160/4.5 took 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on Symbicort had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of Symbicort 400/5 and Symbicort 160/4.5 once daily. The daily group was composed of mostly Caucasian (84%) patients with a mean age of 38 years. A mean predicted FEV1 of 75% predicted PEV1, at baseline of 70 and 68 for the 400/5 mg and 160/4.5 mg treatment groups, respectively. Control arms for comparison included 2 inhalations of beclometasone HFA (metered dose inhaler) (MDI) (80 mg) and foradila (0.125 mg) inhaler (DPI) (4.5 mg), or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of 2% in any one Symbicort group and more commonly than in the placebo group during daily dosing. In considering these data, the increased average duration of patient exposure for Symbicort patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.
Lung cancer metastatic sites differ by subtype

BY NEIL OSTERWEIL
Frontline Medical News
GENEVA – A review of data on more than 75,000 patients with lung cancer has revealed distinct patterns of metastasis according to subtype, a finding that could help in surveillance, treatment planning, and prophylaxis, an investigator contends.

Patients with small cell lung cancer (SCLC) had significantly higher rates of metastasis than patients with non-small cell lung cancer (NSCLC), while patients with NSCLC had significantly higher rates of metastases to bone, reported Mohamed Hendawi, MD, a visiting scholar at the Ohio State University Medical Center in Columbus.

Predictors for liver metastasis were small cell and adenocarcinoma histology, lower lobes and upper lobe locations, and high-grade tumors. Predictors for metastasis to brain were advanced age at diagnosis, adenocarcinoma and small-cell histology, lower lobe [and] main bronchus locations, and high-grade tumors,” he wrote in a scientific poster presented at the European Lung Cancer Conference.

Dr. Hendawi drew records on all patients with metastatic lung cancer included in the 2010-2013 Surveillance, Epidemiology, and End Results database. He used univariate and multivariate logistic regression models to evaluate predictors of metastasis.

The data set included a total of 76,254 patients with metastatic lung cancer, of which 17% were SCLC and 83% were NSCLC tumors. In 54% of patients, the primary tumor was in the right lung; in 38%, it was in the left lung; and, in 8%, patients of the primary tumor was bilateral.

The rates of metastases to bone were high in both major lung cancer types but, as noted before, were significantly higher in patients with NSCLC: 37% compared with 34% for patients with SCLC (P less than .001).

In contrast, the incidence of liver metastases in SCLC was more than double that of NSCLC: 46% vs. 20%, respectively (P less than .001). There were slightly, but significantly, fewer cases of brain metastases at the time of diagnosis among patients with SCLC: 25% vs. 26% (P = .03).

Histologic subtypes significantly associated with both brain and liver metastases were, in descending order, adenocarcinomas, small cell, and squamous cell cancers.

Although carcinoid lung cancers accounted for only 2.1% of all tumors, they were associated with a high rate of metastasis to brain at diagnosis (44.8%).

As noted, independent risk factors for liver metastasis were small cell and adenocarcinoma histologies (P less than .001), tumors in the upper lobe (P = .028), and high-grade tumors (P less than .001).

Independent predictors for brain metastases were advanced age at diagnosis (P less than .001), adenocarcinoma and small-cell histologies (P less than .001), lower lobe or main bronchus locations (P = .004), and higher-grade tumors (P less than .001).

Continued on page 36

Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SYMBICORT</th>
<th>Budesonide</th>
<th>Formoterol</th>
<th>Placebo</th>
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<tr>
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1. All treatments were administered at 2 intervals twice daily.
2. All data are expressed as percentages.

Table 2

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2. All data are expressed as percentages.
More early-stage cancer diagnosis since ACA

BY SUSAN LONDON
Frontline Medical News

Implementation of the Affordable Care Act (ACA) has been associated with a shift toward earlier stage at diagnosis for common screenable cancers, finds an analysis of nearly 273,000 patients reported in a press-cast leading up to the annual meeting of the American Society of Clinical Oncology.

"Extensive evidence has shown that people without insurance are more likely to be diagnosed at later stage, especially for the cancers that can be detected earlier through screening or symptoms," said lead study author Xuesong Han, PhD, strategic director of health policy and health care delivery research at the American Cancer Society in Atlanta. "In 2014, two major components of the Affordable Care Act – Medicaid expansion and marketplace exchange – were implemented. As a result, insurance coverage has substantially increased for nonelderly Americans."

Study findings showed that, for five screenable cancers – breast and cervical cancer in women and lung and colorectal cancer in both sexes combined – the proportion of cancers that were stage I at diagnosis, and hence most curable, increased by an absolute 1% or so after the ACA was implemented. Prostate cancer was the outlier: The value for this malignancy decreased by 1%.

"The increases for the first four cancers were consistent with our hypothesis, with more people gaining insurance and access to screening services or access to physicians to detect early symptoms," Dr. Han summarized. "But what about prostate cancer? We think [that pattern] may reflect the recent USPSTF recommendations against routine prostate cancer screening."

"We think that this is an important study," commented ASCO president-elect Bruce E. Johnson, MD, who is also chief clinical research officer and an institute physician at the Dana-Farber Cancer Institute in Boston. "Obviously, the changes are not enormous; they are not dramatic. But … because the uptake of screening is relatively slow, this is certainly consistent with the idea that, by doing additional screening, you can potentially find more stage I patients, and, the earlier the stage, the more likely one is to be cured."

"The other important thing is that ASCO strongly supports the relative ease of access to screening capabilities, and that’s one of the characteristics of the Affordable Care Act, that most of the cancer screening is covered," he further stated. "Whatever form our health care takes over the next several years, we advocate for patients to have early access to screening, which can identify cancers at an earlier stage in their more curable forms."

Study details

For the study, the investigators used the National Cancer Database—which captures 70% of newly diagnosed cases in the United States—to identify patients younger than 65 who were eligible for cancer screening and who received a diagnosis of any of the five screenable cancers in 2013 or 2014. They compared stage distribution before ACA implementation (first 9 months of 2013) and afterward (last 9 months of 2014).

Analyses were based on data from 121,402 female breast cancer patients aged 40-64 years, 39,418 colorectal cancer patients aged 50-64 years, 11,190 cervical cancer patients aged 21-64 years, 59,210 prostate cancer patients aged 50-64 years, and 41,436 lung cancer patients aged 55-64 years.

Results showed that the proportion of cancers that were stage I at diagnosis increased after ACA implementation from 47.8% to 48.9% for breast cancer (adjusted prevalence ratio, 1.02) and from 47.3% to 48.8% for cervical cancer (APR, 1.02) in women, and from 16.6% to 17.7% for lung cancer (APR, 1.07) and from 22.8% to 23.7% for colorectal cancer (APR, 1.04) in men and women combined. Dr. Han reported.

Prostate cancer was the exception, with the proportion of cases that were stage I at diagnosis falling from 18.5% to 17.2% (APR, 0.93).

In a stratified analysis, the significant downshift in lung and colorectal cancer stage was seen only in states that had actually adopted the Medicaid expansion component of the ACA, which covers low-income individuals, according to Dr. Han. The downshift in female breast cancer stage and upshift in prostate cancer stage occurred regardless of whether states had done so.

Dr. Han reported that she had no disclosures.

Critical Skills for Critical Care
A State-of-the-Art Update and Procedures for ICU Providers

August 11-13
CHEST Innovation, Simulation, and Training Center

Join an expert panel of nurse practitioners, physician assistants, and physicians for this state-of-the-art update in critical care medicine for the whole team, featuring intensive, hands-on, and simulation-based experience in high-yield ultrasound, mechanical ventilation, and airway management procedure skills.

Attend to:
- Study the latest evidence in critical care medicine from a team-based perspective.
- Get hands-on training in ultrasound imaging and interpretation, mechanical ventilator modes and settings, and airway management for the critically ill patient.
- Participate in concise, evidence-based reviews, case-based discussions, audience response, and expert debates in areas of clinical controversy.

Gain practical experience with:
- Necessary technical aspects of the CPET equipment
- The skills required for performing CPET, including calibration, maneuvers, testing, and biologic controls
- Data interpretation, including report creation and how to make informed CPET study recommendations

Prominent national and international exercise experts guide you through didactic and hands-on sessions about high-level interpretive strategies you can use to better support your exercise laboratory.

Target Audience
- Pulmonary physicians; pulmonary function testing and cardiology laboratory directors; advanced practice providers; family medicine, critical care, and pulmonary rehabilitation providers; pulmonary fellows; intensists; hospitalists; exercise physiologists; CPET laboratory medical directors; and cardiologists are encouraged to attend.

Learn More: livelearning.chestnet.org/critical-care

Cardiopulmonary Exercise Testing (CPET)
September 22-24

Prominent national and international exercise experts guide you through didactic and hands-on sessions about high-level interpretive strategies you can use to better support your exercise laboratory.

Gain practical experience with:
- Necessary technical aspects of the CPET equipment
- The skills required for performing CPET, including calibration, maneuvers, testing, and biologic controls
- Data interpretation, including report creation and how to make informed CPET study recommendations

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Learn More: chestnet.org/live-learning
Women may benefit from less cancer screening

BY NEIL OSTERWEIL
Frontline Medical News

GENEVA – A lung-cancer screening CT interval of once-yearly for men and once every 3 years for women appears to be the optimum schedule for detecting most early-stage lung cancers while minimizing radiation exposure, results of a retrospective study suggest.

Among 96 patients with lung cancers detected on follow-up screening CT, the mean interval time between initial CT and diagnostic CT was significantly longer among women than among men, at 5.6 vs. 3.6 years ($P = .02$), reported Mi-Young Kim, MD, a radiologist at Asan Medical Center in Seoul, South Korea, at the European Lung Cancer Conference.

Men tended to have a higher stage at diagnosis, however. Stage I cancers were diagnosed in 82% of women, but only 49% of men. Tumor size was also larger among men at presentation at a mean of 29.5 mm vs. 15.5 mm, Dr. Kim and her colleagues found.

Current lung cancer screening guidelines vary somewhat, but most recommend annual screening for people aged 55-80 years who have a 30-pack-year or greater smoking history and are current smokers or have quit within the last 15 years. Prior studies to see whether longer screening intervals were safe have yielded mixed results, possibly because of differences in clinical and radiologic presentation between men and women, Dr. Kim said.

To explore sex differences in lung cancer at the time of diagnosis, she and her colleagues retrospectively reviewed records for 46,766 patients who underwent screening at their center from January 2000 through February 2016, during which time, 282 patients were diagnosed with lung cancer. Of this group, 186 were...
diagnosed from the initial screening CT scan, and 96 – the cohort included in the study – were diagnosed from subsequent scans. The authors found that the majority of men (72%) had solid nodules as the primary pathology. In contrast, ground-glass opacities were the most common nodular finding among women, occurring in 45% of the cases. The most common histology among men was adenocarcinoma (42%), followed by squamous-cell carcinoma (35%), small cell lung cancer (18%), and others (9%). All women presented with adenocarcinoma histology.

“Because ground-glass opacity nodule is the most common feature of lung cancer in women, and all cases are adenocarcinoma, the growth rate of cancers might be low,” Dr. Kim said in a statement.

The investigators found that 100% of tumors detected at 1 year in men were operable, compared with 94% of those detected at 2 years, and 55% for those detected at the 3-year interval. In contrast, among women, there were no tumors detected at 1 year, one operable tumor and no inoperable tumors at 2 years, and two operable and no inoperable tumors at 3 years. Beyond 3 years, however, the rate of inoperable tumors at the time of diagnosis was 32% in men and 25% in women.
Family Fun in Toronto!

While attending CHEST 2017 from October 28 to November 1, your days will be filled with cutting-edge sessions on pulmonary, critical care, and sleep medicine. However, if you take the week and bring your family along, you can have a fun and memorable vacation with the variety of family-friendly activities Toronto has to offer!

**Family Escape Room - Loonie/Luck/The Moonshine Mile**

**Weekly Friday-Sunday**

Enter these escape and mystery rooms to solve fun mysteries. Follow the clues, solve the puzzles, open the locks, and beat the clock! Enter the Loonie for Luck room, where you and your group have to recover Canada’s Lucky Loonie hockey puck and return it to Team Canada. Or, enter The Moonshine Mile room, where you play the owner of a race horse and must find the culprit who poisoned your horse, Hoof Hearted. You have 60 minutes, can you solve these mysteries? Special family pricing available.

**Royal Ontario Museum - Dinosaur Gallery**

Enter a gallery showcasing one of the world’s best dinosaur collections. See the mighty T. rex, visit Gordo, the enormous Barosaurus, or stand beside the famous hadrosaur Parasaurolophus.

**Ripley’s Aquarium of Canada**

Visit the many amazing galleries at Ripley’s Aquarium of Canada, including Waters, Dangerous Lagoon, Discovery Center, Planet Jellies, the dive shows at Rainbow Reef and Ray Bay, and more! There are many activities and programs you and your kids will love.

**Toronto’s Ultimate Chocolate Tour**

Saturdays, 1:00 PM - 4:00 PM

If you consider yourself a chocolate lover, you must go on the only chocolate tour in Toronto that divulges the art of chocolate tasting and sampling chocolate from bean to bar. Enjoy chocolates and chocolate sweets while learning more about chocolate from chocolatiers and store owners. There will even be an exclusive demonstration of chocolate making by an award-winning chocolatier!

**Ontario Science Centre**

An iconic cultural attraction and Toronto’s only children’s museum, the Ontario Science Centre is home to interactive and engaging experiences with science and technology. KidSpark is the extremely popular ball hall designed for children under eight to learn, explore and create with their caregivers.

Check out exhibits like In Space with a state-of-the-art planetarium, The Astrazeneca Human Edge, A Question of Truth, Living Earth that includes a state-of-the-art planetarium, The As-

**UPTRAVI® (selexipag)**

**Geriatic Use**

Of the 1368 subjects in clinical studies of UPTRAVI 248 subjects were 65 years of age and older. No overall differences were observed between these subjects and younger subjects, and other reported clinical experience with selexipag and its active metabolite have not identified differences between the elderly and younger patients, but greater sensitivity cannot be ruled out.

**Patients with Hepatic Impairment**

No adjustment to the dosing regimen is in patients with mild hepatic impairment.

A once-daily regimen is recommended in patients with moderate hepatic impairment (AUC ratio = 1.0 vs healthy volunteers) due to the increased exposure to selexipag and its active metabolite.

There is no experience with UPTRAVI in patients with severe hepatic impairment (see Clinical Pharmacology: Pharmacokinetics).

No adjustment to the dosing regimen is in patients with estimated glomerular filtration rate <30 mL/min/1.73 m² (see Clinical Pharmacology: Pharmacokinetics).

**Clinical Pharmacology**

**Pharmacodynamics**

In subjects with mild Child-Pugh class A or moderate Child-Pugh class B hepatic impairment, exposure to selexipag was 2-4-fold that seen in healthy subjects. Exposure to the active metabolite of selexipag remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment.

Based on pharmacometric modeling of data from a study in subjects with hepatic impairment, the changes in the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice-daily regimen.

**Renal Impairment**

A 40% increase in maximum plasma concentration and area under the plasma concentration-time curve to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate <15 mL/min/1.73 m²) (see Use in Specific Populations: Drug Interactions).

**Drug Interactions**

**Strong CYP2C8 Inhibitors**

Concomitant administration with strong inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite. Avoid concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) [see Clinical Pharmacology: Pharmacokinetics].

**Use in Specific Populations**

**Pregnancy**

No information is available regarding the use of selexipag in pregnant women. Animal reproduction studies have not demonstrated a risk to the human fetus. There are no adequately controlled studies in pregnant women. The results of in vitro drug interaction studies are presented in Table 1.

**Artificial Data**

Pregnant rats were treated with selexipag using oral doses of 2, 6, and 20 mg/kg/day, up to 47 times the exposure at the maximum recommended human dose of 1600 mcg twice daily on an area under the curve (AUC) basis during the period of organogenesis (gestation days 7 to 17). Selexipag did not cause adverse developmental effects to the fetus in this study. A slight reduction in fetal body weight was observed in parallel with a slight reduction in maternal body weight at the high dose.

Pregnant rabbits were treated with selexipag using oral doses of 3, 10, and 30 mg/kg up to 50 times the exposure to the active metabolite at the maximum recommended human dose on a body weight basis during the period of organogenesis (gestation days 6 to 18). Selexipag did not cause adverse developmental effects to the fetus in this study.

**Pulmonary Arterial Hypertension**

**Drug Interaction Studies:**

Selexipag and its active metabolite are substrates of OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of breast cancer resistance protein (BCRP). The glucuronidation of the active metabolite is catalyzed by UGT1A3 and CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and CYP3A4.

**Renal Impairment:**

A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. There is no experience with UPTRAVI in patients with severe hepatic impairment (see Clinical Pharmacology: Pharmacokinetics).

**OVERDOSAGE:**

No cases of overdose were reported in clinical studies in patients under 65 years of age.

**STORAGE AND HANDLING:**

Selexipag is stable under a wide range of environmental conditions. Keep out of the reach of children.

**HOE Hearted**

Your days will be filled with cutting-edge sessions on pulmonary, critical care, and sleep medicine.
Expanding Disease Awareness Campaigns

In 2017, we’ve continued to push our disease awareness efforts in lung cancer, sarcoidosis, asthma, and COPD, trading our “awareness months” for longer, more sustainable campaigns.

Lung Cancer
Our lung cancer disease awareness campaign launched mid-May and goes through World Lung Cancer Day on August 1, 2017. The foundation is partnering with the Bonnie J. Addario Lung Cancer Foundation and LUNGevity to produce:
• Biopsy-specific infographics
• An animated biopsy video to show the importance of collecting core tissue to create targeted therapies
• Social media shareable postcards
• An updated lung cancer guide and infographic
• New lung cancer landing page and website

Sharing these resources through the CHEST social media channels, we have so far been able to reach more than 34.2K social media accounts and earn 512 social interactions, including likes/reactions, clicks, and shares/retweets from Twitter, Facebook, and LinkedIn. We are also excited to participate in a Lung Cancer Living Room discussion with the Bonnie J. Addario

Continued on page 41

This Month in CHEST:
Editor’s Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief, CHEST

GiANTS IN CHEST MEDICINE
John B. West, MD, PhD, DSc
By Dr. F. L. Powell

ORIGINAL RESEARCH
Endothelial Permeability and Hemo-
stasis in Septic Shock: Results From the ProCESS Trial.
By Dr. P. C. Hou, et al.

Maximal Inspiratory Pressure: Does the Choice of Reference Values Actually Matter?
By Dr. A. Rodrigues, et al.

Research Into Childhood Obstructive Sleep-Disordered Breathing: A Systematic Review
By Dr. R. P. Venekamp, et al.

Topics in Practice Management
Low-Dose CT Scan for Lung Cancer Screening: Clinical and Coding Considerations
By Drs. Y. Shieh and M. Bohnenkamp

References:
SLEEP STRATEGIES: Group 3 pulmonary hypertension linked to sleep-disordered breathing

BY RAVISH SINGHAL, MD, AND RUTH MINKIN, MD

Pulmonary hypertension (PH) is a progressive disease characterized by an increase in pulmonary arterial pressure and pulmonary vascular resistance (PVR) leading to right ventricular failure. Although substantial progress has been achieved in the treatment of PH, mostly due to improved pharmacotherapy, it remains a life-threatening disease with a poor prognosis. Increased pulmonary arterial pressure is a common feature of many chronic lung diseases, and chronic lung disease is the second most common cause of pulmonary hypertension. PH caused by chronic lung disease, including PH due to sleep-disordered breathing (SDB), is referred to as group 3 PH in the classification of pulmonary hypertension (Simonneau et al. J Am Coll Cardiol. 2013;62:D34 e41). Many reports since have linked pulmonary arterial hypertension to obstructive sleep apnea (OSA). These were validated in animal trials, when rodents were exposed to intermittent hypoxia for several hours over a few weeks, similar to what is seen in patients with OSA; this resulted in pulmonary vascular remodeling, sustained PH, and right ventricular hypertrophy. As with other chronic lung disease, prevalence rates of PH in SDB vary greatly, with some studies suggesting prevalence of pulmonary hypertension in OSA to be as high as 40%, although a lack of large-scale studies with clearly defined patient populations makes it difficult to determine the true prevalence rate. Most studies suggest that about 20% to 30% of patients with OSA have some degree of PH. OSA has been shown to be an independent causal factor for the development of PH (Hurdman et al. Eur Respir J. 2012; 39, 945–955). PH associated with OSA appears to be mild and may be due to a combination of precapillary and postcapillary factors, including pulmonary arteriolar remodeling, hyperreactivity to hypoxia, and left ventricular diastolic dysfunction resulting in left atrial enlargement. Despite differences in reported prevalence rates, most studies consistently reported mild increases in pulmonary arterial pressure with mPAP averaging less than 30 mm Hg. In one of the largest studies to date, the prevalence rate of PH in 220 patients with SDB was 17%, and the mPAP was 26 ± 6 mm Hg (Chauvat et al. Chest. 1996;109(2):380). The other consistent finding in most studies was that PH correlated with the severity of obesity, daytime hypoxia and hypercapnia, obstructive airways disease, and nocturnal oxygen desaturation. PH seems to be more common and more severe in obesity hyperventilation syndrome (OHS) than in “pure” OSA patients (58% vs 9%) (Kessler et al. Chest. 2001;120(2):369).

The incidence of OSA is rising in parallel with the rising global incidence of extreme obesity, and it is increasingly becoming a rapidly growing health problem in the United States and worldwide. It remains largely undiagnosed and has been linked to an increased incidence of stroke, heart failure, myocardial infarction, and arrhythmia. OSA is characterized by repetitive nocturnal arterial oxygen desaturations and hypercapnia, large intrathoracic pressure swings, and acute increases in pulmonary arterial pressure. PH in patients with OSA is thought to be due to hypoxia-related vasoconstriction that occurs during these apneic periods and can lead to progressive vascular damage resulting in accelerated inflammation and sympathetic activity; this eventually leads to subclinical myocardial injury and the potential development of biventricular systolic and diastolic dysfunction and resultant elevated cardiac biomarkers (Adegunsoye et al. Pulm Med. Published online 2012 Jul 11. doi: 10.1155/2012/273591). It is still unclear whether PH associated with chronic lung disease (CLD) and SDB is a direct consequence of hypoxemia (as seen in CLD and SDB) or whether this is due to a cascade of events that leads to pulmonary vascular disease that is separate from or out of proportion to the underlying lung injury from existing pulmonary processes.

Patients with OSA who have PH are more likely to be obese, have decreased respiratory function (FEV₁, vital capacity, and FEV₁/VC ratio), and lower oxygen saturation/higher carbon dioxide content in blood (Chauvat et al. Chest. 1996;109(2):380). These patients frequently present with shortness of breath and dyspnea on exertion. Echo-cardiogram remains the main screening tool for evaluation of PH. With that said, right-sided heart catheterization remains the gold standard for the diagnosis of all classes of PH; however, use of right-sided heart catheterization in group 3 pulmonary hypertension is reserved for select patients. This is likely because PH in patients with OSA is accepted as a more benign prognostic marker compared with other group 3 forms. Furthermore, patients with OHS are more prone to developing PH and cor pulmonale compared with patients with isolated OSA. OSA with PH has lower survival rates than OSA without PH. Studies showed that patients with OHS tend to do worse than patients with OSA alone (Aljohara et al. J Thorac Dis. 2017;9(3):779).

AHI and PH Various studies have looked at different polysomnographic variables to understand the relationship between PH and OSA. Initial studies showed that the apnea hypopnea index (AHI) does not predict development of PH among patients with OSA. Decrements in nocturnal oxygen saturation, however, is predictive of the development of PH; the only predictor of developing PH among patients with OSA in one study was time spent with oxygen saturation below 70% during sleep (Wong et al. Eur Arch Otorhinolaryngol. 2017;274(2):2601). In addition, recent data suggest there is no statistically significant association between age, gender, body mass index, or AHI and chance for development of PH (Wong et al. 2017). It was found that the percentage of time during sleep with oxygen saturation below 90% was significant and independently associated with higher PAP. Furthermore, a recent study demonstrated that patients with moderate to severe OSA (AHI over 15/h) who develop PH tend to have worse hemodynamics (higher PVR and mPAP) and subclinical myocardial damage (evaluated by troponin T), as well as increased ventricular wall stress (assessed by probNP) when compared with patients with mild OSA (AHI less than 15/h).

Treatment The mainstay treatment for OSA and OHS is positive airway pressure (PAP). This therapy has been shown to improve sleep and respiratory parameters, including sleep quality, overall quality of life, as well as promote reduction in mean pulmonary arterial pressure. The regular use of noninvasive positive-pressure ventilation has also been shown to reverse daytime hypoxia and hypercapnia, as well as influence inflammatory markers: decrease circulating levels of endothelin-1, interleukin-6, and C-reactive protein, thereby improving vascular endothelial function and reducing platelet activation and aggregation (Yokoe et al. Circulation. 2003;107[8]:11129). Indeed, there is a decrease in mean pulmonary arterial pressure in some patients with long-term daily use of PAP, but, in some patients, both pulmonary and right ventricular dysfunction persists, suggesting vascular remodeling and/or endothelial dysfunction. These findings indicate the need for early recognition of OSA and early treatment for patients, thus preventing remodeling and further development of PH and right ventricular dysfunction. Adequate control of OSA/OHS has important long-term effects on overall health, because it significantly reduces the risk of systemic hypertension, congestive heart failure, arrhythmias, and stroke. It is imperative to control underlying SDB before considering PAH-specific medications to treat PH associated with OSA or OHS unless the patient is demonstrating signs of right-sided heart failure; in such cases, concomitant therapy may be considered upfront. It is recommended that patients with SDB should have an assessment for PH before starting therapy for their SDB and then again after 3 to 4 months of effective PAP confirmed by device data monitoring. For patients who have persistent PH despite achieving adequate control of their SDB, pulmonary vasodilator therapy may be indicated following standard treatment guidelines for WHO group 1 PAH (Galie et al. J Am Coll Cardiol. 2013;62[suppl 25]:D60–72). Medications that are currently approved for the treatment of PAH have not been well studied in PH associated with SDB and, at present time, the available data do not demonstrate sustained benefit.

Dr. Singhal is a second-year fellow in Pulmonary/Critical Care and Dr. Minkin is Director, Pulmonary Hypertension Program, New York Presbyterian-Brooklyn Methodist Hospital. Dr. Minkin is also Assistant Professor of Clinical Medicine, Weill Cornell Medical College, New York.
Lung Cancer Foundation. This presentation will bring lung cancer specialists, physicians, patients, and the public together to discuss lung cancer in a relaxed and comfortable setting. Attendees will have the opportunity to ask questions, share their stories, and discuss issues surrounding lung cancer. The event will also be live-streamed and archived on the Bonnie J. Addario Lung Cancer Foundation’s website.

Asthma
We launched our asthma campaign at “The Air We Breathe” Summit with The Atlantic. We were able to reach more than 24.2K social accounts through live tweeting during the event and follow up posts on CHEST’s Twitter and Facebook accounts. The Atlantic was able to earn an impressive reach of 868K social accounts through their own social media promotion for the event. To read more about the event that focused on severe and difficult-to-control asthma, this campaign has already garnered over 53.4K social media impressions through CHEST channels, and over 1.3K social interactions. New components to the campaign include:

- Severity assessment tool
- Shared decision making tool
- Patient testimonial videos

Our campaign also included an 8-minute segment on the Access Health program, which aired two times in May on Lifetime NetWork, with an additional 200+ airings via syndication throughout 100 US markets.

Sarcoidosis
For the third consecutive year, we’ve partnered with the Foundation for Sarcoidosis Research to spread awareness on the disease. We also partnered with the American Osteopathic Association, the COPD Foundation, and The Society of Thoracic Surgeons to create and disseminate campaign materials. Their social media and member communication efforts gained more than 19.4K social media impressions and reached a total of over 44.5K members from each organization.

In CHEST member communications, our campaign reached more than 20,000 people, and our social media posts have reached more than 61.7K social accounts. CHEST’s press release on sarcoidosis has reached well over 11.6M clinicians and patients.

We are very grateful and proud of the work our partners have done to help us spread awareness on these diseases, so clinicians and patients will be able to use our resources to champion lung health.

In Memoriam
CHEST has been informed of the following deaths. We extend our sincere condolences.

Henry J. Heimlich MD, FCCP (December 2016)
Sylvan Lee Weinberg, MD, FCCP (Past President-1983-84) (January 2017)
Clive Deutscher, MD, FCCP (January 2017)
Sandra Willisie, DO, FCCP (March 2017)
Arthur F. Reimann, MD, FCCP (March 2017)
Cynthia Ray, MD, FCCP (April 2017)
Brian J. Sproule, MD, MS, FCCP (April 2017)
Michael R. Bye, MD, FCCP (April 2017)
Paul J. Mathews, MD, FCCP (May 2017)
Oxygen therapy, electronic consent, diagnosing ILD

Airways Disorders

**Oxygen therapy in patients with COPD with moderate desaturation**


They studied 738 stable patients with COPD with mild to moderate resting desaturation (\(\text{SpO}_2\) 89%-93%) or exercise-induced moderate desaturation (\(\text{SpO}_2\) greater than or equal to 80% for greater than or equal to 5 minutes and \(\text{SpO}_2\) less than 90% for greater than or equal to 10 seconds during 6-minute walk test). After a median follow-up of 18.4 months, LTOT did not demonstrate a decrease in the time to death or first hospitalization and did not show improvement in quality of life or functional status. Notable adverse events from oxygen included 23 instances of tripping over equipment, with two patients requiring hospitalization and six fires with one patient hospitalized for burns.

A Cochrane meta-analysis, which did not include LOTT data, revealed that oxygen relieved breathlessness during acute exercise in mildly-moderately hypoxic patients with COPD, but there was insufficient evidence of benefit in daily life or in health-related quality of life (Cochrane Database Syst Rev. 2016;11:CD006429).

**Clinical Research**

**Informed consent: Do we need to change our practice?**

Informed consent is the cornerstone of clinical research and helps respect and protect the rights of the participants/subjects. While the informed consent process has been standardized, some challenges still remain, such as pieces of information that should be disclosed, how to disclose information and document understanding of participants, and how detailed that disclosure should be (Grady C. *N Engl J Med.* 2015;372[9]:855). Digital technology can and has been used to improve the process of obtaining informed consent. Smartphones now comprise 75% of all mobile phones sold worldwide. They are being used to reach a larger and diverse population to conduct trials.

Substituting long and complex consent forms with short and simple ones is likely to be welcomed by both patients and researchers. Clinical research informed consent documents benefit from being brief, clear, and patient-friendly.
written forms with electronic consent (e-consent), however, has issues. Few people read through online agreements before clicking “agree,” which may lead to participants consenting without a clear understanding of what they are consenting to. On the other hand, it is also possible to use e-consent to improve comprehension by including videos and graphics. Interactive quizzes can assess the understanding of the participants, and embedded links to audios or videos can further enhance the grasp of information. With e-consents, queries from participants can be answered via phone call or email, etc. When e-consent is obtained remotely, the identity can be confirmed by electronic signatures, username, password, or biometrics.

E-consent has advantages, can be done remotely, no paper is needed, etc. It has potential disadvantages like being costly, videos can add time to the process, and multicenter international trials can be difficult (Grady C, et al. N Engl J Med. 2017;376(20):e43).

Studying e-consents to identify gaps in communication between the researcher and the participant in the digitalized world may help improve the process and allow research to proceed with better understanding of the risks and benefits of involvement in clinical research.

Mooskin Ijaz, MD, FCCP
Steering Committee Member

Home-Based MV and Neuromuscular Disease

The changing landscape of home mechanical ventilation

The greatest advances in home mechanical ventilation for conditions associated with chronic respiratory failure have been associated with the implementation of noninvasive positive pressure ventilation (NIPPV) via mask interface. This dynamic growth is attributed to NIPPV efficacy and technologic improvements in ventilator and mask. For neuromuscular and respiratory impairment overlapping of the three factors is a possible explanation. The authors argue that the safety of this combined therapy and potential benefit justifies its implementation pending the confirmation of this single-center study. What is clear is that these encouraging results deserve further study in clinical trials.

MaximilianoTamae Kakazu, MD, FCCP
Steering Committee Member

Critical Care

Early ID and treatment in sepsis

PRISM, the latest meta-analysis of three multicenter trials (ProCESS, ARISE, and ProMISE) found no difference in mortality with early goal-directed therapy vs usual care (N Engl J Med. 2017;376(23):2223). These clinical trials promoted early recognition of sepsis and prompt delivery of IV fluids and antimicrobial agents before randomization. It seems that early identification and treatment of sepsis and the rapid administration of antibiotics (following the timing recommended for sepsis bundle protocols) are the most effective interventions in sepsis (Seymour WS, et al. N Engl J Med. 2017;376(23):2235). Other interventions over the past decade designed to reduce mortality associated with sepsis have been unsuccessful.

However, the recent results of a retrospective before-after clinical study in patients with severe sepsis or septic shock and a procalcitonin greater than 2 ng/ml are encouraging. It suggests that the early use of IV vitamin C, hydrocortisone, and thiamine may reduce mortality and prevent progressive organ dysfunction when compared with matched historical control subjects (Marik PE, et al. Chest. 2017;151(6):1229).

Although vitamin C and thiamine have been reported to be low in critically ill patients, their use in patients with sepsis without deficiency is unclear. In addition, the use of steroids in sepsis has been controversial. A synergistic or overlapping effect of the three agents is a possible explanation. The authors argue that the safety of this combined therapy and potential benefit justifies its implementation pending the confirmation of this single-center study. What is clear is that these encouraging results deserve further study in clinical trials.

DR. KAKAZU

DR. CAO

Syst Rev. 2014;13(12):CD001941). From this success, NIPPV has been extended to conditions associated with respiratory impairment (eg, COPD, obesity hyperventilation, sleep-disordered breathing). A recent randomized study comparing home oxygen therapy (HOT) plus NIPPV vs HOT alone in post-hospitalized patients with COPD with persistent hypercapnia showed that addition of NIPPV significantly prolonged time to readmission or death from 1.4 to 4.3 months (Murphy P, et al. JAMA. 2017;317(21):2177). Overall, however, evidence to support NIPPV in these groups is less compelling. NIPPV is available in both ventilator and respiratory assist device (RAD) models. In addition to delivering basic to complex modes, advantages of a ventilator include portability and option of daytime use with mouth piece ventilation. This creates potential for abuse whereby a supplier could bill for a portable ventilator when an RAD at lower cost would suffice. Monthly rental fee for an RAD ($107-$464) is capped at 13 months, whereas ventilator comes with uncapped rental ($660-$1352) [US Dept HHS, OIG Data Brief 2016, OEI-12-15-00370].

Billing claims for ventilator have shifted from neuromuscular disease to chronic respiratory disease (eg, COPD). Ventilator claims for neuromuscular disease have decreased from 56% in 2009 to 7% in 2015, whereas claims for chronic respiratory failure have increased from 29% in 2009 to 85% in 2015. The substantial increase in claims have no doubt increased burden on health-care systems and resulted in reimbursement cuts.

Current CMS guidelines defer to the provider’s clinical judgment regarding the severity of patient’s respiratory condition and if a ventilator or RAD would be most appropriate. It is important to recognize the proper patient (and setting) who would benefit from advanced respiratory support. The choice of ventilator should be reserved for severe or progressive respiratory impairment, specifically for patients who would benefit from daytime use, and for whom interruption of respiratory support would lead to serious consequences.

Michelle Cao, DO, FCCP
Steering Committee Member

“Given the invasive nature of surgical lung biopsy and its associated morbidity in elderly patients, there is a need for safer techniques to obtain lung tissue for histopathologic analysis.”

Interstitial and Diffuse Lung Disease

Improving diagnostic capabilities in diffuse parenchymal lung disease

With the approval of two antifibrotic drugs for the treatment of idiopathic pulmonary fibrosis, there has been renewed focus in the NetWork in improving diagnosis in interstitial lung disease. There is considerable interest in exploring novel techniques and paradigms in the classification and diagnosis of diffuse parenchymal lung diseases (DPLDs). Given the invasive nature of surgical lung biopsy and its associated morbidity in elderly patients, there is a need for safer techniques to obtain lung tissue for histopathologic analysis. Transbronchial cryobiopsy may be a safe and accurate alternative for obtaining lung tissue, and we hope to better understand the role of this procedure in disease diagnosis. It is also possible that in the future, we may be able to classify these diseases without having to obtain lung tissue. More studies are being done in novel imaging techniques, such as molecular imaging, optical coherence tomography, and confocal laser endomicroscopy, that may negate the need for lung tissue in the future. Biomarker discovery and identification of biomarker signatures that can help differentiate DPLDs and provide prognostic information are also a particular focus and of importance for our NetWork. With this increased focus on better diagnostic techniques for classification of DPLD, the NetWork is featuring a lecture at CHEST 2017 on “Molecular Endotyping of Pulmonary Fibrosis,” and two sessions that will explore the current diagnostic difficulties that confront clinicians. As we move forward in our understanding of how to classify and diagnose interstitial lung disease, there is potential for more targeted interventions in individual patients.

Tracy Luckhardt, MD
Steering Committee Member

DR. CAO
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