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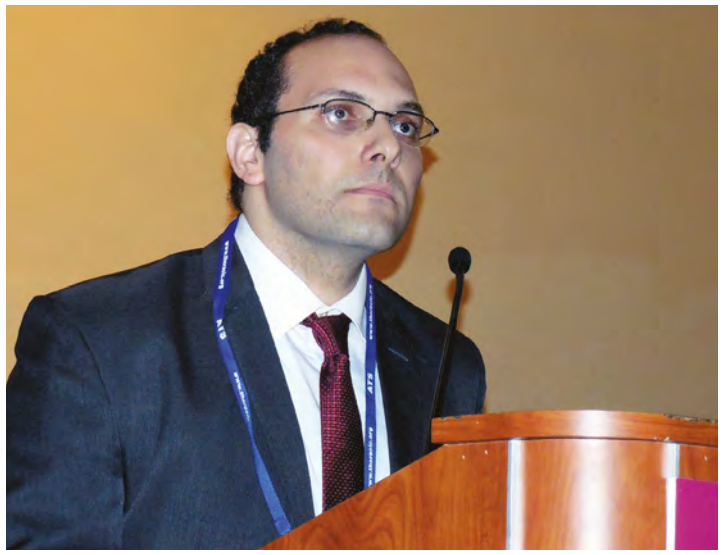

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

The high suicide rate may reflect the low progression-free survival rate often seen, Dr. Mohamed Rahouma noted.

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*

Program predicts who will progress to septic shock

Algorithm monitors patients' EHR entries

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – Researchers have devised a program that can predict severe sepsis or septic shock about 12-30 hours in advance of its onset in hospitalized patients, a feat they hope will allow them to apply early interventions to stave off impending sepsis.

"We'd love to see a change in sepsis mortality. Will earlier recognition and implementation of the sepsis bundle – fluids, antibiotics, etc. – improve outcomes?" wondered Heather M. Giannini, MD, at an international conference of the American Thoracic Society.

The computer program works by monitoring all the data that enter a patient's electronic health record during hospitalization. Researchers developed it and designed it specifically for inpatients who are not in the intensive care unit or emergency department.

Results from initial testing during October-December 2015 in 10,448 patients hospitalized at one of three participating Philadelphia hospitals showed the program predicted subsequent severe sepsis or septic shock with a sensitivity of 26%

See **Septic shock** • *page 7*

Mild OSA linked to hypertension

BY DEBRA L. BECK
Frontline Medical News

BOSTON – Sleep apnea doesn't have to be severe or even symptomatic to increase the risk of hypertension and diabetes, according to a pair of new studies.

"We found that even mild sleep apnea was strongly associated with increased risk of developing hypertension by four times, compared to individuals without sleep apnea," said principal investigator and top sleep researcher Alexandros N. Vgontzas, MD, of Pennsylvania State University College of Medicine in a statement. "Similarly, moderate sleep apnea was associated with increased risk of developing diabetes by almost three times, compared to individuals without sleep apnea."

Dr. Vgontzas presented his team's results on the link between mild to moderate OSA and hypertension at the annual meeting of the American Academy of Sleep Medicine. In a separate session, his colleague at Penn State, Yun Li, MD, presented the diabetes-relat-

See **OSA** • *page 6*

INSIDE

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

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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]

†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).[2] 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 (%DL_{co}) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[3] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{co} ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{co} ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[4] 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]

‡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).[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.

‖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]

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 dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

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

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

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

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

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

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

Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

References: 1. Data on file. Genentech, Inc. 2016. **2.** Esbriet Prescribing Information. Genentech, Inc. January 2017. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083–2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760–1769.

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

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

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

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 6,661 patents 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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VIEW ON THE NEWS

Vera A. De Palo, MD, FCCP, MBA, comments: In those first moments after receiving a diagnosis of lung cancer, patients experience a sense of shock and disbelief, of being overwhelmed with the necessary tests, decisions, and treatments, and at times feelings of hopelessness. The authors have reported high rates of suicide in lung cancer patients compared with other cancer patients, with the highest rates of suicide within the 8 months following diagnosis. Consideration of the psychological, emotional, and spiritual needs of the patient, in addition to the medical needs, will help us treat the whole patient for the best outcomes.

Moderate OSA ups diabetes risk

OSA *from page 1*

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.

"In young and middle-aged adults, our findings suggest that early detection and treatment of mild to moderate sleep apnea is warranted in order to prevent future cardiometabolic disease," said Dr. Li in a press release.

"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.

DEBRA L. BECK/FRONTLINE MEDICAL NEWS

Dr. Vgontzas: yearly monitoring of metabolic symptoms needed.

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.

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

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

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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 as 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 hundred 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.

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VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Early identification and treatment of sepsis should lead to improved outcomes from this serious and life-threatening condition. A new computer-based system that will allow physicians to identify these patients more expeditiously and with greater certainty is likely to improve medical care. However, identification of septic patients is only the first step. Appropriate, evidence-based interventions must be rapidly initiated in septic patients if one is to save the lives of these critically ill individuals. A system that rapidly allows for patient identification, facilitates sepsis treatment bundles, and can rapidly incorporate physician decision-making will represent an ideal future goal.

NIH releases COPD National Action Plan

BY KATIE WAGNER LENNON
Frontline Medical News

WASHINGTON – The National Heart, Lung, and Blood Institute of the 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 pulmonology 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.

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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 prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

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

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

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

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

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

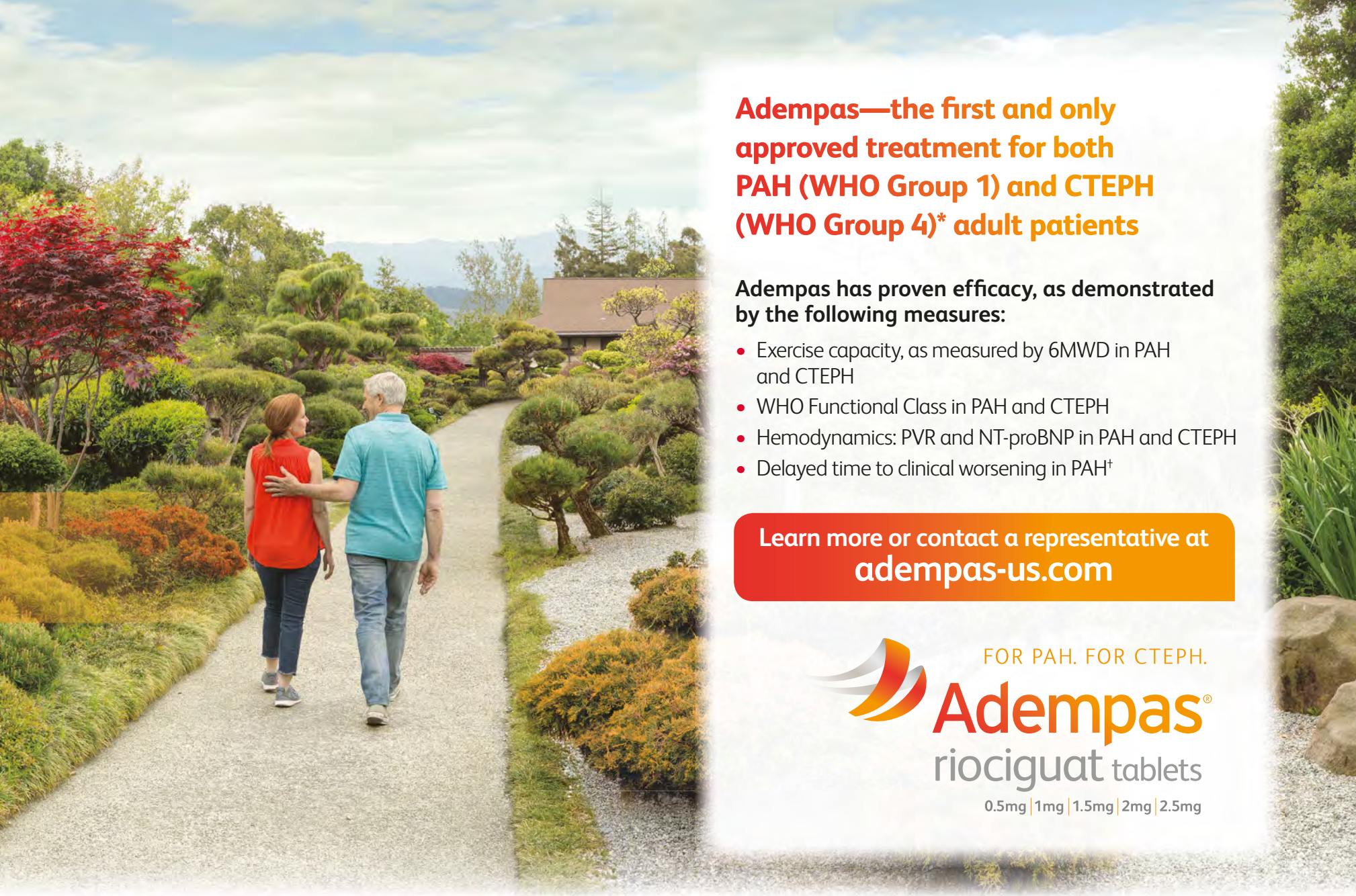
CONTRAINDICATIONS

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.



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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

FOR PAH. FOR CTEPH.

Adempas®

riociguat tablets

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

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.

Bayer
100 Bayer Boulevard, Whippany, NJ 07981 USA

PP-400-US-3547 May 2017

ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

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

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer Adempas to a pregnant female because it may cause fetal harm *[see Contraindications (4.1), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Dosage and Administration (2.3), Warnings and Precautions (5.1, 5.2),and Use in Specific Populations (8.6)]*.**
- **For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program *[see Warnings and Precautions (5.1, 5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

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

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) *[see Clinical Studies (14.2)]*.

4 CONTRAINDICATIONS

4.1 Pregnancy

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

4.2 Nitrates and Nitric Oxide Donors

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

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated *[see Dosage and Administration (2.6), Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.

4.4 Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP)

Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

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

5.2 Adempas REMS Program

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

Important requirements of the Adempas REMS Program include the following:

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

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

5.3 Hypotension

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

5.4 Bleeding

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

5.5 Pulmonary Veno-Occlusive Disease

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

6 ADVERSE REACTIONS

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

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Bleeding *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypo-tension *[see Contraindications (4.2) and Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil *[see Dosage and Administration (2.6)]*. Clinical experience with co-administration of Adempas and other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50% 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 hypotensive effect of riociguat *[see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

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

Animal Data

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Females and Males of Reproductive Potential

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

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

8.7 Renal Impairment

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

8.8 Hepatic Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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 her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

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

Inform female patients (and their guardians, if applicable) of the following important requirements:

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

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

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). 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

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

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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/k^2. 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.

Philips Respironics, ResMed, the ResMed Foundation, and the Guy's and St. Thomas's Charity funded the study. The researchers reported financial support from ResMed, Philips Respironics, and B&D Electromedical.

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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

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.

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: The functional improvement and other gains of pulmonary rehab are wel 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 technology-based programs is needed, but the results of this study (and several others like it) hold great promise for expanding these resources to a larger group of patients. One challenge is to emulate all of the components of a facility-based program in a technology-based platform (e.g., including the self-management educational piece), but with ongoing development and revision, a meaningful program certainly can be devised.

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, know 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

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: The results obtained from the use of this scoring system could be important in the prognostication of patients with ARDS, although it is unclear how the score would be used to alter clinical decision making. Further, issues may arise in its implementation given the somewhat subjective nature of the scoring (e.g., hazy vs. moderate vs. dense opacity), changing factors in the ICU that may affect the lung density on x-ray (e.g., different levels of positive end-expiratory pressure), and the variable quality of chest x-rays in the ICU.

Hyperinflammatory ARDS responds to simvastatin

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – 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

hypoinflammatory group, Carolyn S. Calfee, MD, said at an international conference of the American Thoracic Society.

"Hyperinflammatory patients treated with simvastatin may have improved outcomes, compared with hypoinflammatory 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 hyperinflammatory patients, Dr. Calfee said in a video interview available on mdedge.com/chestphysician.

Currently, the tests Dr. Calfee uses to distinguish hyperinflammatory and hypoinflammatory 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 hyperinflammatory ARDS patients, she said.

"Hypoinflammatory patients also merit study, she added. Although hyperinflammatory patients have significantly worse mortality rates, the hypoinflammatory subclass includes about 70% of ARDS patients, "so we

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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)–2 study, a multicenter UK and Irish study designed to test the efficacy of daily simvastatin treat-

ment in a heterogeneous group of ARDS patients. A 2014 report of the study's primary results showed no significant effect from simvastatin for increasing the number of ventilator-free days nor did the drug improve any other measured efficacy endpoints (New Engl J Med. 2014 Oct 30;371[18]:1695-703).

Applying a statistical analysis called "latent class analysis," which is designed to recognize subclass groupings that might not be readily apparent, Dr. Calfee and her team first confirmed that, in this fourth cohort, the ARDS patients again split into a hyperinflammatory subclass,

Continued on following page

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: Overall, the results from trials examining the use of statins in ARDS were disappointing – but this potential subset of patients may benefit significantly from statin administration. As stated in the article, prospective trials are needed to confirm the survival benefit in this population; and, if confirmed, rapid turnaround or point-of-care testing also would need to be operationalized.

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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 in HARP-2, 28-day survival.

They found that simvastatin produced no significant difference in 28-day survival, compared with placebo among the hypoinflammatory patients, but, in the hyperinflammatory subclass, 28-day survival was 68% for patients on simvastatin and 55% for those on placebo, a statistically significant difference, Dr. Calfee reported (Am J Resp Crit Care Med. 2017;195:A6749).

"I'm excited that we are seeing, for the first time, a different response to pharmacotherapy" after dividing ARDS patients into these two subclasses, she said. But, the work remains in an early stage, she cautioned. "We need to test treatments [like statins] prospectively." The new finding for simvastatin "is not the same as showing benefit in a prospective, randomized trial."

DR. CALFEE

Dr. Calfee is a consultant to Bayer, Boehringer Ingelheim, and GlaxoSmithKline. She received research funding from GlaxoSmithKline.

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MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

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) (N Engl J Med. 2006;354[24]:2564-75). 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.

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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 upshot 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 ularitide in the 2,100-patient TRUE-AHF (Efficacy and Safety of Ularitide 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 6,500 acute heart failure patients in the RELAX-AHF-2 (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF) trial.


DR. RUSCHITZKA

The failure of a 2-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 ularitide 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 ularitide 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,

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS
Dr. Milton Packer

Dr. John G.F. Cleland

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 infusions, with a clinical setting where an IV infusion is challenging to use."


DR. BUTLER

"We are killing good drugs by the way we're testing them," commented Javed Butler, MD, who bemoaned the ignominious outcome of serelaxin 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 ularitide 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

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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."

DR. FELKER

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 and was a coinvestigator for 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 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.

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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 158 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 ng/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.

"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.

As for adverse affects, 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 small sample size, "so the possibility of clinically important side effects attributable to angiotensin II therapy cannot be exuded," 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.

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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 abut 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 Soceity 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 die in hospital, about 65% more likely to die during the 30 days following admission, about 35% more likely to be readmitted, and about half as likely to be discharged home following hospitalization, when compared with patients with no NCC in multivariate analyses that adjusted for demographic and other clinical variables. Patients with three or more NCCs were also about 67% 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.

The researchers' analysis covered 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 difference between the babies in the two groups remained 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 a diagnosis of 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 can't say for sure that 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 also often 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."

We don't know if treating sleep apnea can reverse or prevent birth or maternal complications.

DR. BOURJEILY

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 probably went to their doctors and complained of sleepiness or loud snoring."

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.

Personalized snoring video boosts CPAP adherence

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 is promising. … We hope to present more data next year," said Dr. Aloia, who has board certification in behavioral sleep medicine,

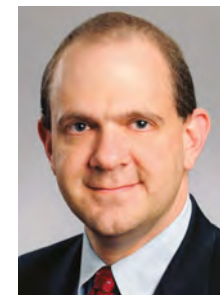
He noted that the video technique used may be jeopardized as more and more patients partake in home-based rather than lab-based sleep studies. That said, he also reported that the research team had to exclude several patients from the study because they had already viewed videos of themselves sleeping and snoring that had been recorded by their partners.

If the intervention proves effective, Dr. Aloia said he thinks it can be modified for use in home testing.

The study is supported by a grant from the National Heart, Lung, and Blood Institute.

Dr. Aloia disclosed that he is a paid employee of Phillips, but that the study used both Phillips and ResMed CPAP devices.

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 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.

Most arrhythmia clinic patients have undetected OSA

BY DEBRA L. BECK
Frontline Medical News

BOSTON – In a study of patients without a previous diagnosis of obstructive sleep apnea (OSA), 85% of participants in outpatient arrhythmia clinics had undetected OSA.

The study, which also excluded patients who had ever been treated for OSA, was presented by Colin Shapiro, MD, of the Department of Psychiatry, Toronto Western Hospital, University of Toronto, at the annual meeting of the Associated Professional Sleep Societies.

On a 2-night home sleep study, 91% of males and 71% of females were found to have an apnea hypopnea index of 5 or more. As far as the degrees of apnea, 28% of patients were found to have severe OSA (AHI greater than or equal to 30 events/hour of sleep), 33% had moderate OSA, 24% had mild OSA, and 15% did not have OSA.

A binary logistic regression analysis showed that only age and male gender were significant predictors of OSA.

Along with a home sleep study, researchers tested 75 nonselected consecutive patients (mean age of 64 years; 72% male) from three outpatient arrhythmia clinics for symptoms indicative of OSA using the Epworth Sleepiness Scale (ESS), the Fatigue Severity Scale (FSS), the Non-Restorative Sleep Scale (NRSS), and other questionnaires.

"High scores suggestive of daytime sleepiness, fatigue, or insomnia did not particularly predict the presence of OSA in patients with arrhythmia," noted Dr. Shapiro.

On the ESS, 32% of patients had a score of 8 or greater, indicating higher than normal daytime sleepiness. Almost half (47%) of patients had a high level of fatigue on the FSS, and symptoms of nonrestorative sleep were detected in 15% (NRSS score greater than or equal to 46).

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 short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No dose adjustment required for renal impaired.

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

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.

Revatio® sildenafil

PP-REV-USA-0090-01

July 2016

Revatio® sildenafil 20 mg tablets

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

INDICATION AND USAGE

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

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

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

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension *[see Warnings and Precautions]*, Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations]*.

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications]*.

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only Rev. June 2015

Telemonitoring with feedback ups CPAP use

BY DEBRA L. BECK
Frontline Medical News

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 director of Kaiser Permanent Fontana (Calif.) Medical Center and his colleagues designed the four-arm Tele-OSA study to evaluate the impact of two automated telemedicine interventions: an obstructive sleep apnea (OSA) education program (provided by Emmi Solutions) and a CPAP remote monitoring system with automated patient feedback (U-Sleep, ResMed). Dr. Hwang, who is also cochair of sleep medicine at Southern 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 consecutive days or CPAP usage greater than 4 hours for 3 consecutive nights, a message was automatically sent either 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 completed 1-year follow-up.

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

However, at 3 months when the study protocol called for the automated 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 never received the automated messaging. 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 receiving any kind of messaging."

DEBRA L. BECK/FRONTLINE MEDICAL NEWS

Dr. Dennis Hwang

"Perhaps serendipitously, we had a group of patients, about one-third, for whom we inadvertently 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. Hwang added that the telemonitoring required no additional provider intervention, "suggesting that this could be a cost-effective strategy."

Only one-third of patients (66.7%) assigned to one of the tele-education groups viewed the video. Additionally, the researchers found that, whether patients used the tele-education alone or in combination with the telemonitoring, tele-education use had no impact on 90-day compliance with CPAP.

Dr. Hwang received support from the American Sleep Medicine Foundation and ResMed Science.

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.

"I want to know the best drug for my patient, [and] unfortunately randomized clinical trials are not completely generalizable. Pathogen distribution and resistance is different in a clinical trial [than it is in] the patients we see," noted Dr. McKinnell.

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* less than .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 mortalities, 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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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.

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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 M*ycobacterium 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
Frontline Medical News

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 an ICU stay. Only 8% of children with severe pertussis were vaccinated, compared with a 58% 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 age 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/mm^3, 18,000/mm^3, and 5,000/mm^3, respectively, significantly greater than the 15,300, 10,700, and 3,900 cells/mm^3 in infants who did not require the ICU.

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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 liver metastases 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 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% of patients, 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* = .003).

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 tumor (*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).

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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 presscast 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 four of 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 were 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.

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

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In a poster discussion session, Paolo Boffetta, MD, MPH, from the Icahn School of Medicine at Mount Sinai in New York City, the invited discussant, commented that, while he thought that the data were interesting, "the main issue I had with this poster is that it's limited to patients with metastasis, so we cannot really evaluate the risk of metastasis according to the different histological types and the absolute risk of developing metastases in one or the other organ but only the relative risk of developing metastasis in one organ versus the other having one or the other histology."

The risk of metastasis by different histological types cannot be evaluated from this research.

DR. BOFFETTA

"So, we really don't know whether the risk is increased in one group or decreased in the other one that generates these differences," he said.

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 (5%). 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!

CHEST Annual Meeting 2017

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 for 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 Canadian 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

Weekly, 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 samples chocolate from bean to bar. Enjoy chocolates and chocolatey 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 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 simulated tornado and a full rainforest environment, and the Science Arcade. You can also see a film at Ontario's only IMAX® Dome theatre!

Don't forget to make your trip to Toronto for CHEST 2017 this October where not just you, but your entire family, can have a great time! Register today at chestmeeting.chestnet.org.

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. Addarrio 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

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CHEST® FOUNDATION

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 Hemostasis 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

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 (Chaouat 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 hypoventilation syndrome (OHS) than in "pure" OSA patients (58% vs 9%) (Kessler et al. *Chest.* 2001;120[2]:369).

DR. SINGHAL

DR. MINKIN

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 (FEV_1, vital capacity, and FEV_1/VC ratio), and lower oxygen saturation/higher carbon dioxide content in blood (Chaouat et al. *Chest.* 1996;109[2]:380). These patients frequently present with shortness of breath and dyspnea on exertion. Echocardiogram 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;74:2601). 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]:1129). 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.

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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 the quality of our air and the implications on our health, visit chestfoundation.org/summit.

We continue to partner with the Allergy & Asthma Network to create and distribute our materials and messaging, which focus 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 Willsie, 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)

INDEX OF ADVERTISERS

NetWorks: Oxygen therapy, electronic consent, diagnosing ILD

Airways Disorders

Oxygen therapy in patients with COPD with moderate desaturation

Two landmark trials from the early 1980s demonstrated survival benefit with long-term oxygen therapy (LTOT) in patients with COPD with severe resting hypoxemia [Sao_2 less than 89%; (Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med*. 1980;93[3]:391) or Pao_2 40-60 mm Hg and cor pulmonale (Report of the Medical Research Council Working Party. *Lancet*. 1981;1[8222]:681).

The potential benefits of LTOT in COPD with mild-moderate hypoxemia have not been clearly established. The LOTT trial (The Long-Term Oxygen Treatment Trial Research Group. *N Engl J Med*. 2016;375[17]:1617), a recent multicenter randomized study, attempted to answer this question. They studied 738 stable patients with COPD with mild to moderate resting desaturation (Spo_2 89%-93%) or exercise-induced moderate desaturation (Spo_2 greater than or equal to 80% for greater than or equal to 5 minutes and 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 hypoxemic 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).

Whether or not to continue prescribing oxygen to patients with moderate desaturation remains a controversial issue. A trial of oxygen may be warranted in those who are already on maximal evidence-based therapy for COPD and still complain of severe breathlessness (Ekstrom M; *N Engl J Med*. 2016;375[17]:1683). Conversely, a patient with COPD and moderate desaturation who resists being placed on supplemental oxygen, can be reassured that this is a reasonable course based on current evidence (Baliksoon R. *COPD*. 2017;4:71).

Navitha Ramesh, MD, MBBS
Fellow-in-Training
Steering Committee Member

Allen Blaivas, DO, FCCP
Steering Committee Member

Clinical Research

Informed consent: Do we need to change our practice?

Informed consent is the keystone 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

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.

Moshsin Ijaz, 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

Maximiliano Tamae Kakazu, 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 noninvasivepositive pressure ventilation (NIPPV) via mask interface. This dynamic growth is accredited to NIPPV efficacy and technologic improvements in ventilator and mask. For neuromuscular and restrictive thoracic diseases, NIPPV has been shown to increase survival, decrease hospital admissions, and improve quality of life (Chatwin A, et al. *Plos One*. 2015;10[5]:e0125839; Annane D, et al. *Cochrane Database Syst Rev*. 2014;13[12]:CD001941). From this success, NIPPV has been extended to conditions associated with respiratory impairment (eg, COPD, obesity hypoventilation, 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.

"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."

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 failure (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.


DR. CAO

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

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.

"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."

Tracy Luckhardt, MD
Steering Committee Member

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1 Tapson, et al, "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

2 Lin, P., et al., "Comparison of Percutaneous Ultrasound-Accelerated Thrombolysis versus Catheter-Directed Thrombolysis in Patients with Acute Massive Pulmonary Embolism." *Vascular*, Vol. 17, Suppl. 3, 2009, S137-S147.

3 Nykamp M., et al. "Safety and efficacy of ultrasound-accelerated catheter-directed lytic therapy in acute pulmonary embolism with and without hemodynamic instability." *J Vascular Surgery: Venous and Lymphatic Disorders* 2015; 3(5): 251-7.

4 Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. **THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS: Peripheral Vasculature:** The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. **Pulmonary Embolism:** The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25mmHg) or echocardiographic evaluation.

BTG

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