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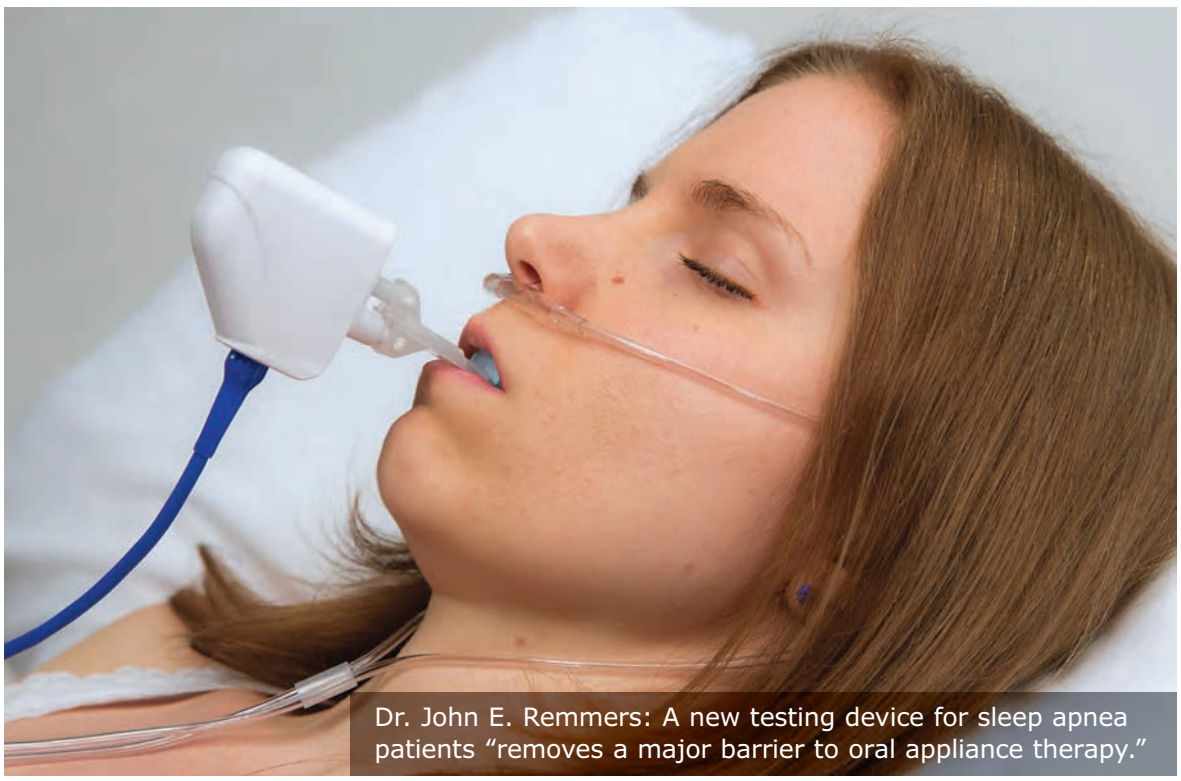

ICOM Productions

Dr. John E. Remmers: A new testing device for sleep apnea patients "removes a major barrier to oral appliance therapy."

New test could cause OSA's treatment success rate to rise

BY KATIE WAGNER LENNON
Frontline Medical News

A novel device has shown a high rate of accuracy in predicting which patients with obstructive sleep apnea (OSA) will improve with oral appliance therapy, according to a study.

"At the present time CPAP is our go-to standard medical therapy [for treating OSA]. While it is a wonderful therapy, it has a very serious drawback, which is poor compliance, and that undercuts its long-term effectiveness in reducing the incidence of cardiovascular disease," said John E. Remmers, MD, the principal investigator, in an interview.

Referring to the Sleep Apnea Cardiovascular Endpoints (SAVE) trial's finding that continuous positive airway pressure (CPAP) did not reduce long-term cardiovascular incidents, he claimed that "these incidents are not being reduced by CPAP, because people don't use it" (N Engl J Med. 2016 Sept 8;375[10]:919-31).

We seem to be making no progress in reducing the prevalence of untreated, undiagnosed sleep apnea because we are using overnight studies in the lab and we are using a treatment that people don't like and don't want to use," added Dr. Remmers, who is chief medical officer of Zephyr Sleep Technologies.

In Dr. Remmers' new two-part study, 202

TEST HAD A SPECIFICITY OF 93% // *continued on page 6*

Pediatric version of SOFA effective

pSOFA outperformed other organ dysfunction scores

BY BIANCA NOGRADY
Frontline Medical News

An age-adjusted version of the Sequential Organ Failure Assessment score for sepsis has been found to be at least as good, if not better than, other pediatric organ dysfunction scores at predicting in-hospital mortality.

Writing in the Aug. 7 online edition of JAMA Pediatrics, researchers reported the outcome of a retrospective observational cohort study in 6,303 critically ill patients aged 21 years or younger, which was used to adapt and validate a pediatric version of the Sequential Organ Failure Assessment (SOFA) score.

"One of the major limitations of the SOFA score is that it was developed for adult patients and contains measures that vary significantly with age, which makes it unsuitable for children," wrote Travis J. Matics, DO, and L. Nelson Sanchez-Pinto, MD, of the department of pediatrics at the University of Chicago.

Several pediatric organ dysfunction scores

pSOFA COMPARABLE TO OTHER SCORES // *continued on page 4*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Meet a keynote speaker for CHEST's annual meeting

Page 56

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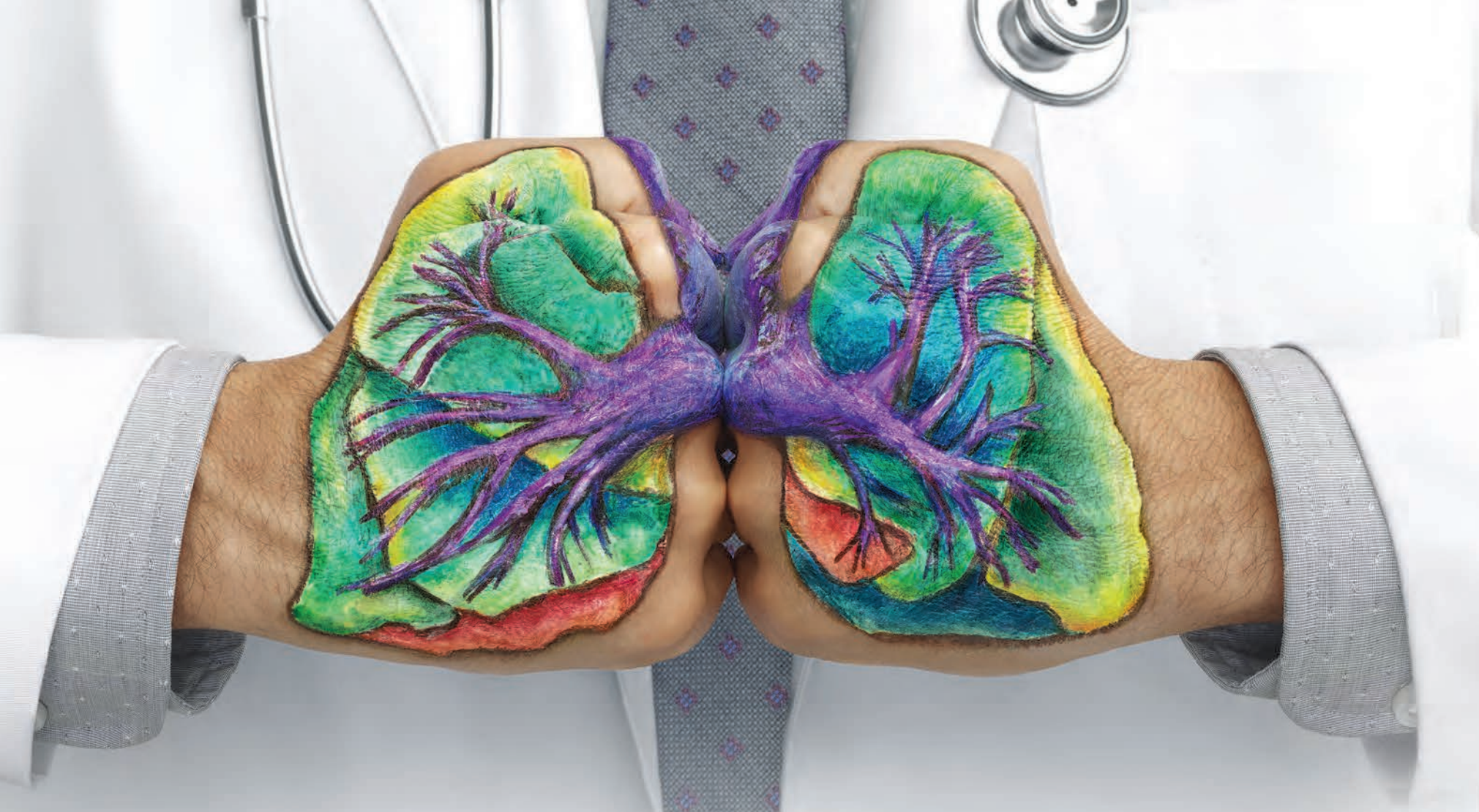

Indication

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.

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

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Help preserve more lung function. Reduce lung function decline.[1–4]

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

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

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More than 31,000 patients have taken pirfenidone worldwide[1§]

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

IPF=idiopathic pulmonary fibrosis.

*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).[1,2,4] **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]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

pSOFA comparable to other scores // *continued from page 1*

exist, but their range, scale, and coverage are different from those of the SOFA score, which makes them difficult to use concurrently (JAMA Pediatr. 2017 Aug 7. doi: 10.1001/jamapediatrics.2017.2352).

"Fundamentally, having different definitions of sepsis for patients above or below the pediatric-adult threshold has no known physiologic justification and should therefore be avoided," the authors wrote.

In this study, they modified the age-dependent cardiovascular and renal variables of the adult SOFA score by using validated cut-offs from the updated Pediatric Logistic Organ Dysfunction (PELOD-2) scoring system. They also expanded the respiratory subscore to incorporate the SpO_2:FiO_2 ratio as an alternative surrogate of lung injury.

The neurologic subscore, based on the Glasgow Coma Scale, was changed to a pediatric version of the scale. The coagulation and hepatic criteria remained the same as the adult version of the score.

Validating the pediatric version of the SOFA score (pSOFA) score in 8,711 hospital encounters, researchers found that nonsurvivors had a signifi-

cantly higher median maximum pSOFA score, compared with survivors (13 vs. 2, *P* less than .001). The area under the curve (AUC) for discriminating in-hospital mortality was 0.94 (95% confidence interval, 0.92-0.95) and remained stable across sex, age groups, and admission types.

The maximum pSOFA score was as good as the PELOD and PELOD-2 scales at discriminating in-hospital mortality and better than the Pediatric Multiple Organ Dysfunction Score. It also showed "excellent" discrimination of in-hospital mortality among the 48.4% of patients who had a confirmed or suspected infection in the pediatric intensive care unit (AUC, 0.92; 95% CI, 0.91-0.94), Dr. Matics and Dr. Sanchez-Pinto reported.

The clinical utility on the day of admission of pSOFA and of the Pediatric Risk of Mortality III score was similar, while the pSOFA outperformed other organ dysfunction scores in this setting.

Researchers also looked at the clinical utility of pSOFA on the day of admission, compared with the Pediatric Risk of Mortality (PRISM) III score, and found the two were similar, while the pSOFA outperformed other organ dysfunction scores in this setting.

Overall, 14.1% of the pediatric intensive care population met the sepsis criteria according to the adapted definitions and pSOFA scores, and this group had a mortality of 12.1%. Four percent of the population met the criteria for septic shock, with a mortality of 32.3%.

The SOFA score incorporates respiratory, coagulation, renal, hepatic, cardiovascular, and neurologic variables. The authors, however, argued that it does not account for age-related variability, in particular in renal criteria and the detrimental effects of kidney dysfunction in younger patients.

The pSOFA showed "excellent" discrimination of in-hospital mortality among the 48.4% of patients who had a confirmed or suspected infection in the pediatric intensive care unit, Dr. Matics and Dr. Sanchez-Pinto reported.

"In addition, the respiratory subscore criteria – based on the ratio of PaO_2 to the fraction of inspired oxygen (FiO_2) – have not been modified in previous adaptations of the SOFA score even though the decreased use of arterial blood gases in children is a known limitation," they wrote.

"Having a harmonized definition of sepsis across age groups while recognizing the importance of the age-based variation of its measures can have many benefits, including better design of clinical trials, improved accuracy of reported outcomes, and better translation of the research and clinical strategies in the management of sepsis," Dr. Matics and Dr. Sanchez-Pinto said.

They acknowledged, however, that their findings were limited because they were generated using retrospective data and needed to be validated in a large multicenter sample of critically ill children. They also pointed out that they did not evaluate the performance of pSOFA as a longitudinal biomarker and suggested that such studies would improve understanding of pSOFA's clinical utility.

No conflicts of interest were reported.

Test had a specificity of 93%

// continued from page 1

adults – primarily overweight, middle-aged men, diagnosed with moderate sleep apnea – were divided into two groups. The first included 149 people who were given a two-night, in-home, feedback controlled mandibular positioner (FCMP) test, using equipment manufactured by Zephyr Sleep Technologies. In this test, a custom-fit oral appliance is simulated using a temporary set of trays and impression material. The trays are connected to a small motor controlled by a little computer that sits on the stomach and moves the mandible when the patient has a problem breathing.

All patients received a custom oral appliance designed using data acquired from the test. The patients then wore the custom oral appliances while connected to a validated monitor as an outcomes study.

Finally, the researchers fed all of the data they collected from this first group of patients into a machine learning model. Then the second set of patients participated in the testing. Outcomes data on the appliance's performance in each individual in the first group were used to create a classification system to predict therapeutic outcomes for the 53 patients in the second group. The patients in the second group then received their custom oral appliances, connected to the same type of monitor used by the first group.

Therapeutic success or failure was defined as having mean oxygen desaturation index values of less than or greater than 10 events/hour, respectively. The investigators determined that the test had an 85% sensitivity level with 93% specificity, a positive predictive value of 97%, and a negative predictive value of 72%. Of those who were predicted to respond to therapy, the mandibular protrusive position was efficacious in 86% of patients.

The high rate of accuracy for predicting who will derive the most benefit from the appliance, along with the demonstrated preference for oral appliances compared to continuous positive airway pressure devices among patients, increases the clinical utility of the appliance, and expands options for clinical management of sleep apnea, according to the study authors (Clin Sleep Med. 2017;13[7]:871-80).

"Our test allows the physician to prescribe the therapy knowing it will get rid of sleep apnea, and it tells the dentist how far the mandible needs to be pulled out by the custom fit device," Dr. Remmers explained.

Dentists will also benefit from the test, because it allows them to make an appliance that will not need to be adjusted and will have a higher success rate than the current 60% success rate that oral appliances have at treating sleep apnea, he noted.

"This opens up a new an alternative clinical avenue at a critical time, when we have just learned over the past few years that there are serious questions about the effectiveness of CPAP in the long term," Dr. Remmers added. "[With oral appliance therapy] you have an opportunity for higher compliance, because people prefer the less obtrusive oral appliance therapy over CPAP, and they use it more than CPAP. ... Because our product says you don't treat everybody, you only undertake oral appliance therapy for those who we know in advance will have a favorable outcome, it removes a major barrier to oral appliance therapy that has been the barrier for many years."

Dr. Remmers noted that his test was not nearly as good at identifying people who would be failures as it was at identifying people who would be successes and that he is carrying out another trial with a similar device.

Some participants reported sore gums when using the device, but there were no long-lasting adverse events reported.

The mandibular positioner home test has not been approved or cleared for use by the Food and Drug Administration, but is currently being sold in Canada, according to Dr. Remmers.

Zephyr Sleep Technologies and Alberta Innovates Technology Futures sponsored the study. It is registered on clinicaltrials.gov as NCT03011762. All of the investigators, other than Nikola Vranjes, are employed or associated with Zephyr Sleep Technologies.

Whitney McKnight contributed to this report.

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VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, PhD, FCCP, comments: This is an interesting study on promising technological advances in the area of mandibular advancement devices for sleep disordered breathing.

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

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PICU admission not needed for high-flow nasal cannula

Frontline Medical News

BY M. ALEXANDER OTTO
Frontline Medical News

NASHVILLE, TENN. – Young children with acute bronchiolitis do not need to be admitted to the pediatric ICU for high-flow nasal cannula treatment of up to 6 L/min and 50% oxygen; it is safe to administer it on the floor, according to a review of 6,804 acute bronchiolitis cases in children younger than 2 years treated at the University of Texas Southwestern Medical Center, Dallas.

Use of high-flow nasal cannulas (HFNC) has increased dramatically in recent years at UT Southwestern and elsewhere. It soothes children and can rapidly improve breathing without the nasal edema and nose bleeds common with cooler, drier, 100% oxygen. At Southwestern, HFNC use on the pediatric wards increased from 5% of acute bronchiolitis cases in the September 2010 to April 2011 season to 60% in the 2015-2016 season. Use for bronchiolitis in the PICU increased from 82% to 98% over the same period.

The increase correlated with a drop in intubation for acute bronchiolitis from 14% of children in 2010-2011 to just 2% in 2015-2016. The only HFNC adverse events were minor air leaks in two children.

As HFNC became more common, however, the Dallas team found that length of stay for acute bronchiolitis increased from 1.8 days in 2011-2012 to 2.4 days in 2015-2016, perhaps because the use of HFNC gives providers the impression that children are sicker than they actually are.

To counter the problem, lead investigator Vineeta Mittal, MD, associate professor of pediatrics, and her colleagues created an HFNC weaning protocol that gradually steps down treatment based on blood oxygen saturation levels and breathing effort, leading ultimately to a room-air challenge. It helped; the mean length of stay as of November 2016 was 1.7 days.

There's been pushback in some places about giving HFNC on the floor: Intensivists sometimes consider it a form of ventilation that should be administered in the PICU. At levels up to 6 L/min and 50% oxygen, though, HFNC is "safe to give on the floor, because there's no pneumothorax risk," Dr. Mittal explained. HFNC "is not a ventilator; it's an effective form of noninvasive respiratory support in children with moderate to severe respiratory distress from bronchiolitis."

At Southwestern, "we are managing 80% of cases on the floor" with the help of HFNC, Dr. Mittal said at Pediatric Hospital Medicine.

At least for now, children at Southwestern go to the PICU if they need higher flow rates, but Dr. Mittal said it's not clear if that's necessary. "We said [6 L/min] is safe," but maybe "we could even use 8 L/min or even 12 L/min" – the maximum delivered in the PICU over the study period – "because we know it's safe," she said. In addition, keeping kids on the floor also saves money, she noted at the meeting, which was sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, and the Academic Pediatric Association.

Dr. Mittal is concerned HFNC might be overused. "We have gotten so used to this machine that the moment we see distress, we put the kid on high flow," rather than observing them for a bit to see if they recover on their own. More data are needed to determine when HFNC should be initiated, and when to pull the plug on HFNC and intubate, she said.

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CAP with empyema successfully treated with oral antibiotics

BY BRUCE JANCIN
Frontline Medical News

MADRID – Outpatient oral antibiotics were more successful than outpatient parenteral antibiotic therapy at treating children with community-acquired pneumonia (CAP) complicated by empyema, in a study presented at the annual meeting of the European Society for Paediatric Infectious Diseases.

Thirty-five percent of the patients were culture positive, a typically low rate that makes treatment of this disease particularly challenging, Lauren Kushner, a medical student at the University of California, Irvine, and one of the study's authors, said at the meeting.

The treatment success rates, which were defined as improvement with no change in treatment, were 93% for the patients taking oral antibiotics and 58% in the patients on outpatient parenteral antibiotic therapy.

This retrospective observational study included 149 patients under age 18 years hospitalized for community-acquired pneumonia complicated by empyema, at Children's Hospital of Orange County, Calif. Only 12 of the patients were treated with parenteral antibiotic therapy and none of the study participants had comorbid chronic medical conditions. As in other studies, *Streptococcus pneumoniae* was the most commonly identified pathogen.

Laboratory markers of inflammation are useful in guiding oral antibiotic therapy for children with CAP complicated by empyema, reported Ms. Kushner.

"A rapid drop in C-reactive protein [CRP] in combination with a decrease in white blood cell count can be used acutely in the hospitalization phase to tell you the patient is improving on the selected antibiotic and also to help dictate when the patient might be able to go home, whereas improvement in the erythrocyte sedimentation rate [ESR] does not happen until much later in the course of treatment but can be used to tell you when a patient has been adequately treated," said Ms. Kushner.

One hundred thirty-seven patients were discharged on oral antibiotic therapy, as is strongly recommended in Infectious Diseases Society of America guidelines for postdischarge treatment of complicated pneumonia, even though there are no randomized clinical trials demonstrating it to be superior or even noninferior to outpatient parenteral antibiotics. An aminopenicillin was the most frequently prescribed type of oral antibiotic, while ceftriaxone was the top choice for outpatient parenteral therapy.

The average total duration of antibiotic therapy, inpatient plus outpatient, was similar in the two groups: 30.4 days in the oral antibiotic group and 33.2 days in children on outpatient IV therapy.

The transition to oral therapy occurred a median of 6 days after admission. At that point, CRP levels had dropped sharply by a mean of 204 mg/L from a baseline of more than 250 mg/L at admission. In the same time frame, mean WBC dropped by 6,400 cells/mcL from close to 20,000/mcL at admission. Thus, sharp declines in these two inflammatory markers while a patient is still in the hospital provide reassurance that antibiotic therapy is on the right track. Their rate of decline slowed considerably after the switch to oral therapy: for example, mean CRP decreased by only another 44 mg/L from switch to discharge, and by a further 19 mg/L from discharge to end of treatment.

In contrast, the mean ESR remained elevated at a level approaching 100 mm/hour with little fluctuation from admission through discharge. Weekly monitoring of ESR post discharge showed that this inflammatory marker improved only late in the course of oral therapy. A drop to less than 30 mm/hour indicates the infection has resolved, Ms. Kushner said.

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E-cigarettes: A health threat or cessation tool?

BY BRUCE JANCIN
Frontline Medical News

DENVER – Can e-cigarettes help smokers quit?

"So far, the evidence regarding e-cigarettes' effectiveness for smoking cessation is equivocal at best," Alison Breland, PhD, said at the annual meeting of the Teratology Society.

But Dr. Breland noted that there is significant controversy around this topic. "I can tell you that, at the conferences I go to, where there are lots of people studying nicotine and tobacco, scientists are fighting with each other over this question," said Dr. Breland, a psychologist and project director at the Center for the Study of Tobacco Products at Virginia Commonwealth University in Richmond.


DR. BRELAND

Several small, randomized, controlled trials suggest electronic cigarettes have efficacy comparable to the nicotine patch. But the bulk of the literature indicates otherwise. Dr. Breland found persuasive a systematic review and meta-analysis of 38 studies: Its investigators at the University of California, San Francisco, concluded that the odds of quitting smoking were 28% lower in smokers using e-cigarettes, compared with those not using the devices (Lancet Respir Med. 2016 Feb;4[2]:116-28).

That being said, she noted that this meta-analysis has generated unusually harsh printed comments from its critics.

"We could argue about the methodology of the studies all day. If you think all the studies are garbage then you won't believe the odds ratio, either. But I think right now the evidence shows that e-cigarettes don't seem to help people quit," she said. "That may change in the future with testing of different kinds of devices."

To be useful for smoking cessation, she explained, a device would need to consistently deliver enough nicotine to enable the smoker to fend off withdrawal symptoms but not so much that the wish to quit evaporates. It's a matter of finding the sweet spot in what is technically termed device nicotine flux.

There is a great deal of misconception about e-cigarettes, Dr. Breland said, some of it promoted through misleading product advertising. She sought to set the record straight.

How e-cigarettes work

What are e-cigarettes? They are basically nicotine delivery devices. They use electricity to power a heating element that aerosolizes a liquid containing varying concentrations of nicotine; solvents, such as propylene glycol and vegetable glycerins; and flavorants. As a class, e-cigarettes are rapidly evolving. A vast array of devices are marketed with wide differences in design, materials, construction, amount of nicotine delivered, and electrical power – which, along with puff duration, is a key factor in how much nicotine gets into a user's blood.

"Most of the devices have a battery, but it's important to know that some of them can be plugged directly into a USB port on a computer," Dr. Breland said.

E-cigarettes don't generate a vapor, as is widely believed. It's an aerosol, and it contains toxic byproducts. On the plus side, unlike combustible cigarettes, e-cigarettes don't deliver carbon monoxide.

A vast array of flavorant mixtures are sold, including some that are clearly designed to be attractive to children, with names like "blue cotton candy" and "Apple Jacks."

User demographics

Who is using e-cigarettes? Primarily adolescents and young adults in prime reproductive age. National surveys indicate e-cigarettes are now the most widely used tobacco product among U.S. high school students, well ahead of combustible cigarettes.

Of particular concern, data from the Centers for Disease Control and Prevention's National Health Interview Survey indicate that, among 18- to 24-year-olds who use e-cigarettes, about 40% also currently use conventional cigarettes, about 20% are former cigarette smokers, and about 40% are never smokers – that is, have never smoked combustible cigarettes (MMWR Morb Mortal Wkly Rep. 2016;65:1177. doi: 10.15585/mmwr.mm6542a7).

"We don't know what's going to happen to these never smokers who are currently using e-cigarettes. Are they starting on a lifetime of nicotine dependence via e-cigarettes, or perhaps even worse, are they going to transition to combustible cigarettes? There's more and more evidence showing that's happening," Dr. Breland said.

The CDC survey also showed that 59% of adult users of e-cigarettes are what Dr. Breland called "dualies," individuals who also smoke conventional cigarettes.

"That really diminishes any potential benefit of e-cigarettes," she said.

Impact on pregnancy

What is known about the impact of e-cigarettes on pregnancy and birth outcomes? Almost nothing at this point. E-cigarettes deliver nicotine to the bloodstream, and nicotine is known to cause unwelcome, long-term changes in fetal brain development and in that of adolescents as well. The other aerosolized toxicants have not been well studied. A few small surveys conducted in obstetric practices indicate some pregnant women perceive e-cigarettes as posing only minor health risks and safer than combustible cigarettes. And some pregnant women are using e-cigarettes.

Dr. Breland is an investigator in an ongoing, multicenter, longitudinal study enrolling pregnant smokers during their first trimester and following them through childbirth. So far, the investigators have enrolled 93 conventional cigarette users and 24 dualies but have managed to enroll only three exclusive e-cigarette users.

"I think it's notable that we're not finding exclusive e-cigarette users. It's early in the study, but so far the dual users are smoking the same number of cigarettes per day as cigarette-only users, and they have the same expired carbon monoxide levels. It makes me feel concerned in particular about dual use in pregnancy," she said.

Dr. Breland's research is supported by the National Institute on Drug Abuse and the Food and Drug Administration.

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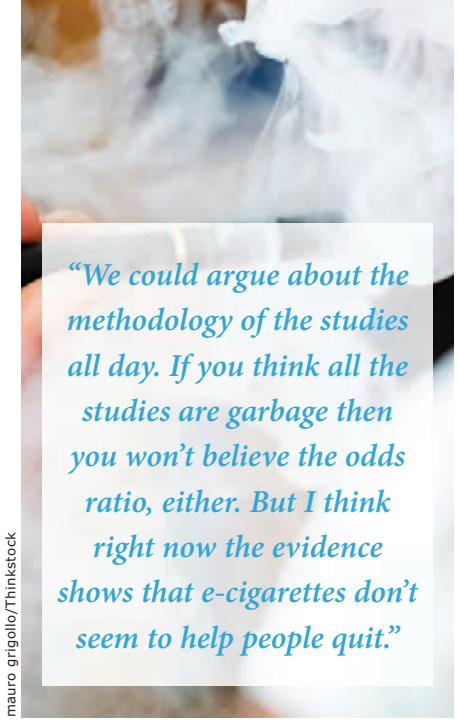
mauro grigollo/Thinkstock

"We could argue about the methodology of the studies all day. If you think all the studies are garbage then you won't believe the odds ratio, either. But I think right now the evidence shows that e-cigarettes don't seem to help people quit."

Monotherapy effective for antibiotic-resistant infections

BY MICHELE G. SULLIVAN
Frontline Medical News

VIENNA – A single, well-targeted antibiotic may be enough to effectively combat serous bloodstream infections in patients who have a low baseline mortality risk.

Among these patients, overall mortality was similar among those receiving a single antibiotic and those getting multiple antibiotics (35% vs. 41%). Patients with a high baseline mortality risk, however, did experience a significant 44% survival benefit when treated with a combination regimen, Jesus Rodríguez-Baño, MD, said at the European Society of Clinical Microbiology and Infectious Diseases annual congress.

The finding is important when considering the ever-increasing imperative of antibiotic stewardship, Dr. Rodríguez-Baño said in an interview.

"In areas where these pathogens are common, particularly in intensive care units, where they can become epidemic and infect many patients, the overuse of combination therapy will be fueling the problem," said Dr. Rodríguez-Baño, head of infectious diseases and clinical microbiology at the University Hospital Virgin Macarena, Seville, Spain.

Continued on page 11

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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

Continued from page 8

"This is a way to avoid the overuse of some broad-spectrum antibiotics. Selecting the patients who should not receive combination therapy may significantly reduce the total consumption" on a unit.

The retrospective study, dubbed INCREMENT, was conducted at 37 hospitals in 10 countries. It enrolled patients with bloodstream infections caused by extended-spectrum beta-lactamase- or carbapenemase-producing *Enterobacteriaceae*. Dr. Rodríguez-Baño reported results for 437 patients whose infections were caused by the carbapenemase-producing strain.

It was simultaneously published in Lancet Infectious Diseases (2017. doi: 10.1016/S1473-3099[17]30228-1).

These patients were a mean of 66 years old; most (60%) were male. The primary infective agent was *Klebsiella pneumonia* (86%); most infections were nosocomial. The origin of infections varied, but most (80%) arose from places other than the urinary or biliary tract. Sources were vascular catheters, pneumonia, intraabdominal, and skin and soft tissue. About half of the patients were in severe sepsis or septic shock when treated.

The group was first divided into those who received appropriate or inappropriate therapy (78% vs. 22%). Appropriate therapy was considered to be the early administration of a drug that could effectively target the infective organism. Next, those who got appropriate therapy were parsed by whether they received mono- or combination therapy (61% vs. 39%). Finally, these patients were stratified by a specially designed mortality risk score, the INCREMENT Carbapenemase-Producing *Enterobacteriaceae* (CPE) Mortality Score (Mayo Clinic Proceedings. doi: 10.1016/j.mayocp.2016.06.024):

- Severe sepsis or shock at presentation (5 points)
- Pitt score of 6 or more (4 points)
- Charlson comorbidity index of 2 or more (3 points)
- Source of bloodstream infection other than urinary or biliary tract (3 points)
- Inappropriate empirical therapy and inappropriate early targeted therapy (2 points)

Patients were considered low risk if they had a score of 0-7, and high if they had a score of 8 or more.

The risk assessment tool is quick, easy to figure, and extremely important, Dr. Rodríguez-Baño noted. "This is a very easy-to-use tool that can help us make many patient management decisions. All of the information is already available in the patient's chart, so it doesn't require any additional assessments. It's a very good way to individualize treatment."

In the initial analysis, all-cause mortality at 30 days was 22% lower among patients who received appropriate early therapy than those who did not (38.5% vs. 60.6%). This translated to a 55% decrease in the risk of death (hazard ratio, 0.45 in the fully adjusted model).

The investigators next turned their attention toward the group that received appropriate therapy. All-cause 30-day mortality was 41% in those who got monotherapy and 34.8% among those who got combination therapy. Finally, this group was stratified according to the INCREMENT-CPE mortality risk score.

"This is a very easy-to-use tool that can help us make many patient management decisions."

DR. RODRÍGUEZ-BAÑO

In the low-risk category, combination therapy did not confer a survival advantage over monotherapy. Death occurred in 20% of those getting monotherapy and 24% receiving combination treatment – not a significant difference (HR, 1.21).

Combination therapy did, however, confer a significant survival benefit in the high-risk group. Death occurred in 62% of those receiving monotherapy and 48% of those receiving combination therapy – a 44% risk reduction (HR, 0.56).

As long as they were appropriately targeted against the infective organism, all drugs used in the high-mortality risk group were similarly effective at reducing the risk of death. Compared to colistin monotherapy, a combination that included tigecycline reduced the risk of death by 55% (HR, 0.45); combination with aminoglycosides by 58% (HR, 0.42); and combination with carbapenems by 44% (HR, 0.56).

A secondary analysis of this group determined each day delay after day 2 significantly increased the risk of death, Dr. Rodríguez-Baño said.

INCREMENT was funded in large part by the Spanish Network for Research in Infectious Diseases. Dr. Rodríguez-Baño has been a scientific adviser for Merck, AstraZeneca, and InfectoPharm.

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Short, simple antibiotic courses effective in latent TB

BY JENNIE SMITH
Frontline Medical News

Latent tuberculosis infection can be safely and effectively treated with 3- and 4-month medication regimens, including those using once-weekly dosing, according to results from a new meta-analysis.

The findings, published online July 31 in Annals of Internal Medicine, bolster evidence that shorter antibiotic regimens using rifamycins alone or in combination with other drugs are a viable alternative to the longer courses (Ann Intern Med. 2017;167:248-55).

While the new study looked at efficacy and toxicity across treatment strategies only and found no significant differences between shorter rifamycin-based regimens and isoniazid-based regimens lasting 6 months or longer, short courses are considered likely to see better patient adherence, previous research in latent TB has indicated (BMC Infect Dis. 2016;16:257).

For their research, Dominik Zenner, MD, an epidemiologist with Public Health England in London, and his colleagues updated a meta-analysis they published in 2014. The team added 8 new randomized studies to the 53 that had been included in the earlier paper (Ann Intern Med. 2014 Sep;161:419-28).

Using pairwise comparisons and a Bayesian network analysis, they found comparable efficacy among isoniazid regimens of 6 months or more; rifampicin-isoniazid regimens of 3 or 4 months, rifampicin-only regimens, and rifampicin-pyrazinamide regimens, compared with placebo (*P* less than .05 for all).

Importantly, a rifapentine-based regimen in which patients took a weekly dose for 12 weeks was as effective as the others.

"We think that you can get away with shorter regimens," Dr. Zenner said in an interview. Although 3- to 4-month courses are already recommended in some countries, including the United Kingdom, for most patients with latent TB, "clinicians in some settings have been quite slow to adopt them," he said.

The U.S. Centers for Disease Control and Prevention currently recommend multiple treatment strategies for latent TB, depending on patient characteristics. These include 6 or 9 months of isoniazid; 3 months of once-weekly isoniazid and rifapentine; or 4 months of daily rifampin.

In the meta-analysis, rifamycin-only regimens performed as well as did those regimens that also used isoniazid, the study showed, suggesting that, for most patients who can safely be treated with rifamycins, "there is no added gain of using isoniazid," Dr. Zenner said.

Longer isoniazid-alone regimens are nonetheless effective and appropriate for some, including people who might have potential drug interactions, such as HIV patients taking antiretroviral medications, he noted.

About 2 billion people worldwide are estimated to have latent TB, and most will not go on to develop active TB. However, because latent TB acts as the reservoir for active TB, screening of high-risk groups and close contacts of TB patients and treating latent infections is a public health priority.

But many of these asymptomatic patients will get lost between a positive screen result and successful treatment completion, Dr. Zenner said.

"We have huge drop-offs in the cascade of treatment, and treatment completion is one of the worries," he said. "Whether it makes a huge difference in compliance to take only 12 doses is not sufficiently studied, but it does make a lot of sense. By reducing the pill burden, as we call it, we think that we will see quite good adherence rates – but that's a subject of further detailed study."

The investigators described the lack of availability of hepatotoxicity outcomes for all studies as a limitation, and said some of the included trials had a potential for bias. They did not see statistically significant differences in treatment efficacy between regimens in HIV-positive and HIV-negative patients, but noted in their analysis that "efficacy may have been weaker in HIV-positive populations."

The U.K. National Institute for Health Research provided funding for the study. One coauthor reported nonfinancial support from Sanofi and financial support from Otsuka.

Prophylaxis prevents PCP in rheumatic disease patients

BY SARA FREEMAN
Frontline Medical News

MADRID – The benefits of primary prophylaxis for pneumocystis pneumonia (PCP) outweighed the risks of treatment in patients taking prolonged, high-dose corticosteroids for various rheumatic diseases in a study presented at the European Congress of Rheumatology.

In a single-center, retrospective cohort study of 1,522 corticosteroid treatment episodes in 1,092 patients with a variety of rheumatic conditions given over a 12-year follow-up period, the estimated incidence of PCP was 2.37 per 100 person-years.


DR. PARK

Significantly fewer cases of PCP occurred at 1 year, however, in the 262 patients who were cotreated with the antibiotic combination of trimethoprim and sulfamethoxazole (TMP-SMX), than in the 1,260 patients who received no such antibiotic prophylaxis in addition to their steroid therapy.

The adjusted hazard ratio for no PCP at 1 year of follow-up in the prophylaxis group, versus the no prophylaxis group, was 0.096 (*P* = .022).

The TMP-SMX combination significantly reduced the mortality associated with PCP, with an adjusted HR of 0.09, versus no prophylaxis (*P* = .023).

"Pneumocystis pneumonia is a major opportunistic infection in immunocompromised patients associated with high morbidity and mortality," explained the presenting study investigator Jun Won Park, MD, of Seoul National University Hospital, South Korea.

Dr. Park added that corticosteroid therapy was an important risk factor for PCP but that the risk-benefit ratio had not been evaluated sufficiently in patients with rheumatic diseases and that there was "different opinion among rheumatologists regarding [the value of] PCP prophylaxis."

The current study aimed to see if primary antibiotic prophylaxis could prevent PCP in patients with rheumatic diseases, which included patients with systemic lupus erythematosus (SLE), dermatomyositis, rheumatoid arthritis, and Behçet's disease.

For inclusion, patients had to have been treated with prednisolone at a dose of 30 mg/day or more (or its equivalent) for at least 4 weeks and observed for 1 year. Patients with a prior history of PCP or conditions associated with this opportunistic infection, such as HIV, cancer, or solid organ or hematopoietic stem cell transplantation, were excluded. PCP prophylaxis was given at the discretion of the treating physician, and the mean duration of TMP-SMX was 230 days.

In the prophylaxis group, 34 adverse drug reactions occurred. Two of these reactions were serious – one case of pancytopenia and one case of Steven's Johnson syndrome – but both resolved after the antibiotic treatment was discontinued.

A sensitivity analysis was performed, giving consistent results, and a risk-benefit analysis showed that the number needed to treat to prevent one case of PCP was 52, considering all rheumatic disease studied, while the number needed to cause one serious adverse drug reaction was 131.

Taken together, these results suggest a role for TMP-SMX as primary prophylaxis for PCP in patients with rheumatic diseases who need prolonged treatment with high-dose corticosteroids, Dr. Park said.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: As is standard in many conditions requiring long-term immunosuppression with corticosteroids of a certain dose, prophylaxis for PCP is advocated assuming no contraindication. Additionally, further consideration for starting prophylaxis is warranted if additional immunomodulating agents are concurrently being used (as is often the case in rheumatic diseases) – even if the corticosteroid dosing is deemed "not high."

Metastasectomy prolongs soft-tissue sarcoma survival

BY RICHARD MARK KIRKNER
Frontline Medical News

The rate of soft-tissue sarcoma has nearly doubled over the past two decades, and up to 50% of patients with tissue sarcoma develop lung metastasis. A single-center study of 539 patients who had treatment for soft-tissue sarcoma has revealed disease and treatment characteristics that may aid patient selection and help predict overall and disease-free survival after diagnosis and treatment.

"Histologic subtype and size of the primary tumor were significantly associated with overall survival," said lead author Neel P. Chudgar, MD, and his coauthors in the July issue of the Journal of Thoracic and Cardiovascular Surgery (2017;154:319-30).

"Patients who underwent pulmonary metastasectomy [PM] for pleomorphic sarcoma/malignant fibrous histocytoma had the shortest median overall survival (23.6 months), whereas those who underwent PM for leiomyosarcoma had a median overall survival of 42 months," he said.

The study subjects had pulmonary metastasectomies at Memorial Sloan Kettering Cancer Center, New York, during September 1991–June 2014. The median overall survival was 33.2 months, and median disease-free survival was 6.8 months for the entire cohort.

Among the disease characteristics associated with a lower hazard ratio of death shown by multivariable analyses were leiomyosarcoma histologic subtype (HR, 0.57), primary tumor size of 10 cm or less (HR, 1.00 vs. HR, 1.37 for those greater than 10 cm), increasing time from primary tumor resection to development of metastases (HR, 0.4 at less than 24 months vs. 1.0 at less than 6 months), solitary lung metastasis (HR, 1.0 vs. 1.8 for one year or more), and minimally invasive resection (HR, 0.71), all of which were statistically significant differences. Disease-free interval of more than 1 year and one pulmonary metastasis were significantly associated with lower hazard of disease recurrence.

Of patients, 70% had pulmonary metastasectomy as their primary treatment. The remainder had induction chemotherapy. In addition, 71% had open procedures over the 23-year study period, but minimally invasive operations became more common with time, increasing more than fourfold from the first half of the study period, vs. the last. They accounted for more than half of all procedures in the last 5 years of the study.

With regard to tumor type, fibrosarcoma was associated with longest median overall survival (65.2 months). Dr. Chudgar and his colleagues noted that 43% of these patients had low-grade primary tumors. Patients with low-grade tumors of all types had a median overall survival of 71.8 months, vs. 30.8 months for those with high-grade tumors.

"Our results indicate that therapeutic-intent pulmonary metastasectomy

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for soft-tissue sarcoma can be associated with prolonged survival," Dr. Chudgar and his coauthors said. "The median survivals in our study are comparable with those in previous studies." However, their analysis went beyond previous studies because they identified positive prognostic factors.

Dr. Chudgar and his coauthors acknowledge that various studies have drawn conflicting conclusions about the validity of histologic subtype as a prognostic factor, but their study differs from previous studies because it is a single-center cohort, "which increases the power to potentially identify significant differences, and we focused on soft-tissue sarcoma exclusively to enhance the homogeneity of the study population."

Nonetheless, the researchers noted some limitations of their study, namely their collective analysis of the various soft-tissue sarcoma subtypes and the lack of a control group. Soft-tissue sarcoma, because of its heterogeneous nature, challenges the adoption of precision medicine for this cancer type, but, until clinicians better understand the underlying mechanism of metastasis in these tumor types, Dr. Chudgar and his coauthors said, pulmonary metastasectomy "remains the best available treatment for soft tissue sarcoma pulmonary metastases."

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: Pulmonary metastasectomy (PM) is a well-established component in the management of sarcoma. Although better survival has been reported with fewer metastases and longer intervals between diagnosis and the appearance of metastases, data have been conflicting regarding outcomes based on histologic subtypes. Prior studies have revealed no significant difference in survival between patients with high-grade vs. low-grade tumors, histological type, and unilateral vs. bilateral lung metastasis (Thorac Cardiovasc Surg. 2016;64:1460). This large single-institution study reports prolonged survival following PM and identifies clinical features that confer better prognosis including histologic subtype, disease-free interval, number of pulmonary metastases, and minimally invasive resection. This information will help in identifying patients best suited for undergoing pulmonary metastasectomy for soft-tissue sarcoma.

Immune signature shows good prognostic performance

BY SUSAN LONDON
Frontline Medical News

A new tumor immune-related gene signature may help take the guesswork out of prognostication in patients with early-stage non–small cell lung cancer (NSCLC), according to a retrospective cohort study.

"Various components of the immune system have been shown to be a determining factor during cancer initiation and progression," note the investigators, who were led by Bailiang Li, PhD, of Stanford (Calif.) University. "Recent immunotherapies targeting specific immune checkpoints such as programmed death 1 or programmed death ligand 1 have demonstrated a remarkable, durable response in NSCLC. Certain histopathologic patterns, such as intratumoral infiltration by cytotoxic lymphocytes, have also been associated with better prognoses in several cancer types, including NSCLC."

For the study, the investigators developed and validated an immune-related gene signature using frozen tumors from 2,414 patients with stage I or II nonsquamous NSCLC from 19 public cohorts who underwent resection with negative margins and did not receive any neoadjuvant or adjuvant therapy.

The new signature contained 25 gene pairs consisting of 40 unique immune-related genes, Dr. Li and associates report (JAMA Oncol. 2017 Jul 6. doi: 10.1001/jamaoncol.2017.1609).

Processes such as chemotaxis were enriched among the included genes.

The signature significantly stratified patients into groups that have high and low risks of death during follow-up, both across and within subsets with stage I, IA, IB, or II dis-

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Invasive mediastinal staging rates run the gamut

BY BRUCE JANCIN
Frontline Medical News

COLORADO SPRINGS – Significant variability exists between hospitals in Washington state in their rates of invasive mediastinal staging for lung cancer, Farhood Farjah, MD, reported at the annual meeting of the Western Thoracic Surgical Association.

Frontline Medical News

Dr. Farhood Farjah

"We found evidence of a fivefold variation in hospital-level rates of invasive mediastinal staging not explained by chance or case mix," according to Dr. Farjah of the University of Washington, Seattle.

Prior studies from across the country have documented widespread underutilization of invasive mediastinal staging in situations where the staging is recommended in major guidelines such as those published by the National Comprehensive Cancer Network.

"This has led to substantial concerns about quality of thoracic surgical care in the community at large," he noted.

The Washington study is the first to show hospital-by-hospital variation in rates of invasive mediastinal staging.

Invasive mediastinal staging for lung cancer is considered important because imaging is known to have a substantial false-negative rate, and staging results have a profound impact on treatment recommendations, which can range from surgery alone to additional chemoradiation therapy.

Yet the meaning of the hospital-level huge variability in practice observed in the Washington study remains unclear.

"Our understanding of the underutilization of invasive mediastinal staging is further complicated by the fact that patterns of invasive mediastinal staging are highly variable across hospitals staffed by at least one board-certified thoracic surgeon with a noncardiac practice," Dr. Farjah explained. "This variability could be a marker of poor-quality care. However, because the guidelines are not supported by level 1 evidence, it's equally plausible that this variability might represent uncertainty or even disagreement with the practice guidelines – and specifically about the appropriate indication for invasive staging."

He presented a retrospective cohort study of 406 patients whose non–small cell lung cancer was resected during July 2011–December 2013 at one of five Washington hospitals, each with at least one board-certified thoracic surgeon with a noncardiac practice on staff. The four participating community hospitals and one academic medical center were involved in a National Cancer Institute–funded, physician-led quality improvement initiative.

Overall, 66% of the 406 patients underwent any form of invasive mediastinal staging: 85% by mediastinoscopy only; 12% by mediastinoscopy plus endobronchial ultrasound-guided nodal aspiration (EBUS); 3% by EBUS only; and the remaining handful by mediastinoscopy, EBUS, and esophageal ultrasound-guided nodal aspiration. The invasive staging was performed at the time of resection in 64% of cases. A median of three nodal stations were sampled.

After statistical adjustment for random variation and between-hospital differences in clinical stage, rates of invasive staging were all over the map. While an overall mean of 66% of the lung cancer patients underwent invasive mediastinal staging, the rates at the five hospitals were 94%, 84%, 31%, 80%, and 17%.

Dr. Farjah and his coinvestigators are now conducting provider

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ease. Relative to counterparts falling into the signature-defined low-risk group, those falling into the signature-defined high-risk group had roughly twice the risk of death after adjustment for clinical and pathologic characteristics, with a hazard ratio range of 1.72 (*P* less than .001) to 2.36 (*P* less than .001).

Accuracy of the immune signature exceeded that of two commercialized gene signatures for estimating survival in similar validation cohorts (mean concordance index, 0.64 vs. 0.53 and 0.61).

Moreover, the combination of the immune signature with clinical factors outperformed the signature alone (mean C-index, 0.70 vs. 0.63) and another commercialized clinical-molecular combination signature (mean C-index, 0.68 vs. 0.65).

"The proposed immune-related gene pair–based signature is a promising prognostic biomarker in nonsquamous NSCLC, including early-stage disease," concluded the investigators. "Prospective studies are needed to further validate its analytical accuracy for estimating prognoses and to test its clinical utility in individualized management of nonsquamous NSCLC."

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: As lung cancer screening implementation increases, it is expected that the prevalence of early-stage non–small cell lung cancer (NSCLC) will increase.

While surgical resection confers a good 5-year survival in early-stage NSCLC, the patients most likely to achieve long-term benefit are those with small tumors, T1a lesions.

Currently, adjuvant therapy is reserved for patients with tumors greater than 4 cm or those with N1 disease. Having reliable biomarkers to identify patients at a high risk for recurrence after surgical resection is a significant clinical advantage in order to guide adjuvant therapy. The clinical-immune signature described in this study is an exciting and promising biomarker for estimating overall survival in NSCLC.

interviews and focus groups in an effort to understand what drove the participating surgeons' wide variability in performing invasive mediastinal staging.

Discussant Jane Yanagawa, MD, of the University of California, Los Angeles, commented, "I think this is a really interesting study because, historically, lower rates of mediastinoscopy are assumed to be a reflection of low-quality care – and you suggest that might not be the case, that it might be more complicated than that."

Dr. Yanagawa sketched one fairly common scenario that might represent a surgeon's reasonable avoidance of guideline-recommended invasive mediastinal staging: a patient who by all preoperative imaging appears to have stage IA lung cancer and wishes to avoid the morbidity, time, and cost of needle biopsy, instead choosing to go straight to the operating room for a diagnosis by wedge resection, followed by a completion lobectomy based upon the frozen section results. Could such a pathway account for the variability seen in the Washington study?

"I think it could have," Dr. Farjah replied. "I would say that's probably one driver of variability."

As for the generalizability of the findings of a five-hospital study carried out in a single state, Dr. Farjah said he thinks the results are applicable to any academic or community hospital with at least one board-certified thoracic surgeon with a noncardiac practice.

He reported having no financial conflicts of interest regarding the study.

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VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: Staging of lung cancer is essential to select the best treatment strategy for a given patient. However, despite multiple guideline recommendations for mediastinal staging, a significant number of stage IIIA NSCLC do not receive guideline-adherent mediastinal staging. This study highlights the marked variability in mediastinal staging that persists across clinical centers. Lower rates of mediastinal staging have been blamed on lack of board-certified thoracic surgeons with training in mediastinoscopy, but in this study, each center involved had at least one board-certified thoracic surgeon. Striking is that only a small percentage (15%) of patients in this study underwent staging with bronchoscopic ultrasound-guided needle aspiration. Given the high sensitivity and low invasiveness, ultrasound-guided staging modalities should be considered before surgical techniques for hilar and mediastinal staging. The "gold standard" of mediastinoscopy for invasive staging is challenged by ultrasound-guided techniques, which guidelines recommend to be the initial invasive test in most instances for which lymph node staging is required. This study underscores the importance of continual education and training of pulmonologists and thoracic surgeons in ultrasound-guided techniques in order to improve mediastinal staging application and accuracy.

Tips and tricks for appealing an audit

BY ALICIA GALLEGOS
Frontline Medical News

CHICAGO – The question is not if a physician will face a Medicare or Medicaid billing audit, but when, according to Abby Pendleton, a New York–based health law attorney. That's why it pays to know how to handle an audit before one probe disrupts your practice. At a recent American Bar Association meeting, Ms. Pendleton and H. Rusty Comley, a Jackson, Mississippi–based health law attorney, offered answers to top audit questions and provided guidance on how physicians can successfully appeal an audit.

MS. PENDLETON

MR. COMLEY

When should you appeal?

There are a number of factors to consider when deciding whether to appeal audit findings. For starters, consider the cost of the payback amount and the basis of the findings.

If the amount of money is nominal, the audit involves a one-time mistake and the decision is not really disputable, a doctor may just want to pay the audit request, Mr. Comley said in an interview.

"In other words, the provider would spend more money and time to appeal the audit than to pay the audit, and the issue or mistake is not likely repeated in past or future claims," it might make sense to just pay, he said.

On the other hand, if the findings are arguable, the monetary amount is significant, and/or the audit could affect more than just one billing, the doctor may want to consider appealing. Paying a small monetary amount could become problematic when the audit issue or "mistake" may have been repeated or will be repeated, Mr. Comley cautioned, adding that paying without dispute could create a precedent for future audits.

If the basis of the findings stem from

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an interpretation of a local coverage decision that the physician disagrees with, he or she may also want to appeal, Ms. Pendleton added.

"If you don't fight it, there's an argument that, 'Well, guess what? You had that issue going back 6 years for all these other claims, and now we get into the [Medicare] 60-day overpayment identification [rule],'" she said at the meeting. "If a physician is [not] aware of payments they're not entitled to, even if they think they were right on the front end, but they later become aware, they have 60 days to refund it or it's a false claim. Those are considerations that really need to be looked at."

What should you expect from an appeal?

Expect to go through more than one appeals process step to succeed. There are five stages to the appeals process (see box, pg. 23).

"At the redetermination stage, I don't see a whole lot of movement in terms of great success at that first stage," Ms. Pendleton said. "So, don't think, 'If we get to that first level of appeal, we're expecting to win.' If you look at the statistics, it's not really that realistic."

Although a provider has 120 days to file an appeal, it's smarter to file within the first 30 days, Ms. Pendleton advised. If an appeal is filed within 30 days, the government cannot recoup its demand from

a doctor's current Medicare payments.

Expect a lengthy time frame for a final outcome. Under federal law, once an appeal gets to the administrative law judge (ALJ) stage (the third stage), the appellant should receive a hearing decision within 90 days. However, because of heavy case backlogs, physicians typically don't get a hearing for 3 years, Ms. Pendleton said.

"The problem is, your MAC [Medicare administrative contractor] can start taking your money after the [second] stage," she said. "If it's a huge dollar amount, you're probably going to have to enter into a payment plan [with the government]. You will eventually get your money back, if you win, 3-4 years later."

Note that physicians generally experience a higher degree of success at the ALJ stage, so it may be worth continuing the appeal through this stage, she noted.

Overall, more than one-third of audit findings are reversed in providers' favor during the appeals process. Of 170,482 Medicare appeal decisions in 2015, 37% were made in favor of the health provider, an increase from 23% in 2014, according to 2015 Medicare data and 2014 reports.

The cost to appeal varies significantly between Medicaid and Medicare and depends largely on

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the complexity of the audit, Mr. Comley said. A Medicaid audit appeal, through an ALJ hearing and written appeal to a court, may cost between $20,000 and $60,000 depending on the circumstances, he said. By contrast, a Medicare appeal resolved in the first stage of appeal may cost only a few thousand dollars for a relatively simple audit.

"Of course, the costs will rise at each level of the Medicare appeal process, especially in the third stage involving the ALJ telephonic hearing, but, in most cases, the Medicare appeal costs will still be below a similar Medicaid appeal," he said.

What strategies can help you win?

Consider reaching out to your congressional representative or senators, Mr. Comley advised. Particularly if the issue involves a medical treatment decision or a medically necessary determination, it may be helpful to copy "your favorite Congressman or senator's office" on correspondence with the MAC. Clearly state your argument against the findings and how/why the medical decision was made. Legislators will often get involved and could help your appeal, Mr. Comley said.

Further, don't review just the claims that auditors denied. Also evaluate the claims they have approved in the past, he added.

"In almost every case I've been involved in, they'll approve claims that, on the other hand, they deny," Mr. Comley said. "Under most legal standards, that's a good way to win – it's called arbitrary and capricious."

Find the best experts to back your case, Ms. Pendleton advised. Consider including expert opinions in written responses to the government that support the services provided and/or have medical experts ready to testify during hearings. If the government based

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: The most effective way to handle an audit is not to be involved in one. This requires an appropriate knowledge of coding and billing tempered with a strong dose of honesty. While CMS rules for coding and billing can occasionally be confusing,

they are not intended to "trick" physicians into making errors. Rather, either through lack of understanding, poor documentation, or dishonesty (upcoding), mistakes can be made. Unfortunately, the physician is considered guilty until proven otherwise. The 37% success rate of appeals argues that this is true more often than not. As noted in the article, a CMS audit can be a very anxiety-provoking, time-consuming, and expensive process that one should avoid at all costs. The key to doing this and improving the physician success rate if one is audited is through education of the providers and advocating to amend poorly written CMS policy. Dishonesty will have to correct itself.

its findings on statistics or cited statistics in its review, involve a statistical expert who can argue against the government's conclusion.

If the case is significant enough, consider skipping steps in the appeals process to get the case before a federal court sooner. Appellants can escalate their appeal through the process at nearly every stage if the government fails to respond within a timely manner. At the second stage, for example, if the qualified independent contractor does not issue a decision within 60 days, an appellant generally has the right to escalate the case to an administrative law judge. If the ALJ does not issue a decision within 90 days, the appeal can generally be escalated to the Appeals Council level, and, if the council does not issue a decision within 90 days, appellants can seek judicial review.

It may be worth it to have your day in court sooner, Ms. Pendleton said.

"It might be an option for providers if you have a large audit with a lot at stake," she said. "Escalate it through. Get it to federal court and argue it."

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The 5 steps of the Medicare appeals process

There are five stages of the Medicare audit appeals process. They include what follows:

1. Redetermination by the Fiscal Intermediary. A redetermination is an examination of a claim by a Medicare administrative contractor (MAC) separate from the personnel who made the initial claim determination. The appellant has 120 days from the date of initial claim determination receipt to file an appeal.

2. Reconsideration by a Qualified Independent Contractor (QIC). A QIC is an independent contractor who didn't take part in the level 1 decision. The QIC will review the request for a reconsideration and make a decision. An appellant must file a request for reconsideration within 180 days of Medicare redetermination notice or remittance advice receipt.

3. Administrative Law Judge (ALJ) hearing. Appellants present their case to an ALJ who will review the facts of the appeal and listen to testimony before making a decision. An ALJ hearing is usually held by phone or video conference. Appellants can ask the ALJ to make a decision without a hearing. The ALJ may also issue a decision without holding a hearing if evidence in the record supports a decision that's fully in the appellant's favor.

4. Medicare Appeals Council review. If you disagree with the ALJ decision or wish to escalate the appeal because the ALJ ruling time frame has passed, a request for a Medicare Appeals Council review can be made. A request for a Medicare Appeals Council review must be made within 60 days of receipt of the ALJ's decision or after the ALJ ruling time frame expires.

5. Judicial review in U.S. District Court. A party may file an action in federal district court within 60 calendar days after the date receiving notice of the Medicare Appeals Council's decision or after a council notice that it is not able to reach a decision. To get a judicial review in federal district court, the case amount must meet a minimum dollar amount ($1,560 in 2017).

Each state has its own Medicaid appeals process. Contact your state's Medicaid office to find out how to appeal a Medicaid audit finding.

Source: The Centers for Medicare & Medicaid Services

Physicians express mixed views on FDA tobacco plan

BY ALICIA GALLEGOS
Frontline Medical News

Physicians associations are expressing mixed opinions about the Food and Drug Administration's new plan for regulating tobacco products, such as flavored cigars, hookah tobacco, and e-cigarettes.

As part of the new plan, announced July 28, the FDA will relax previous application deadlines set for makers of newer tobacco products. The agency will also seek more public input on the role of flavors in tobacco products before moving forward with specific regulations.

The American Thoracic Society (ATS) expressed disappointment with the FDA's new plan, calling it a move that centers on delayed action. The agency already has more than enough information to proceed with regulation of flavored nicotine products, the ATS said in a statement.

"The delay outlined in [FDA Commissioner Scott Gottlieb's] vision will cost the American public continued death and disease as a result of tobacco use," Enid Neptune, MD, vice chair of the ATS Tobacco Action Committee said in the statement. "In short, Dr. Gottlieb's announcement of the FDA's new vision for regulating tobacco products is long on delay and short on action. The health of the American public, and particularly today's youth, will suffer as a result of the FDA's failure to act."

The American College of Chest Physicians, meanwhile, expressed its support of the actions outlined.

"We welcome opportunities and actions that reduce tobacco use, addiction, and tobacco-related disease and death," said Gerard Silvestri, MD, president for the college, in a statement. "We support the actions proposed by the FDA, which are likely to improve public health and reduce the burden of disease on patients and our country."

As part of the FDA's revised plan, the agency intends to begin a public dialogue about lowering nicotine levels in combustible cigarettes to nonaddictive levels through "achievable product standards." The agency also plans to issue an advance notice of proposed rule making to seek input on the potential public health benefits and possible adverse effects of lowering nicotine in cigarettes.

Under revised time lines, applications for newly regulated combustible products, such as cigars, pipe tobacco, and hookah tobacco, must be submitted by makers to the FDA by Aug. 8, 2021, and applications for noncombustible products, such as e-cigarettes, must be submitted by Aug. 8, 2022. Manufacturers can continue to market their products while the agency reviews their product applications. The time frames push back previous deadlines that were established in a May 2016 final rule by the FDA. In the prior rule, manufacturers of all new tobacco products had 12-24 months to prepare and send applications for marketing authorization to the FDA and a 12-month continued compliance period after those dates in which to obtain FDA authorization.

The agency also plans to seek new public input on a range of related topics, including approaches to regulating kid-appealing flavors in e-cigarettes and cigars; the role that flavors in tobacco products, such as menthol, play in attracting youth; and the patterns of use and resulting public health impacts from premium cigars. Additionally, the agency will examine actions to increase access and use of FDA-approved medicinal nicotine products and work with sponsors to consider what steps can be taken under the safety and efficacy standard for products intended to help smokers quit, according to the FDA plan.

"This comprehensive plan and sweeping approach to tobacco and nicotine allows the FDA to apply the powerful tools given by Congress to achieve the most significant public health impact," Mitch Zeller, director of the FDA's Center for Tobacco Products said in a statement. "Public input on these complex issues will help ensure the agency has the proper science-based policies in place to meaningfully reduce the harms caused by tobacco use."

However, the ATS said that many of the issues raised in the FDA's revised plan have already been discussed at length in the scientific literature and with the public.

"Scientific literature documenting the role cigars play in tobacco-related disease is extensive," and the FDA has already received public and industry input regarding exempting cigars, noted Harold J. Farber, MD, chair of the ATS Tobacco Action Committee. Additionally, multiple reports have been issued on the role of flavoring agents, showing that flavoring agents increase tobacco initiation and make tobacco cessation harder, noted Dr. Neptune.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: While I always try to be open to others' opinions and encourage dialogue in situations where compromise is most appropriate, I must side with the "less than happy" group regarding this ruling. There is certainly enough scientific evidence to take a stand against tobacco products of any kind because of their lack of health benefits. Despite the potential benefit of aiding tobacco cessation efforts, adding flavoring to e-cigarettes does not enhance this benefit but certainly can enhance the taste and thereby nicotine addiction. It is past time for the FDA to step up to the plate and discourage business entities from developing products and services that are of little use to the health of the nation.

Fewer than half of office visits involve primary care

BY RICHARD FRANKI
Frontline Medical News

Visits to primary care generalists, which made up two-thirds of the visits to physician offices in 1980, now represent less than half of all visits, according to the results of a survey by the National Center for Health Statistics (NCHS).

Primary care physicians' share of office visits fell from 66.2% in 1980 to 49.1% in 2013, the NCHS reported in "Health, United States, 2016." The corresponding increase among specialty care physicians gave them a total of 50.9% of all office visits in 2013, up from 33.8% in 1980.

Age may be playing a part in this shift. The generalists mostly held their own among patients younger than 18 years, who made 77.8% of all their office visits to primary care physicians in 1980, compared with 73.8% in 2013. The shift away from primary care, however, increased along with patient age: from 65.3% of visits in 1980 to 53.7% in 2013 for those aged 18-44 years; 60.2% to 42.1% for 45- to 64-year-olds, and 61.6% to 38.3% for those aged 65 years and over, the NCHS said.

The NCHS estimates are based on data collected by the National Ambulatory Medical Care Survey, which excluded Alaska and Hawaii in 1980.

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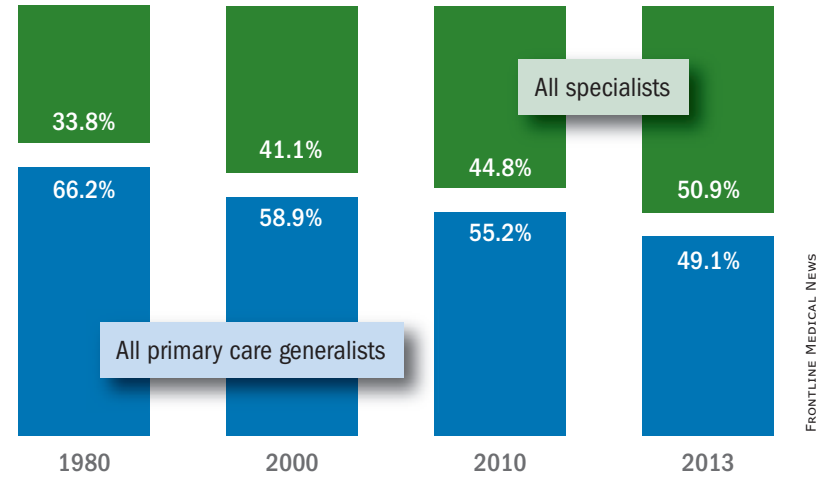
Distribution of visits to physician offices



Note: Based on data from the National Ambulatory Medical Care Survey.
Source: National Center for Health Statistics

Mild OSA: Does it affect cardiovascular health and should it be treated?

BY SOWJANYA DUTHULURU, MD; USMAN NAZIR, MD; AND DAMIEN R. STEVENS, MD, FCCP

The definition of mild obstructive sleep apnea (OSA) has varied over the years depending upon several factors, but based upon all definitions, it is highly prevalent. Depending upon presence of symptoms and gender, the prevalence may be as high 28% in men and 26% in women. (Young et al. *N Engl J Med.* 1993;328:1230). Typically, a combination of symptoms and frequency of respiratory events is required to make the diagnosis. Based upon the International Classification of Sleep Disorders-3rd edition (ICSD-3), the threshold apnea hypopnea index (AHI) for diagnosis depends upon the presence or absence of symptoms. If an individual has no symptoms, an AHI of 15 events per hour or more is required to make a diagnosis of OSA. However, there are several concerns about whether or not an individual may be "symptomatic." This is most relevant when driving privileges may be at risk, such as with a commercial drivers' licensing. If a person knows that their response to a list of questions could lead to further testing, additional costs, and/or treatment, then symptoms could be unreported or underestimated. Notwithstanding, specific symptoms that are typically noted include some sign of sleepiness or non-restorative sleep and apneic episodes. The presence of snoring, gasping, choking, or breathing interruptions, either witnessed or noted by the individuals themselves, are included in the criteria. The Epworth Sleepiness Scale is the most common measure of sleepiness, which includes the likelihood of falling asleep in eight different scenarios. However, there is only a weak correlation between the scale and severity of OSA with sensitivity as low as 0.36 reported in some studies, especially if only mild OSA is present. The presence of other comorbid disease can be used as criteria, including hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, and type 2 diabetes mellitus. If no signs, symptoms, or comorbid diseases are present, then an AHI greater than 15 events per hour or more is required to make the diagnosis of OSA (Chowdrui et al. *Am J Respir Crit Care Med.* 2016;193:e37).

There is still debate regarding the association of mild OSA and cardiovascular disease and whether treatment may prevent or reduce cardiovascular outcomes. The four main clinical outcomes typically reported are hypertension, cardiovascular events, cardiovascular and all-cause mortality, and arrhythmias. Regarding mild OSA and hypertension, 5 prospective and 18 cross-sectional studies have

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Continued from previous page

been reported with the two main studies being the Wisconsin Sleep Cohort study and the Sleep Heart Health Study. The Wisconsin Sleep Cohort study found mild OSA was associated with an increased risk of hypertension (Peppard et al. *N Engl J Med.* 2000;342:1378). However, the Sleep Heart Health study followed individuals without hypertension, including 629 with mild OSA, for 5.2 years and assessed risk of incident hypertension. Stratified analyses found no evidence for an elevated risk of hypertension in subgroups defined by age, sex, BMI, or degree of sleepiness (O'Connor et al. *Am J Respir Crit Care Med.* 2009;179:1159). Therefore, it ap-

pears current data are contradictory when it comes to mild OSA and subsequent risk of hypertension when stratified by age, sex, and BMI. Only retrospective analyses have been used to assess the risk of cardiovascular events. A large clinical cohort of patients referred for sleep studies showed no association of mild OSA with different composite outcomes. Kendzerska and colleagues evaluated a composite outcome (myocardial infarction, stroke, CHF, revascularization procedures, or death from any cause) during a median follow-up of 68 months. No association of mild OSA with the composite cardiovascular endpoint was identified compared with those without OSA (Kendzerska et al. *PLoS Med.* 2014;11[2]:e1001599). Only one population-based study (MrOS Sleep Study) looked at the association between mild OSA and nocturnal arrhythmias in elderly men. The study did not find an increased risk for atrial fibrillation or complex ventricular ectopy in patients with mild OSA vs no OSA (Mehra et al. *Arch Intern Med.* 2009; 169:1147). Several cohort studies have reported mild OSA is not associated with increased cardiovascular mortality. In the 18-year follow-up of the Wisconsin Cohort Study, it was found that mild OSA was not associated with cardiovascular mortality (HR, 1.8; 95% CI, 0.7–4.9).

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All-cause mortality was also not significantly increased in the mild OSA group compared with the no-OSA group in the Wisconsin cohort after 8 years of follow-up (adjusted HR, 1.6; 95% CI, 0.8–2.8). In summary, compared with subjects without OSA, available evidence from population-based longitudinal studies indicates that mild OSA is not associated with increased cardiovascular or all-cause mortality.

Does treatment of mild OSA vs no treatment change cardiovascular or mortality outcomes? This is still debated with no definitive answer. There have been several studies that have examined different therapies for OSA to reduce cardiovascular events. Typical events include coronary artery disease, hypertension, heart failure, stroke, arrhythmias, and cardiovascular disease-related mortality. However, most studies have examined cohorts with moderate to severe OSA with limited evaluation in the mild OSA category. The effect of treatment of mild OSA on hypertension has been evaluated. A single clinical trial randomized patients with mild OSA to either a very low calorie diet with supervised lifestyle modifications vs control arm and followed patients for 1 year (Tuomilehto et al. *Am J Respir Crit Care Med.* 2009;179:320). Participants in the intervention arm lost more weight than the control group. Hypertension was a secondary

outcome measured from the study. There was no significant change in systolic and diastolic blood pressure after successful weight loss with diet and lifestyle modifications. Follow-up at 2 and 5 years did not show significant changes in systolic and diastolic blood pressure. Patients in the treatment group lost more weight than the control group (10.7kg vs 2.4kg, respectively) and had greater resolution of sleep apnea (63% vs 35%, respectively).

An observational study evaluated the effects of CPAP specifically in patients with mild OSA. There was no significant difference in the risk of developing hypertension among those patients ineligible for CPAP therapy, active on therapy, or those who declined therapy (Marin et al. *JAMA*. 2012; 307:2169). In contrast, a retrospective longitudinal cohort with normal blood pressure at baseline (mild OSA without preexisting cardiovascular disease, diabetes, or hyperlipidemia) did show decrease in mean arterial blood pressure of 2 mm Hg in the treatment group (Jaimchariyatam et al. *Sleep Med.* 2010;11:837). The MOSAIC trial was a multicenter randomized trial that evaluated the effects of CPAP on cardiac function in minimally symptomatic patients with OSA. The use of CPAP reduced the oxygen desaturation index (ODI) and Epworth Sleepiness Scale values. However, 6 months of therapy did

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the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

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

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

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, BMD for total hip and total spine regions for the 12-month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information]*.

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

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

ADVERSE REACTIONS

Long-acting $beta_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Pneumonia or lower respiratory tract infections in patients with COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Growth effects in pediatric patients *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

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

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 taken 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

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not change functional or structural parameters measured by echocardiogram or cardiac magnetic resonance scanning in patients with mild to moderate OSA (Craig et al. *J Clin Sleep Med.* 2015;11[9]:967). A single retrospective study reported the effects of CPAP in patients with mild OSA and all-cause mortality. The study compared treatment with patients using CPAP more than 4 hours vs a combined group of nonadherent and those who refused therapy (Hudgel et al. *J Clin Sleep Med.* 2012;8:9). There was no significant difference in all-cause mortality in the two groups. However, this study did not analyze the impact of therapy on cardiovascular-specific mortality. To date, there have been no studies that have evaluated the impact of treatment of mild OSA on cardiovascular events, arrhythmias, or stroke. In addition, there have been no randomized studies assessing treatment of mild OSA on fatal and nonfatal cardiovascular events. There is inadequate evidence regarding the effect of mild OSA on elevated blood pressure, neurologic cognition, quality of life, and cardiovascular consequences. Future research is needed to investigate the impact of mild OSA on these outcomes.

In summary, mild OSA is a very prevalent disease but the association with hypertension remains unclear and the literature to date suggests no association with other cardiovascular outcomes. In addition, no clear prevention of cardiovascular outcomes with treatment has been proven in the setting of mild OSA.

APAP improves aerophagia symptoms

BY JENNIE SMITH
Frontline Medical News

Switching continuous positive airway pressure–treated patients to autotitrating positive airway pressure (APAP) systems resulted in reduced severity of patient-reported aerophagia symptoms, according to results from a double-blind, randomized study.

Aerophagia, the swallowing of air leading to gastrointestinal distress, is a frequently reported adverse effect among people treated for obstructive sleep apnea with continuous positive airway pressure (CPAP).

The APAP-treated group saw significantly reduced median therapeutic pressure levels compared with the CPAP-treated patients (9.8 vs. 14.0 cm H_2O, *P* less than .001) and slight but statistically significant reductions in self-reported symptoms of bloating, flatulence, and belching. No significant difference was seen in compliance with therapy between the two treatment groups in this study, published in the August 2017 issue of Journal of Clinical Sleep Medicine (2017;13[7]:881-8).

For their research, Teresa Shirlaw and her colleagues in the sleep clinic at Princess Alexandra Hospital in Woolloongabba, Queensland, Australia, analyzed results from 56 adult patients with sleep apnea who had been recently treated with CPAP and reported bloating, flatulence, or belching following therapy.

Patients were randomized 1:1 to in-clinic nighttime CPAP or APAP for 2 weeks and blinded to treatment assignment, while investigators recorded therapy usage hours, pressure, leak, and residual apnea-hypopnea index across the study period. Most of the subjects

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Sleep apnea is often a comorbidity of nocturia

BY DOUGLAS S. PAAUW, MD

A 65-year-old man comes to a clinic concerned about frequent nocturia. He is getting up four times a night to urinate, and he has been urinating about every 5 hours during the day. He has been seen twice for this problem and was diagnosed with benign prostatic hyperplasia and started on tamsulosin.

He found a slight improvement when he started on 0.4 mg qhs, reducing his nocturia episodes from four to three. His dose was increased to 0.8 mg qhs, with no improvement in nocturia.

Exam today: BP, 140/94; pulse, 70. Rectal exam: Prostate is twice normal size without nodules. Labs: Na, 140; K, 4.0; glucose, 80; Ca, 9.6.

He is frustrated because he feels tired and sleepy from having to get up so often to urinate every night.

What is the best treatment/advice at this point?

A. Check hemoglobin A_{1c}.
B. Start finasteride.
C. Switch tamsulosin to terazosin.
D. Evaluate for sleep apnea.

At this point, I think an evaluation for sleep apnea is the next appropriate step. It is unlikely that he has diabetes with high enough blood sugars to cause polyuria, with a random glucose of 80. His daytime sleepiness is a clue to a possible sleep disorder, and his nocturia is a symptom that is often overlooked or not appreciated in patients with sleep apnea.

Umpei Yamamoto, MD, of Kyushu (Japan) University Hospital and colleagues studied the prevalence of sleep disordered breathing among patients who presented to a urology clinic with nocturia and in those who visited a sleep apnea clinic with symptoms of excessive daytime sleepiness.[1] Sleep disordered breathing was found in 91% of the patients from the sleep apnea clinic and 70% of the patients from the urology clinic. The frequency of nocturia was reduced with continuous positive airway pressure (CPAP) in both groups in the patients who had not responded to conventional therapy or nocturia.

The symptom of nocturia as a symptom of sleep apnea might be even more common in women.[2] Ozen K. Basoglu, MD, and Mehmet Sezai Tasbakan, MD, of Ege University, Izmir, Turkey, described clinical similarities and differences based on gender in a large group of patients with sleep apnea. Both men and women with sleep apnea had similar rates of excessive daytime sleepiness, snoring, and impaired concentration. Women had more frequent nocturia.

Nocturia especially should be considered a possible clue for the presence of sleep apnea in younger patients who have fewer other reasons to have nocturia. Takahiro Maeda, MD, of Keio University, Tokyo, and colleagues found that men younger than 50 years had more nocturnal urinations the worse their apnea-hypopnea index was.[3] Overall in the study, 85% of the patients had a reduction in nighttime urination after CPAP therapy.

Treatment of sleep apnea has been shown in several studies to improve the nocturia that occurs in patients with sleep apnea. Hyoung Keun Park, MD, of Konkuk University, Seoul, South Korea, and colleagues studied whether surgical intervention with uvulopalatopharyngoplasty (UPPP) reduced nocturia in patients with sleep apnea.[4] In the study, there was a 73% success rate in treatment for sleep apnea with the UPPP surgery, and, among those who had successful surgeries, nocturia episodes decreased from 1.9 preoperatively to 0.7 postoperatively (*P* less than .001).

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Minoru Miyazato, MD, PhD, of University of the Ryukyus, Okinawa, Japan, and colleagues looked at the effect of CPAP treatment on nighttime urine production in patients with obstructive sleep apnea.[5] In this small study of 40 patients, mean nighttime voiding episodes decreased from 2.1 to 1.2 (*P* less than .01).

I think that this information helps us increase our recognition of sleep apnea and also counsel patients on the benefits of treatment.

Sleep apnea should be considered in the differential diagnosis of patients with nocturia, and treatment of sleep apnea may decrease nocturia.

References

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(n = 39) used full face masks, while others used nasal-only systems.

The researchers considered differences in PAP therapy usage of at least 30 minutes per night to be statistically significant. The APAP group used the assigned therapy a mean 7 hours per night, vs. 6.8 for the CPAP group. Daytime sleepiness outcomes were also similar for the two treatment groups.

Ms. Shirlaw and her colleagues described the compliance findings as "somewhat surprising," noting that an earlier meta-analysis had shown slight improvements in compliance associated with APAP (Syst Rev. 2012;1[1]:20). In clinical practice, patients complaining of aerophagia associated with CPAP are frequently switched to APAP based on the belief that doing so "will lead to improved therapy acceptance and … improved compliance," they wrote.

"Aerophagia is one of the common side effects of CPAP that has not been adequately studied" and the experience of any side effect of CPAP treatment may impair adherence, noted Pedro Rodrigues Genta, MD; Gustavo Freitas Grad, MD; and Sara Herculano, University of São Paulo School of Medicine, São Paulo, Brazil, in an editorial (J Clin Sleep Med. 2017;13[7]:881-8).

"Auto-CPAP may improve aerophagia symptoms by reducing mean overnight CPAP level. ... Although auto-CPAP failed to improve adherence to therapy as compared to CPAP, aerophagia symptoms were significantly improved. These results provide clear evidence to switch treatment of patients experiencing aerophagia from fixed CPAP to auto-CPAP," wrote the editorial's authors, who reported having no conflicts of interest.

The investigators noted that they "could not demonstrate any difference in APAP pressure requirements (median and 95th centile pressures), leak, residual [Apnea-Hypopnea Index], or compliance between subjects using a full face mask and subjects using a nasal mask." They also found that "the use of a full face mask was associated with greater aerophagia symptoms in comparison with a nasal mask during the CPAP trial arm but not the APAP trial arm."

The researchers described the self-reporting of aerophagia symptoms as one of the study's limitations. They surmised that the lack of difference seen for compliance measures might be explained in part by the 30-minute usage increments in the study design (compared with 10-minute increments used in some other studies), and the fact that the cohort had relatively high compliance with CPAP at baseline (5.5 hours/night), suggesting a motivated patient population at entry.

The study received some funding from the government of Queensland, and the researchers disclosed no conflicts of interest related to their findings.

VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, PhD, FCCP, comments: This is an interesting study, as currently we have very few therapeutic modalities available for patients with obstructive sleep apnea and positive airway pressure–induced or exacerbated aerophagia. The interesting findings of auto-adjusting continuous positive airway pressure being superior to fixed positive airway pressure therapy may be related to the large differences between the pressures seen in the two groups (larger than in prior studies). Nevertheless, this may be of help to clinicians. What does one do when a patient on autoPAP therapy has significant aeoropagia? Well, this is for another article and another editorial …

RELEASE THE POTENTIAL OF NUCALA

The first subcutaneous anti-interleukin 5 (IL-5) targeted therapy for severe asthma with an eosinophilic phenotype

Indication

NUCALA is indicated for the add-on maintenance treatment of patients 12 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

Important Safety Information

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA, compared with none in placebo. Consider varicella vaccination, if medically appropriate, prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasms, 3% (<1%).

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for NUCALA and 5% for placebo. Manifestations included rash, flushing, pruritus, headache and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection site reactions (eg, pain, erythema, swelling, itching, burning sensation) occurred in subjects treated with NUCALA.

Benefits of NUCALA:

- **SIGNIFICANTLY REDUCED EXACERBATIONS* BY 53%** in the MENSA trial (NUCALA: 0.83/year vs placebo: 1.74/year; *P*<0.001)[1]
- **SIGNIFICANTLY REDUCED DAILY OCS DOSE WHILE MAINTAINING ASTHMA CONTROL,** in the SIRIUS trial (vs placebo; *P*=0.008)[2]
- **IMPROVED QUALITY OF LIFE** in the MENSA trial (SGRQ responder rate: NUCALA, 71%, vs placebo, 55%; odds ratio: 2.1; 95% CI: 1.3, 3.2)†

Statistical hierarchy was not met; endpoint is exploratory and results are descriptive only.[3]

MENSA (Trial 2)[1]: 32-week study comparing treatment with NUCALA or placebo, added to regular treatment with high-dose ICS and at least 1 other controller with or without OCS, in 576 patients with severe asthma with an eosinophilic phenotype.‡
Primary endpoint: Frequency of exacerbations.

SIRIUS (Trial 3)[2]: 24-week study comparing treatment with NUCALA or placebo in 135 patients with severe asthma with an eosinophilic phenotype‡ who required at least 5 mg to 35 mg of prednisone equivalent per day in addition to regular use of high-dose ICS plus an additional controller.
Primary endpoint: Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control.

ICS=inhaled corticosteroid; OCS=oral corticosteroid; SGRQ=St. George's Respiratory Questionnaire.

*Defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients on maintenance oral/systemic corticosteroids, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

†The SGRQ is a validated measure of health impairment for chronic respiratory diseases and is able to address the impact asthma has on a patient's quality of life. Response was defined as a reduction in score of 4 points or more.[4]

‡Identified by blood eosinophil counts ≥150 cells/μL at initiation of treatment (within 6 weeks of dosing) or ≥300 cells/μL in the past 12 months.

Visit **NUCALAHCP.COM** to learn more

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothertobaby.org/asthma.

The data on pregnancy exposures from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters.

References: 1. Ortega HG, Liu MC, Pavord ID, et al; for the MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198-1207. **2.** Bel EH, Wenzel SE, Thompson PJ, et al; for the SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197. **3.** Data on file, GSK. **4.** Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J*. 2002;19(3):398-404.

Please see Brief Summary of Prescribing Information for NUCALA on the following pages.

Nucala® (mepolizumab) for Subcutaneous Injection 100 mg/vial

BRIEF SUMMARY

NUCALA®
(mepolizumab) for injection, for subcutaneous use

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. *[See Clinical Studies (14) of full prescribing information.]*

Limitations of Use
- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

5.3 Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo *[see Adverse Reactions (6.1)]*. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

5.4 Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.5 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:
- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14) of full prescribing information]*. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial
Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions
In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions
Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-term Safety
Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

6.2 Immunogenicity

Overall, 15/260 (6%) subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.3 Postmarketing Experience

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

Immune System Disorders
Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

Risk Summary
The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data
Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation

Risk Summary
There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14) of full prescribing information.]* Subjects had a reduction in the rate of exacerbations

8.4 Pediatric Use (cont'd)
that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) 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, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE
Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks (approximately 70 times the MRHD on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

17. PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease
Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster
Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients varicella vaccination should be considered before starting treatment with NUCALA.

Reduction of Corticosteroid Dosage
Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry
Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations (8.1)]*.

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Low-dose aspirin bests dual-antiplatelet therapy in TAVR

BY BRUCE JANCIN
Frontline Medical News

PARIS – Single-antiplatelet therapy with low-dose aspirin following transcatheter aortic valve replacement (TAVR) reduced the occurrence of major adverse events, compared with guideline-recommended dual-antiplatelet therapy (DAPT), in the randomized ARTE trial.

The TAVR guideline recommendation for DAPT with low-dose aspirin plus clopidogrel is not based on evidence. It relies on expert opinion.

DR. RODÉS-CABAU

ARTE (Aspirin Versus Aspirin + Clopidogrel Following TAVR) is the first sizable randomized trial to address the safety and efficacy of aspirin alone versus DAPT in the setting of TAVR, Josep Rodés-Cabau, MD, noted in presenting the ARTE results at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

Although a confirmatory randomized trial would be welcome, "in the meantime, the results of the ARTE trial may help us to guide clinical practice beyond empirical recommendations," he said. "At the Quebec Heart and Lung Institute, we've stopped using DAPT completely for our TAVR patients unless they have a specific indication for it, such as a recently implanted coronary stent."

VIEW ON THE NEWS

Frank J. Podbielski, MD, FCCP, comments: As TAVR becomes more widely employed for older patients with aortic valve disease, optimal anticoagulation strategies become critical. The ARTE trial elegantly demonstrates that sometimes "less" is actually "more." The general enthusiasm for widespread use of anticoagulants in the elderly coupled with their increasing potency has resulted in significant life-threatening bleeding complications – as is borne out in the data from this trial. While the trial did not reach its accrual goal and was concluded prematurely, these preliminary data are encouraging for patients requiring anticoagulation therapy who are at increased risk for bleeding due to age and other medical comorbidities.

ARTE was a multicenter, prospective, international open-label study of 222 TAVR patients who were randomized to 3 months of single-antiplatelet therapy (SAPT) with aspirin at 80-100 mg/day or to DAPT with aspirin at 80-100 mg/day plus clopidogrel at 75 mg/day after a single 300-mg loading dose. Participants had a mean Society of Thoracic Surgery Predicted Risk of Mortality score of 6.3%. The vast majority of participants received the balloon-ex-

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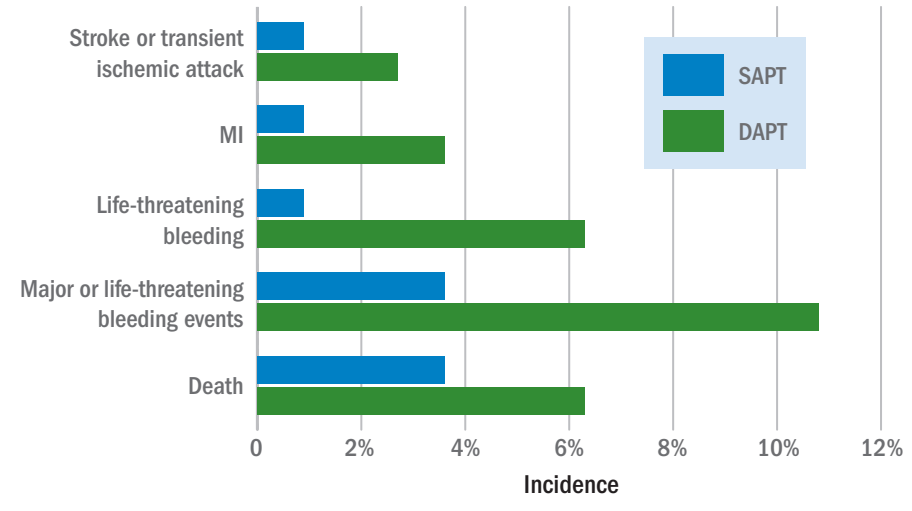
Outcomes: Single- vs. double-antiplatelet therapy in TAVR patients



Note: Based on data from a multicenter, prospective, open-label study of 222 patients.
Source: Dr. Rodés-Cabau

Continued from previous page

pandable Edwards Lifesciences Sapien XT valve. The remainder got the Sapien 3 valve.

The primary outcome was the 3-month composite of death, MI, major or life-threatening bleeding, or stroke or transient ischemic attack. It occurred in 15.3% of the DAPT group and 7.2% on SAPT, a difference that didn't reach statistical significance ($P = .065$) because of small patient numbers.

ARTE was halted prematurely. The original plan was to recruit 300 TAVR patients for 12 months of follow-up. However, the investigators wound up capping the trial at 220 patients and 3 months of follow-up because of slow enrollment and withdrawal of financial support by the study sponsors. As a result, while all of the components of the composite endpoint showed strong, consistent benefit favoring SAPT, only the difference in major or life-threatening bleeding achieved statistical significance (see graphic).

All subjects were on a proton pump inhibitor. The type, timing, and severity of bleeding events differed between the two study arms. All 4 bleeding events in the SAPT group were vascular in nature, while 5 of the 12 in the DAPT group were gastrointestinal. All the bleeding events in the SAPT group occurred within 72 hours after TAVR, whereas 5 of 12 in the DAPT recipients occurred later. Only one patient on SAPT experienced life-threatening bleeding, compared with seven DAPT patients who did.

One prior study "showed no differences, and an Italian one showed a tendency toward more bleeding with DAPT. So, I think there has been no sign to date that adding clopidogrel protects this group of patients from anything," noted Dr. Rodés-Cabau of Laval University in Quebec City. "

Discussant Luis Nombela-Franco, MD, an interventional cardiologist at San Carlos Hospital in Madrid, pronounced the ARTE trial guideline changing despite its limitations.

"With the expansion of TAVR to moderate- and, very soon, to low-risk patients, the results of this study are encouraging for the treating physicians and confirm the value of evidence-based medicine over expert opinion or empirical therapy," noted Hossein Almassi, MD, FCCP.

ARTE was supported by grants from Edwards Lifesciences and the Quebec Heart and Lung Institute.

Simultaneous with Dr. Rodés-Cabau's presentation in Paris, the ARTE trial was published online (JACC Cardiovasc Interv. 2017 May 11. pii: S1936-8798[17]30812-9).

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Five-year outcomes favor on-pump CABG

BY DOUG BRUNK
Frontline Medical News

Compared with adults who underwent off-pump coronary-artery bypass grafting surgery, those who underwent on-pump CABG had significantly lower rates of mortality and major adverse cardiovascular events at 5 years, results from a large randomized trial demonstrated.

"Given the results, it appears that innovative surgical approaches – such as the more technically demanding off-pump procedure – may not always provide superior clinical outcomes," researchers led by A. Laurie Shroyer, PhD, wrote (N Engl J Med. 2017 Aug

Continued on following page

High TAVR rates linked to fewer readmissions

BY ELI ZIMMERMAN
Frontline Medical News

WASHINGTON – Hospitals with a higher volume of transcatheter aortic valve replacements (TAVRs) have significantly lower 30-day readmission rates, according to an observational study.

In a study of 129 hospitals, those that performed more than 100 TAVR procedures had a 24% and 25% lower readmission rate compared with hospitals that performed 50-100 TAVRs (*P* less than .001) and hospitals that performed fewer that 50 TAVRs (*P* = .007) respectively (JAMA Cardiol. 2017 May 11. doi: 10.1001/jamacardio.2017.1630).

This finding could have serious financial and medical implications for hospitals that are deciding whether or not to focus on this minimally invasive procedure, according to Sahil Khera, MD, MPH, chief resident and cardiology fellow at New York Medical College, Valhalla, and his colleagues.

"Lower readmission rates at high-volume hospitals substantially reduce health care expenditure," said Dr. Khera and colleagues. "As new TAVR programs open across the country, these data will guide policymakers to identify targets for optimizing and standardizing TAVR outcomes across hospitals."

To study the correlation between TAVR procedures and readmission rates, the investigators gathered records on hospitals that performed at least five TAVRs in 2014, which were then categorized into high-, medium-, or low-volume categories, and cross-referenced with the 2014 Nationwide Readmissions Database.

Of the 16,252 TAVR procedures conducted in 2014, 663 (4%), 3,067 (19%), and 12,522 (77%) were performed at low-, medium-, and high-volume hospitals, respectively, according to the investigators.

Patients undergoing these procedures were on average 81 years of age, with an average of four Elixhauser comorbidities, most commonly dyslipidemia (64%), hypertension (80%), heart failure (75%), and known coronary artery disease (69%), with a majority having undergone an endovascular procedure (83%).

However, the researchers found the population of TAVR patients of high-volume hospitals were slightly younger, had fewer women, were more likely to be in a higher-income household, and were less likely to undergo a transapical procedure than in low-volume hospitals, which Dr. Khera and fellow researchers believe may have some impact on their findings.

"Low-volume hospitals were more likely to operate on patients with a higher number of comorbidities compared with high-volume hospitals and were more likely to use the TA approach," according to investigators, "Transapical TAVR is associated with poorer short- and intermediate-term mortality, increased use of skilled nursing care facilities, longer hospital stays, and readmissions when compared with transfemoral TAVR."

Overall, there were 2,667 readmissions reported, among which high-volume hospitals reported a 30-day readmission rate of 15.6%, while low- and medium-volume hospitals reported similarly higher rates of 19.5% and 19%.

When looking into the causes for these readmissions, the investigators found that 1,619 (61%) were due to noncardiac causes, which appeared in all three hospitals, despite a larger proportion present in low-volume hospitals as opposed to medium- and high-volume hospitals (65.6% vs. 60.1% and 60.6%, respectively). Infection, respiratory, endocrine/metabolic, renal, and trauma problems were more common in low-volume hospitals, while gastrointestinal and transient ischemic attack/stroke issues were more common in medium- and high-volume hospitals.

One investigator received personal fees from Edwards Lifesciences and Medtronic; another received grants and personal fees from various pharmaceutical companies, educational institutions, and publications; and a third consulted for Medtronic.

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Continued from previous page

17;377:623-32). "Additional long-term follow-up, evaluating these same outcomes rigorously at 10 years after CABG, appears to be warranted. "

Dr. Shroyer, of the Northport (N.Y.) VA Medical Center, and her associates conducted a 5-year follow-up study of patients who had participated in the original Randomized On/Off Bypass (ROOBY) trial, which compared the effectiveness of the two surgical approaches (N Engl J Med. 2009 Nov 5;361:1827-37). During February 2002 – June 2007, 2,203 patients at 18 medical centers were randomly assigned to either on-pump or off-pump CABG, with 1-year assessments completed by May 2008. The primary outcomes were the rates mortality and major adverse cardiovascular events at 5 years, while the secondary 5-year outcomes included death from cardiac causes, repeat revascularization, and nonfatal myocardial infarction.

The mean age of patients was 63 years, nearly all were male, 46% were between the ages of 55 and 64, and about 21% had chronic obstructive pulmonary disease. The researchers found that at 5 years the rate of death was 15.2% in the off-pump group, compared with 11.9% in the on-pump group, which translated into a relative risk of 1.28 (*P* = .02). In addition, the rate of major cardiovascular events at 5 years was 31% in the off-pump group, compared with 27.1% in the on-pump group, which translated into a relative risk of 1.14 (*P* = .046). None of the secondary outcomes at 5 years met the prespecified threshold of a *P* value of .01 or less for statistical significance, when the off-pump and on-pump groups were compared. This included the rates of nonfatal myocardial infarction (12.1% vs. 9.6%, respectively; *P* = .05); death from cardiac causes (6.3% vs. 5.3%; *P* = .29); repeat vascularization (13.1% vs. 11.9%; *P* = .39); and repeat CABG (1.4% vs. 0.5%; *P* = .02).

DR. ALMASSI

"In combination with findings from other randomized trials and a 2012 Cochrane systematic review [Cochrane Database Syst Rev. 2012;14:CD007224], the 5-year outcomes in our study support the conclusion that off-pump CABG does not offer any substantial advantages over on-pump CABG except possibly in unusual situations such as, for example, in patients with an extensively calcified (porcelain) aorta, in whom the off-pump technique may result in less manipulation of the aorta, potentially decreasing the risk of aortic emboli or stroke," the researchers wrote. "In light of the low rates of use of off-pump CABG in the United States, the findings in our trial may provide more of a real-world experience than those in the CORONARY and GOPCABE trials, which required surgeons with a very high volume of experience with off-pump procedures, as compared with the ROOBY trial and with most other surgeons who are based in the United States."

G. Hossein Almassi, MD, FCCP, one of the study's other authors, noted that ROOBY was the world's first large prospective randomized trial comparing off-pump to conventional CABG.

"The off-pump CABG was associated with a 28% higher risk of mortality at 5 years and more major adverse cardiovascular events. The long-term outcomes of this study along with data from other randomized trials suggest that off-pump not only does not provide an advantage over the conventional on-pump but it may actually lead to worse long-term outcomes," Dr. Almassi said.

The study was supported by a grant from the Department of Veterans Affairs. Dr. Shroyer reported having received grants from the VA Cooperative Studies Program during the conduct of the study. Dr. Almassi is on the Editorial Advisory Board of this publication.

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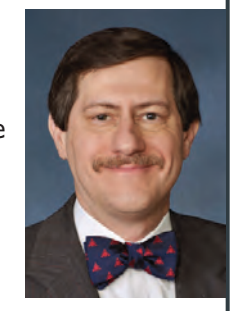
VIEW ON THE NEWS

Frank J. Podbielski, MD, FCCP, comments: The authors of this study conducted within the VA system demonstrated that the rate of death and the rate of major cardiovascular events are lower in patients undergoing on-pump vs. off-pump CABG. Not examined in this study were neurocognitive differences between the two groups. The potential neurological benefit of off-pump CABG needs to be weighed against its increased technical complexity.



VIEW ON THE NEWS

Dangers of using readmissions as a measurement

Considering the idea of using readmissions in comparison to rate of TAVR procedures is interesting, but the number of confounds are too great to give any kind of accurate representation of medical practice. While the authors of this study do address its limitations, including a learning curve as it relates to the risk of inpatient mortality, the number of adjustments that must be made to account for the additional confounding factors are simply too insurmountable to give an accurate estimate of statistical and clinical importance.

For example, researchers found TAVR readmissions were associated with certain baseline comorbidities, access sites, and complications. However, association does not mean causation and so the categorization of cardiac-related vs. noncardiac-related readmissions must be approached with some caution.

If one were to try to use readmission rates after TAVR to argue for reimbursement of the procedure, one would need to determine a well-established, validated reimbursement rate for TAVR readmissions, which has not been done.

Also, the advancing nature of this procedure, combined with a constant focus from hospitals to reduce readmission rates means any baseline for readmissions used would most likely be out of date.

It would be unlikely for investigators to factor in the cause of reduced readmission rates, which could be a factor of increased technology, more experienced physicians, lower-risk patients, or any combination thereof. Holding TAVR sites accountable for quality of care is of course important, but using readmission rates to determine something like funding is not appropriate when the measurement being used is so complex.

Perhaps a better approach would be to widen access for low-volume hospitals to resources that would improve the TAVR processes and encourage using financial incentives.

Evaluations by physical therapists or a similar procedure should be put into place before discharge to assess a patient's risk of readmission.

Overall, this is a multifaceted issue that would be better helped by promoting TAVR best practices and encouraging hospitals to compare themselves against each other to reduce unnecessary readmissions.

John D. Carroll, MD, is professor of medicine and director of the Cardiac and Vascular Center at the University of Colorado, Denver, and a member of the Steering Committee of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. He made his remarks in an editorial in JAMA Cardiology (doi: 10.1001/jamacardio.2017.1650).

Bailout stenting doubles adverse CV events risk

BY BRUCE JANCIN
Frontline Medical News

PARIS – Bailout stenting during percutaneous coronary intervention for coronary bifurcations doubled the risk of major adverse cardiovascular events in the world's largest registry of patients with these often-challenging lesions treated using bioactive stents, Marco Zimarino, MD, reported at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

Indeed, resort to bailout stenting stood out as the major potentially modifiable risk factor for adverse outcomes among the 4,306 participants in the P2BiTO registry, an international collaboration supported by members of the EuroBifurcation Club. Most of the other independent risk factors identified in a multivariate regression analysis of the P2BiTO database were beyond operator control, including diabetes, advanced age, and presentation with an acute coronary syndrome, according to Dr. Zimarino of the University of Chieti (Italy).


DR. ZIMARINO

"The message is that the relevant player in determining adverse outcomes is bailout stenting, meaning any stent deployed beyond the planned strategy of either single or double stenting," he said.

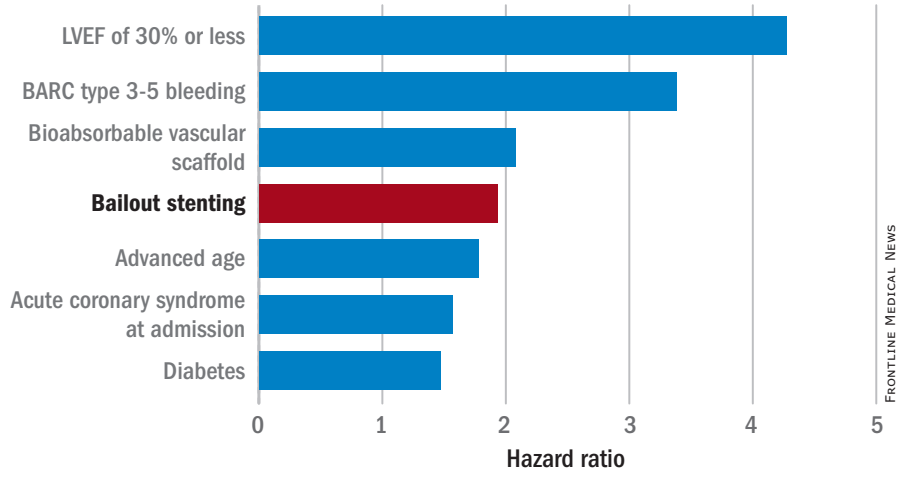
Bailout stenting is largely avoidable through meticulous procedural planning, the interventional cardiologist added.

"Careful planning is always mandatory because bailout stenting is associated with an unacceptably higher risk of both in-hospital and 1-year adverse outcomes," Dr. Zimarino emphasized. "It's much better to leave a degraded side branch instead of using bailout stenting to get an excellent angiographic outcome that's a predictor of a worse clinical outcome."

Conventional wisdom holds that single stenting of either the main artery or a side branch in a patient with coronary bifurcation is safer than double stenting of both. However, that wasn't really borne out in the P2BiTO registry provided the operator's plan was for double stenting. The difference in 1-year major adverse cardiovascular events (MACE) between patients treated

Continued on following page

Risk factors for MACE in patients treated for coronary bifurcations



Note: Based on data from 4,306 participants in the P2BiTO registry. LVEF = left ventricular ejection fraction; BARC = Bleeding Academic Research Consortium.

Source: Dr. Zimarino

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The findings of this study suggest that a careful preplanning and adherence to the planned procedure is in the best interest of the patient.

Sinus of Valsalva preserved in aortic valve replacement

BY MARK S. LESNEY
Frontline Medical News

The sinus of Valsalva segment can be preserved during aortic valve replacement irrespective of the type of valve pathology, according to a recent study by Rita Karianna Milewski, MD, and her colleagues at the Hospital of the University of Pennsylvania, Philadelphia.

Severe aortic root dilation coupled to aortic valve disease requires root replacement in patients with a tricuspid or bicuspid aortic valve. Commonly, an aortic valve replacement and supracoronary ascending aorta replacement (AVRSCAAR) procedure has been used for patients who have a mild to moderately dilated sinus segment. One advantage of the procedure is that it retains the sinus of Valsalva (SOV) and preserves the intact coronary ostia.

However, the long-term behavior and risk of aortic events for the retained SOV in both BAV and TAV patients remains unclear, according to Dr. Milewski and her colleagues.

Previous researchers have suggested that patients with BAV and TAV have different rates of complications of the remaining aorta and dilation of the proximal aorta and retained sinus segment. In addition, it has been suggested that the cause of aortic dilation is different in patients with aortic stenosis (AS) and aortic insufficiency (AI) and is based on TAV and BAV morphology, histology, and hemodynamic flow patterns.

However, in the August issue of the Journal of Thoracic and Cardiovascular Surgery, Dr. Milewski and her colleagues reported on their study showing that, in patients with nonaneurysmal SOV undergoing AVRSCAAR, the sinus of Valsalva segment can be preserved regardless of the type of valvular pathology (aortic stenosis vs. aortic insufficiency) or valvular morphology (BAV vs. TAV).

The researchers retrospectively reviewed a prospectively maintained institutional database to stratify all patients by BAV or TAV valvular pathology with concomitant ascending aortic aneurysm who underwent an elective AVRSCAAR from 2002 to 2015 (J Thorac Cardiovasc Surg. 2017;154:421-32).

The distribution of the 428 patients meeting inclusion criteria by subgroups was: BAV group (254 patients: BAV-AS = 178; BAV-AI = 76); TAV group (174 patients: TAV-AS = 61; TAV-AI =113). Preoperative sinus of Valsalva dimensions were divided into three subgroups (less than 40 mm, 40-45 mm, and greater than 45 mm).

The mean patient age for patients with BAV and TAV was 59 years and 72 years (*P* less than .001), respectively (with 78% with BAV being men and 57% with TAV being men). There was a significantly higher subpopulation of AS in the BAV cohort vs. TAV-AS (70% vs. 35%; *P* less than .001).

With regard to SOV sizing, there was no significant difference in mean preoperative aortic root diameters between BAV and TAV cohorts for the AS or AI subpopulations.

In-hospital/30-day mortality was significantly higher in patients with TAV (5.2%) than in patients with BAV (1.6%, *P* = .033). In addition, the incidence of transient ischemic attack/stroke was significantly higher in the TAV group (3.4%) vs. the BAV group (0.8%, *P* = .04).

Valvular morphology and pathology at baseline, preoperative SOV diameter, postoperative time course, and interaction effect of preoperative SOV diameters and postoperative time course were used as covariates to assess outcomes. Within-subject and within–stratified subgroup comparison failed to show main effects across the follow-up times on postoperative SOV size patterns (*P* = .935), implying that the SOV trends were stable and sustained (discharge to greater than or equal to 10 years) irrespective of valvular morphology and pathology (BAV-AI, BAV-AS, TAV-AI, and TAV-AS).

Preoperative SOV dimensions significantly affected the retained postoperative sinus dimensions (*P* less than .001), according to Dr. Milewski and her colleagues.

The data indicated that an initial and pronounced postoperative decrease in SOV dimensions occurs with AVRSCAAR independently of aortic valve morphology, aortic valve pathology, and age, they added.

The 10-year freedom from aortic reoperation rates were 97% and 95% in the BAV and TAV subgroups, respectively. The BAV group had significantly improved reoperation-free survival, compared with the TAV group (*P* less than .001), while the type of valvular pathology within each group did not show a significant survival difference.

"Irrespective of the aortic valve morphology or valve pathology, in patients with mild to moderate aortic root dilatation (less than 45 mm), preservation of the SOV segment in the context of an AVRSCAAR procedure is justified. Continued further follow-up will be important to understand the long-term outcomes of sinus preservation, especially in the younger population with BAVs," the researchers concluded.

The authors reported having no financial conflicts to disclose.

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VIEW ON THE NEWS

It's not cancer

With regard to the question, ''Is it necessary to replace the sinuses of Valsalva in the setting of bicuspid aortic valve aortopathy?'', the researchers "leverage their enormous institutional experience to find an answer. The results suggest that this answer is 'no.' At least not in all cases," Thoralf M. Sundt, MD, wrote in his invited commentary on the paper (J Thorac Cardiovasc Surg. 2017;154:419-20).

"The findings of this study argue for us to take a step back and ask how much really needs be done," he added. And although "it is hard to ask a surgeon to do less rather than more; however, the balance of judgment has to be between the operative risk of the more aggressive approach and the natural history of the disease. In other words, what does it 'cost' to be aggressive, and what do we gain?" he asked.

"Bicuspid aortic valve aortopathy, it would appear, is not cancer after all. Regardless of theoretic arguments that are based on embryology and the migration of neural crest cells, it does not appear to require resection to 'clean margins,' even if we believe that the operative risk 'in our hands' is low," concluded Dr. Sundt.

Thoralf M. Sundt, MD, is at Harvard Medical School, Boston. He reported having no disclosures.

Continued from previous page

using a single- or double-stenting strategy wasn't statistically significant, provided bailout stenting wasn't utilized. If bailout stenting was employed, though, the risk of MACE was 2.2-fold greater than if the cardiologist stuck with the plan.

Ninety-eight percent of patients in the P2BiTO registry received drug-eluting stents. The other 2% got the Absorb bioabsorbable vascular scaffold. The percutaneous coronary intervention access site, treatment strategy, choice of stent, and duration of dual-antiplatelet therapy were left up to the operator's discretion.

The 1-year MACE rate was 10%, including a 5.1% incidence of all-cause mortality, 3.2% cardiovascular mortality, 1.7% stroke, 3.4% acute MI excluding periprocedural MI, 2.5% stent thrombosis, and 1.7% Bleeding Academic Research Consortium type 3-5 bleeding. Bailout stenting was utilized in 8.8% of patients who experienced MACE and 4% of those who didn't.

The risk of MACE was reduced by 39% in patients on dual-antiplatelet therapy for 6-12 months, compared with less than 6 months.

Discussant Graham Cassel, MD, director of the heart transplant unit at Milpark Hospital in Johannesburg, commented, "The message comes through very clearly that, if you plan your procedure well, the chance of bailout is far less – and if you do have to bail out, the results are uniformly bad. If you can avoid putting in two or three stents, that's beneficial."

Dr. Zimarino reported having no financial conflicts of interest regarding his presentation.

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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.

Adempas—the first and only approved treatment for both PAH (WHO Group 1) and CTEPH (WHO Group 4)* adult patients

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

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Whippany, NJ 07981

Manufactured in Germany

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Ventricular assist devices linked to sepsis

BY DAMIAN MCNAMARA
Frontline Medical News

NEW ORLEANS – Back in 2008, there was only one case.

Since then, however, the number of patients with ventricular assist devices who developed sepsis while being treated in the cardiac unit at Queen Elizabeth Hospital in Birmingham, England, appeared to be noticeably growing. So, investigators launched a study to confirm their suspicions and to learn more about the underlying causes.

"Bloodstream infection is a serious infection, so I thought, 'Let's see what's happening,'" explained Ira Das, MD, a consultant microbiologist at Queen Elizabeth Hospital.

A total of 129 ventricular assist devices (VADs) were implanted in 118 patients between January 2008 and December 2016 at this institution. The researchers found 23 patients with a VAD (19.5%) had developed a microbiology-confirmed bloodstream infection. The 25 cases of sepsis in this group included two patients who each experienced episodes associated with different microorganisms.

Coagulase-negative staphylococci were the most common cause, present in 32% of the 25 cases. Sepsis was caused by *Enterococcus faecium* in 12%, *Candida parapsilosis* in 8%, and *Staphylococcus aureus* in 2%. Another 4% were either *Enterococcus faecalis*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *C. guilliermondii*, or *C. orthopsilosis*. The remaining 16% of bloodstream infections were polymicrobial.

Less certain was the source of these infections.

"In the majority of cases, we didn't know where it was coming from," Dr. Das said at the annual meeting of the American Society for Microbiology. In 6 of the 25 cases, VAD was confirmed to be the focus of infection, either through imaging or because a failing component of the explanted device was examined later. An intravascular catheter was the source in another 5 patients, and in 14 cases, the source remained a mystery.

"Some of these infections just might have been hard to see," Dr. Das said. "If the infection is inside the device, it's not always easy to visualize."

The study supports earlier findings from a review article that points to a significant infection risk associated with the implantation of VADs (Expert Rev Med Devices. 2011 Sep;8[5]:627-34). That article's authors noted, "Despite recent improvements in outcomes, device-related infections remain a significant complication of LVAD [left ventricular assist device] therapy."

In a previous study of people with end-stage heart failure, other investigators noted that, "despite the substantial survival benefit, the morbidity and mortality associated with the use of the left ventricular assist device were considerable. In particular, infection and mechanical failure of the device were major factors in the 2-year survival rate of only 23%" (N Engl J Med. 2001 Nov 15;345[20]:1435-43).

Similarly, in the current study, mortality was higher among those with sepsis and a VAD. Mortality was 39% – including eight patients who died with a VAD in situ and one following cardiac transplantation. However, Dr. Das cautioned, "It's a small number, and there are other factors that could have contributed. They all go on anticoagulants so they have bleeding tendencies, and many of the patients are in the ICU with multiorgan failure."

Frontline Medical News

Infection prevention remains paramount to minimize mortality and other adverse events associated with a patient's having a VAD. "We have to make sure that infection control procedures and our treatments are up to the optimal standard," Dr. Das said. "It's not easy to remove the device."

Of the 129 VADs implanted, 68 were long-term LVADs, 11 were short-term LVADs, 15 were right ventricular devices, and 35 were biventricular devices.

The study is ongoing. The data presented at the meeting were collected up until December 2016.

"Since then, I've seen two more cases, and – very interestingly – one was *Haemophilus influenzae*," Dr. Das said. "The patient was on the device, he was at home, and he came in with bacteremia." Again, the source of infection proved elusive. "With *H. influenzae*, you would think it was coming from his chest, but the chest x-ray was normal."

The second case, a patient with a coagulase-negative staphylococci bloodstream infection, was scheduled for a PET scan at the time of Dr. Das's presentation to try to identify the source of infection.

Dr. Das reported no relevant disclosures.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: The young, recently graduated clinic nurse came to see me before I went in to see my patient. "I can't register a pulse or blood pressure", she said, assuming that her failure to do so indicated a lack of clinical acumen on her part. "You won't", I told her. I took her with me into the exam room and watched her listen with her stethoscope in amazement to the mechanical hum of the LVAD device over the patient's chest.

Modern technology saves our patients' lives, but there is always another side to the coin. Reports that LVAD devices are associated with a high incidence of bloodstream infections is important for future clinical practice. The fact that the causes and risk factors for these infections are unknown make this phenomena one of high interest.

New drug choices emerging to battle antibiotic resistance

BY DOUG BRUNK
Frontline Medical News

SAN FRANCISCO – When the Infectious Diseases Society of America released the "Bad Bugs, No Drugs" report in 2004, its authors warned that effective antibiotics may not be available to treat seriously ill patients in the near future.

It also proposed legislative, regulatory, and funding solutions with a goal of developing and licensing 10 new antibiotics by the year 2020.

One such advancement was the Generating Antibiotics Incentives Now Act, which was signed into law in 2012 and created a designation for new antibiotics that are used to treat serious and/or life-threatening diseases due to certain pathogens. It also extends the patent life of these antibiotics and allows for fast-track Food and Drug Administration approval.

"The reason for antibiotic resistance over time has largely been … the direct result of our antibiotic use both in humans and in animals," Kim S. Erlich, MD, said at the UCSF Annual Advances in Internal Medicine meeting. "Many of these organisms have spread globally and are now part of normal flora, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE). It costs more across the board to take care of these patients, and they

Continued on following page

MRSA bacteremia outcomes improved

BY DAMIAN MCNAMARA
Frontline Medical News

NEW ORLEANS – Compared with vancomycin monotherapy, vancomycin combined with cefepime improved some outcomes for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections, a retrospective study of 109 patients revealed.

A lower likelihood of microbiological failure and fewer bloodstream infections persisting 7 days or more were the notable differences between treatment groups.

"The center where I work, where the patients come from, the Detroit Medical Center – their 'go-to therapy' for empiric treatment is vancomycin plus cefepime, because they want to cover the gram positives and the gram negatives," said Safana M. Atwan, a fourth-year pharmacy student at Wayne State University, Detroit. In vitro studies have also shown that "cefepime and vancomycin have a synergistic relationship."

All patients had at least 72 hours of vancomycin therapy to treat MRSA bacteremia confirmed by blood culture. During 2008-2015, 38 adults received vancomycin monotherapy and 71 received vancomycin plus 24 hours or more of cefepime.

Compared with monotherapy, the combination treatment was associated with a nonsignificant reduction in the primary composite treatment failure outcome of 30-day all-cause mortality, in bacteremia duration of 7 days or more, and in 60-day bloodstream-infection recurrence: 55% for monotherapy versus 42% for combination therapy ($P = .195$). The difference was primarily associated with decreased duration of sepsis and fewer MRSA bloodstream infections persisting 7 days or more in the combination cohort.

Rates of bacteremia duration of 7 days or more were 42% in monotherapy patients and 20% in combination patients ($P = .013$). Differences in 60-day bloodstream-infection recurrence were nonsignificant, 8% versus 4%, respectively ($P = .42$).

Thirty-day mortality, however, was lower among monotherapy patients than combination patients – 13% vs. 25% – although the difference was nonsignificant ($P = .21$).

"[It] seems like they will have a lower duration of bacteremia, which is always great," Ms. Atwan said. "You want to decrease length of stay in the hospital," which will cut down on costs and on patients' risks of getting more infections.

Although the primary outcome was a composite endpoint, "when we looked at them separately, we found the patients in the combination group had more mortality," Ms. Atwan said at the annual meeting of the American Society for Microbiology. "That surprised me initially. But those patients are sicker and more likely to get dual coverage."

The investigators confirmed the association between the severity of MRSA bacteremia and combination therapy by looking at Acute Physiology and Chronic Health Evaluation (APACHE II) scores. The median APACHE score was 23 in the combination group, compared with 13.5 in the monotherapy group ($P = 0003$). Higher APACHE scores were associated with greater odds of meeting the composite failure endpoint (adjusted odds ratio, 1.08) and of developing endocarditis (aOR, 3.6) in multivariate analyses.

Continued from previous page

have higher mortality and higher morbidity."

According to Dr. Erlich, chief of staff and medical director of infection control and antibiotic stewardship at Mills Peninsula Medical Center, Burlingame, Calif., increasingly common antibiotic-resistant pathogens besides MRSA and VRE include penicillin-resistant *Streptococcus pneumoniae*, extended-spectrum beta-lactamase–producing gram-negative rods, carbapenem-resistant *Enterobacteriaceae* (CRE), multidrug-resistant *Mycobacterium tuberculosis*, *Salmonella enterica* serotype Typhimurium DT 104, and drug-resistant Candida species.


DR. ERLICH

Since 2010, several new antibiotics have been introduced to the market, including three second-generation lipoglycopeptide antibiotics with gram-positive coverage that are approved primarily for skin and soft-tissue infections: dalbavancin (Dalvance), telavancin (Vibativ), and oritavancin (Orbactiv).

Compared with vancomycin, these new agents have more convenient dosing and a longer half-life, "but they're also more expensive," said Dr. Erlich. Dalbavancin can be dosed once a week intravenously, telavancin can be dosed once daily intravenously, and oritavancin requires just one dose.

Another new agent is tedizolid phosphate (Sivextro), a second-generation oxazolidinone that is in the same drug class as linezolid (Zyvox). Tedizolid phosphate has gram-positive coverage including MRSA, but it is not approved for VRE. "It's FDA approved for skin and soft-tissue infections (SSTI) but can be used for other locations as well," Dr. Erlich said. "It features once-daily dosing IV or PO."

Ceftaroline fosamil (Teflaro), ceftolozane/tazobactam (Zerbaxa), and ceftazidime/avibactam (Avycaz) are broad-spectrum cephalosporins with or without beta-lactamase inhibitors resulting in extended gram-negative coverage. FDA-approved indications include complicated urinary tract infections, complicated abdominal infections, SSTI, and pneumonia.

The primary advantage of these drugs, compared with other agents, is for multidrug-resistant gram-negative bacteria such as extended-spectrum beta-lactamase producers and CRE. "We're not using a lot of these drugs in clinical practice, but they are available for patients with multidrug-resistant gram-negative rods who have no other options," Dr. Erlich said.

Practical ways that clinicians can prevent antibiotic resistance include prescribing antibiotics only when necessary. "Be aware of local resistance patterns, avoid antibiotics for probable viral infections, use narrow-spectrum choices when possible, use shorter durations when appropriate, and consult published guidelines for optimal empiric antibiotic therapy," Dr. Erlich advised.

In addition, "advocate infection control measures to keep patients from developing infections, including proper wound care, hand washing, respiratory etiquette, vaccinations, and social isolation for symptomatic individuals," he noted.

Dr. Erlich reported having no relevant financial disclosures.

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Lithoplasty tames heavily calcified coronary lesions

BY BRUCE JANCIN
Frontline Medical News

PARIS – A novel therapeutic ultrasound-based technology known as lithoplasty is turning heads in interventional cardiology and vascular medicine because it addresses the bane of interventionalists' existence: complex, heavily calcified coronary and peripheral artery lesions.

"Calcification is something we deal with every day in interventional cardiology. It makes the procedures more expensive, longer, and in fact several recent studies have shown that the complication rate for calcified lesions is higher than for any other lesion subtype. Calcification is the next big thing that we're trying to take on in interventional cardiology," Todd J. Brinton, MD, observed at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

As an example of the problems calcified lesions create, he cited an analysis of 6,855 acute coronary syndrome patients in whom percutaneous coronary intervention was performed in the ACUITY and HORIZONS-AMI trials. The 1-year rate of major adverse cardiovascular events (MACE) was 12.9% in those with no or mild coronary calcification, 15.3% with moderate calcification, and 19.9% with severe calcification. Moreover, the 1-year cardiac death rate of 4% in patients with severe calcification was more than twice that in those with no or minimal calcification (J Am Coll Cardiol. 2014 May 13;63[18]:1845-54).

At EuroPCR, he presented the results of DISRUPT CAD, a seven-center study in which 60 patients with heavily calcified coronary lesions underwent lithoplasty in order to facilitate stent placement. The study met all of its safety and performance endpoints. As a result, the week prior to EuroPCR the European regulatory agency granted marketing approval for Shockwave Medical's coronary lithoplasty system; the indication is for coronary vessel preparation prior to stenting. A large phase III U.S. trial aimed at gaining Food and Drug Administration approval is planned.

Moreover, on the basis of the earlier favorable DISRUPT PAD trial, lithoplasty has already been approved for treatment of peripheral artery disease (PAD) in Europe since late 2015 and by the FDA since September 2016. Now underway is DISRUPT PAD III, a large postmarketing randomized trial comparing lithoplasty with conventional balloon angioplasty in patients with heavily calcified PAD, added Dr. Brinton, an interventional cardiologist at Stanford (Calif.) University and cofounder of Shockwave Medical.

Lithoplasty is a potentially transformative technology which he described as "lithotripsy inside a balloon." Lithotripsy has an established 30-year track record for the safe treatment of kidney stones.

However, lithotripsy utilizes focused ultrasound, while lithoplasty relies upon circumferential unfocused therapeutic ultrasound delivered by miniaturized emitters placed inside a 12-mm intravascular balloon. The balloon is crossed to the target lesion, inflated to a modest pressure of 4 atmospheres, then the operator delivers lithoplasty pulses lasting over 1 microsec in duration at a rate of 1/sec for 10 seconds in order to fracture the thick intramedial calcium plaque, allowing the lesion to open up and thereby normalize vessel compliance.

"Once you've cracked the calcium you can easily dilate the lesion. It's the calcium that's restricting the ability to dilate. The real fundamental need here is to maximize acute gain to get really good stent apposition. We're trying to get expansion," the cardiologist explained.

That was readily achieved in the DISRUPT CAD study. The 60 participants had reference vessel diameters of 2.5-4.0 mm, with an average target lesion length of 20 mm. The calcification was heavy, covering on average 270 degrees of the vessel circumference as measured by optical coherence tomography, with an average calcium thickness of 0.97 mm and a calcified segment length of 22.3 mm.

The mean stent expansion was 112%. The minimum luminal diameter improved from 0.9 mm pre-

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treatment to 2.6 mm post treatment, for an acute gain of 1.7 mm. The amount of acute gain was similar across the full range of vessel diameters.

The mean diameter stenosis went from 68% pretreatment to 13% post-treatment.

The primary safety endpoint was the 30-day rate of MACE, defined as cardiac death, MI, or target vessel revascularization. The rate was 5%, consisting of 3 patients with mild non–Q-wave MI defined by creatine kinase–MB elevations more than three times the upper limit of normal. The 6-month MACE rate was 8.5%, which included the three non–Q-wave MIs plus two cardiac deaths not related to the procedure or technology.

Final angiographic results adjudicated in a central core laboratory showed no perforations, abrupt closures, slow or no reflow events, or residual dissections. These are complications commonly seen with debulking devices such as rotational or orbital atherectomy, Dr. Brinton noted.

The primary performance endpoint in DISRUPT CAD was clinical success, defined as a residual stenosis of less than 50% post percutaneous coronary intervention with no in-hospital MACE. dThis was achieved in 57 of 60 patients, or 95%. The device was successfully delivered to the target lesion with subsequent performance of litho-

plasty in 59 of 60 patients. An even more flexible and deliverable device will be released in the coming year, according to the cardiologist.

"I'd say the take-home is that the disease has changed," Dr. Brinton commented. "It's not the same disease that we had when Gruentzig did his first balloon angioplasty. These lesions are more calcified, more complex, yet for the most part we use the same balloon we've been using for the last 40 years. So lithoplasty is really an attempt to modernize the therapy in a new patient subset we now take care of who are much more complicated than the patients we originally took care of."

"The reality is, we're having difficulty taking care of these patients. For myself as an interventionalist, it's not uncommon to look around the table and see a massive amount of tools when we're doing these complex cases. Lithoplasty is intended to bring the simplicity. I would say it's not necessarily to make the best operators better, it's to bring all operators up to the ability to take on these complex lesions that are now usually reserved for high-volume centers that can do debulking," he added.

Session cochair David R. Holmes Jr., MD, of the Mayo Clinic in Rochester, Minn., pronounced lithoplasty "tremendously exciting." He and the other panelists focused on questions of safety and potential collateral damage: Where does the calcified debris go? What are the effects of the unfocused sonic pressure waves on noncalcified plaque? How hot does the vessel get?

Dr. Brinton replied that thick calcium plaque is located mostly in the medial vessel wall and stays there after fracturing. That's why distal embolization wasn't an issue in DISRUPT CAD. In animal studies, even at 20 times the energy dose used in clinical practice, lithoplasty had no effect on softer, noncalcified plaque or normal tissue. Vessel temperature increases by about 1.2 degrees C during lithoplasty, which isn't sufficient to cause injury or drive restenosis.

Frontline Medical News

Dr. Todd J. Brinton

Elsewhere at EuroPCR, Alberto Cremonesi, MD, who chaired a press conference where Dr. Brinton presented highlights of DISRUPT CAD, declared lithoplasty is "in my mind a real breakthrough, not only for coronary disease but also for PAD."

Is it possible that stand-alone lithoplasty could reduce the need for multiple stents in longer coronary lesions, instead making possible more focal stenting? asked Dr. Cremonesi of Maria Cecilia Hospital in Cotignola, Italy.

That's one of several possibilities worthy of future investigation, Dr. Brinton replied. Lithoplasty might also facilitate the results obtainable with bioresorbable coronary scaffolds or drug-coated balloons, he added.

He noted that as cofounder of and a consultant to Shockwave Medical, he has a sizable financial involvement with the company.

bjancin@frontlinemedcom.com

For appropriate patients with DVT/PE

Choose ELIQUIS from the **START**

DVT: deep vein thrombosis; PE: pulmonary embolism.

INDICATIONS

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS.

Eliquis®
(apixaban) tablets 5mg 2.5mg

ELIQUIS for initial DVT/PE treatment*—

And for appropriate patients, continue on a low dose† to reduce the risk of recurrent DVT/PE following initial therapy[1]

To learn more about ELIQUIS, visit

hcp.eliquis.com

*Initial therapy: 10 mg, orally twice daily for the first 7 days. After 7 days, 5 mg orally twice daily.
†Extended therapy: 2.5 mg, orally twice daily. **Please see full dosing information in the Prescribing Information.**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

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

Reference: 1. ELIQUIS® Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY.

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

Bristol-Myers Squibb Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

Reversal of Anticoagulant Effect

A specific antidote for ELIQUIS is not available, and there is no established way to reverse the bleeding in patients taking ELIQUIS. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.
‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.
§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.
¶ GI bleed includes upper GI, lower GI, and rectal bleeding.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

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

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

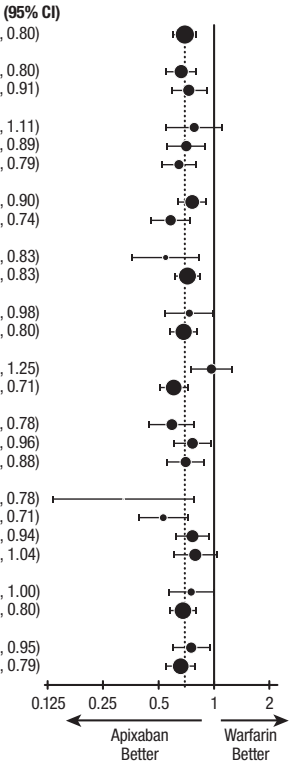
Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.
† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
¶ CRNM = clinically relevant nonmajor.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

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

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1) in full Prescribing Information]*:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1) in full Prescribing Information]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1) in full Prescribing Information]*.

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in full Prescribing Information]*.

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CHEST 2017 Keynote Speaker

Excited to Help Physicians Wake Up and Live Inspired

John O'Leary is a father of four, business owner, speaker, writer, and former hospital chaplain—a fortunate guy. But he attributes the best of everything he has to an unfortunate event that happened back in 1987.

JOHN O'LEARY

At the age of 9, O'Leary was involved in a house fire that left burns on 100% of his body, 87% of which were third degree. Doctors gave O'Leary less than a 1% chance to live, odds that were overwhelming—but not entirely impossible to beat.

Despite what the health-care professionals told his mother, when

CHEST® Annual Meeting 2017

O'Leary asked her if he was going to die, she responded by asking her son if he wanted to die or if he wanted to live: a question that O'Leary says must have taken lot more courage for a mother to ask than it did for a 9-year-old to answer.

Although he was taken aback, the answer seemed obvious to O'Leary. Of course he wanted to live. And live he did, but only after 5 months in the hospital and the amputation of all of his fingers.

After he returned to school 18 months later with his classmates welcoming him back with a parade, O'Leary didn't see the necessity in sharing his story. "I always knew my story, I just never truly embraced it."

O'Leary's father told him that he wanted to thank the community members who truly helped their family through the tough times and that he planned to do so by writing a book. With the help of O'Leary's mother, 100 copies of Overwhelming Odds were originally printed and given to members of the community. Today, over 70,000 copies of their book have been sold.

When some Girl Scouts approached O'Leary and asked him to share his story with their troop and their parents, his life changed. O'Leary says that he now tries to say yes to each person/organization that asks him to share. As a result, he has said yes over 1,500 times and has even made a life of it.

"We confuse being out of bed with being awake, being at work with being fully engaged, or being with a patient with being actively present for and with that patient," O'Leary says of accidental living. "That's not really awake; that's not alive. It's more of sleepwalking through life."

O'Leary believes that too often we give away the freedom of life to things that are out of our control and that he feels it is his job to remind his listeners that there are a lot of things in our control on which we should be fully living. "We want people to realize they have the ability to be actively present in every engagement and every decision, every thought, and every word, and ultimately, every result in their lives."

CHEST Annual Meeting 2017 is one of the events that O'Leary has recently said "yes" to, and he is very excited about it. "As things continue to change…we can forget why we got into what we got into," O'Leary says. "I am excited to remind everyone at CHEST about the profoundly beautiful nature of their work and how it has the ability to affect both the staff and patients."

Members of O'Leary's medical team, as well as other hospital staff members, were crucial to his survival and improved health. One of his doctors was not only a respected physician and surgeon but also a powerful leader who was capable of reminding every member of the hospital of their purpose and necessity to a patient's life, something that O'Leary hopes can be common in every health-care team.

"When you have the chance to influence men and women who serve patients and teams and impact lives and do it generationally—I think we forget that it is a generational ripple effect; my kids are where and who they are today because doctors, nurses, practitioners, and janitors showed up 30 years ago."

NAMDRC Update

The Growing Need to Mix Pulmonary Medicine and Politics

BY PHIL PORTE
Executive Director, NAMDRC

The old adage of not wanting to see how laws or sausage is made holds true today, perhaps more so than ever. But certain clinical realities within pulmonary medicine virtually ensure that legislation is actually part of any reasonable solution.

NAMDRC has initiated an outreach to all the key medical, allied health, and patient societies that focus on pulmonary medicine to determine if consensus can be reached on a focused laundry list of issues that, for varying reasons, lean toward Congress for legislative solutions.

Here is a list of some of the issues under discussion:

- Home mechanical ventilation. Under current law, "ventilators" are covered items under the durable medical equipment benefit. In the 1990s, in order to circumvent statutory requirements that ventilators be paid under a "frequent and substantial servicing" payment methodology, HCFA (now CMS) created a new category – respiratory assist devices and declared that these devices, despite classification by FDA as ventilators, are not ventilators in reality, and the payment methodology, therefore, does not apply.

Over the past several years, the pulmonary medicine community tried its best to convince CMS that its rules were problematic, archaic, and costing the Medicare program tens of millions of dollars in unnecessary expenditures. A formal submission to CMS, a request for a National Coverage Determination reconsideration, was denied with a phrase now echoed throughout health care, "it's complicated." The only effective solution is a legislative one.

- High flow oxygen therapy for ILD patients. Oxygen remains the largest single component of the durable medical equipment benefit and, largely due to competitive bidding, has seen payment drop dramatically since the implementation of competitive bidding.

One can easily argue that com-

Continued on following page

This month in *CHEST*:

Editor's picks

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

GIANTS IN CHEST MEDICINE
Jack Hirsh, MD, FCCP.
By Dr. S. Z. Goldhaber.

ORIGINAL RESEARCH
IVIg for Treatment of Severe Refractory Heparin-Induced Thrombocytopenia.
By Dr. A. Padmanabhan et al.

The Impact of Statin Drug Use on All-Cause Mortality in Patients With COPD: A Population-Based Cohort Study.
By Dr. A. J. Raymakers et al.

Pathologic Findings and Prognosis in a Large Prospective Cohort of Chronic Hypersensitivity Pneumonitis.
By Dr. P. Wang et al.

EVIDENCE-BASED MEDICINE
Etiologies of Chronic Cough in Pediatric Cohorts: CHEST Guideline and Expert Panel Report.
By Dr. A. B. Chang et al, on behalf of the CHEST Expert Cough Panel.

Continued from previous page

petitive pricing is self-inflicted by the DME industry as the rates are set through a complicated formula based on bids from suppliers. But the impact has been particularly hard on liquid systems, the delivery system choice of not only many Medicare beneficiaries but also is the modality of choice for patients with clear need for high flow oxygen. While delivery in the home for high flow needs can be met by some stationary concentrators, the virtual disappearance of liquid systems, attributable to pricing triggered by competitive bidding, results in many ILD patients unable to leave their homes. The only effective solution is a legislative one.

- Section 603. This provision of the Balanced Budget Act of 2015 was designed to inhibit hospital purchases of certain physician practices that were based on aberrations within the Medicare payment system that rewarded hospitals significantly more than the same service provided in a physician office. For example, a physician office-based sleep lab may be able to bill Medicare for a particular service, but if the hospital purchases that physician practice and bills for the same service, it might receive upwards of twice as much payment.

While all involved seem to agree that this provision was not intended to target pulmonary rehabilitation services, it is being hit particularly hard by CMS rules implementing the statute. Any new pulmonary rehab program that is not within 250 yards of the main hospital campus must bill at the physician fee schedule rate, a rate about half of the hospital outpatient rate. Furthermore, existing programs that choose to expand must do so within the confines of their specific current location, unable to move a floor away. Doing so would trigger the reduced payment methodology.

CMS agrees this is clearly an example of unintended consequences, but CMS also acknowledges it does not have the authority to remedy the situation. The agency itself signaled the only way to exempt pulmonary rehabilitation services is to seek Congressional action.

And now to the "sausage" part of the equation. Congressional action on virtually anything except renaming a post office becomes a political, as well as substantive, challenge. Here are just some of the considerations that must be addressed by **any** legislative strategy.

1. Any "fix" must be clinically sound and supported across a broad cross section of physician and patient groups. And the fix must give some level of flexibility to CMS to implement it in a reasonable way but tie their hands to force changes in policy.
2. Any "fix" must have a strong political strategy that can muster support within key Congressional committees (House Ways & Means Committee and Energy & Commerce Committee, along with the Senate Finance Committee, let alone 218 votes in the House and 51 votes in the Senate.

Given these issues, almost regardless of the political environment, it is time to begin working on substantive solutions so that when the political climate improves, pulmonary medicine is ready to move forward with a coordinated cohesive strategy.

CHEST Foundation NetWorks Challenge

The CHEST Foundation is proud to announce the winners of the first round of the 2017 NetWorks Challenge! Our first place winner, Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork, and our second place finisher, Women's Health NetWork, both receive session time at CHEST 2017 on a topic of their choice and two travel grants to help their NetWork members attend CHEST 2017.

Our first place NetWork, Home-Based Mechanical Ventilation and Neuromuscular Disease, reached 100% participation from their Steering Committee in the first round of the challenge. At CHEST 2017, they will host a session titled, "Shift Work Sleep Disorders: Effects of Sleep Deprivation on Occupational Performance and Safety" on Tuesday, October 31, 2:45 PM - 4:15 PM.

The Women's Health NetWork was directly behind our first place finishers with more than 90% participation. Their session, "Care of the Critically Ill Pregnant Woman: Balancing Two Patients and Two Lives" will be on Monday, October 30, 1:30 PM - 2:30 PM. This session will focus on identifying the ethical considerations in managing a critically ill patient, foster appreciation of the complex clinical and ethical issues involved in managing the brain-injured or brain-dead pregnant woman, and identify the indications, method, risks, and benefits of perimortem Cesarean section.

Be sure to attend these two sessions while you are at CHEST 2017, and please join us in congratulating the winners of the first round of the NetWorks Challenge.

Don't forget, there is still time to win Round 2 and Round 3 of the NetWorks Challenge.

Learn more about the challenge at chestfoundation.org/networkschallenge.

Round 2	Round 3
Who: NetWork Steering Committee Members	Who: All NetWork Members
When: July 1 - Beginning of CHEST 2017	When: During CHEST 2017
How to Participate: Members will compete by donating or pledging any amount to the CHEST Foundation in 2017.	How to Participate: Members will compete by donating or pledging any amount to the CHEST Foundation during CHEST 2017.
Where Your Money Goes: Community Service	Where Your Money Goes: Patient Education
How to Win: Total amount contributed by top two NetWork Steering Committees	How to Win: Highest percentage of participation by the top two NetWork memberships
What You Win: New community service initiative and two travel grants to CHEST 2018	What You Win: New patient education guide and two travel grants to CHEST 2018

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PROFESSIONAL OPPORTUNITIES

NETWORKS

Occupational asthma, lactic acidosis, OSA screening

Occupational and Environmental Health

Gender Disparities in Occupational Health

Over the past few decades, the presence of women in the workforce has changed significantly. According to the US Bureau of Labor Statistics Current Population Survey, in 2015, 46.8% of the workforce included women compared with 28.6% in 1948. Along with this change, there has been an increased focus on gender disparities in occupational health.

For example, a meta-analysis of respiratory health among those exposed to organic and inorganic dust demonstrated that overall, when adjusted for smoking status, age, BMI, ethnicity, atopy, and job duration, women had a higher odds of shortness of breath and asthma compared with men. Men had higher odds of chronic phlegm, occasional wheeze, and FEV_1 <80% (Dimich-Ward et al. *Lung*. 2012;190[2]:147).

DR. CLEVEN

Gender differences in occupational asthma were also seen in snow crab processing plant workers. Women were significantly more likely to have occupational asthma than men. However, they found that overall, women had a greater cumulative exposure to crab allergens, which may be a major contributor to this disparity (Howse et al. *Environ Res*. 2006;101[2]:163).

Although several occupational health studies are beginning to highlight gender disparities, a major confounding factor is that of occupational segregation, meaning the under-representation of one gender in some jobs and over-representation in others. Differences in jobs and tasks even within the same job title between men and women are often major contributors to gender disparities [WHO Dept of Gender, Women and Health, 2006]. Also, several studies suggest that more women should be included in toxicology and occupational cancer studies, since currently, they have included mostly men (Sorrentino et al. *Ann Ist Super Sanità*. 2016;52[2]:190). Perhaps future studies can improve the overall understanding of these important contributing factors to gender disparities in occupational health.

Krystal Cleven, MD
Fellow-in-Training Member

Respiratory Care

Does Beta-agonist Therapy With Albuterol Cause Lactic Acidosis?

Cohen and associates (*Clin Sci Mol Med*. 1977;53:405) suggested that lactic acidosis can occur in at least two different physiologic clinical presentations. Type A occurs when oxygen delivery to the tissues is compromised. Dodda and Spiro (*Respir Care*. 2012;57[12]:2115) indicated that type A lactic acidosis was due to hypoxemia, as seen in inadequate tissue oxygenation during an exacerbation of asthma. In severe asthma, pulsus paradoxus and air trapping (causing intrinsic positive end-expiratory pressure, or PEEP) served to decrease tissue oxygenation by decreasing cardiac output and venous return, leading to type A lactic acidosis. Bates and associates (*Pediatrics*. 2014;133[4]:e1087) considered the role of intrapulmonary arteriovenous anastomoses (IPAVs) when a status asthmaticus patient improved after cessation of beta-agonist therapy. Type B lactic acidosis occurs when lactate production was increased or lactate removal was decreased even when oxygen was delivered to tissue. Amaducci (http://www.emresident.org/gasping-air-albuterol-induced-lactic-acidosis/) explained how high dosages of albuterol, beyond 1 mg/kg, created an increased adrenergic state that, with reduced tissue perfusion, increased glycolysis and pyruvate production, resulting in measurable hyperlactatemia. The authors (*Br J Med Pract*. 2011;4[2]:a420) noted that lactic acidosis also occurs in acute severe asthma due to inadequate oxygen delivery to the respiratory muscles to meet an elevated oxygen demand or due to fatiguing respiratory muscles. Ganaie and Hughes reported a case of lactic acidosis caused by treatment with salbutamol. Salbutamol is the most commonly used short-acting beta-agonist. Stimulation of beta-adrenergic receptors leads to a variety of metabolic effects, including increase in glycogenolysis, gluconeogenesis, and lipolysis, thus contributing to lactic acidosis. All authors agreed that the mechanism of albuterol-caused lactic acidosis was poorly understood.

Douglas E. Masini, EdD, FCCP
Steering Committee Member

Sleep Medicine

Withdrawal of OSA Screening Regulation for Commercial Motor Vehicle Operators

Compared with the general US population, the prevalence of sleep apnea (SA) is higher among commercial motor vehicle (CMV) drivers (Berger et al. *J Occup Environ Med*. 2012;54[8]:1017). Additionally, the risk of motor vehicle accidents is higher among individuals with SA compared with those without SA (Tregear et al. *J Clin Sleep Med*. 2009;5[6]:573), and treatment of SA is associated with a reduction in this risk (Mahssa et al. *Sleep*. 2015;38[3]341).

Undiagnosed sleep apnea has been postulated as an underlying cause of several highway and rail accidents investigated by the US National Transportation Safety Board (NTSB). Therefore, in 2016, the Federal Motor Carrier Safety Administration (FMCSA) and Federal Railroad Administration (FRA) published an advanced notice of proposed rulemaking (ANPRM) seeking public input regarding the health and economic effects of screening and treating SA among individuals occupying safety-sensitive positions in highway and rail transportation (Federal Register March 2016).

However, after reviewing the public input and data, the FRA and FMCSA recently announced that there was "not enough information available to support moving forward with a rulemaking action," and, therefore, they are no longer pursuing the regulation that would require SA screening for truck drivers and train engineers (Federal Register August 2017;49 CFR 391,240,242). See CHEST's press release at www.chestnet.org/News/Press-Releases/2017/08/American-College-of-Chest-Physicians-Responds-to-DOT-Withdrawal-of-Sleep-Apnea-Screening. The FMCSA endorses existing resources,-such as the North American Fatigue Management Program (NAFMP) (www.nafmp.org), which is a web-based program designed to reduce driver fatigue and includes information on SA screening and treatment. The medical examiners, however, will have the ultimate responsibility to screen, diagnose, and treat SA based on their medical knowledge and clinical experience.

DR. KUNDEL

DR. SHAH

Vaishnavi Kundel, MD
NetWork Member
Neomi Shah, MD, MPH, MS
Steering Committee Member

Corrections to previous NetWork articles

July 2017

Clinical Research

Mohsin Ijaz's name was misspelled.

August 2017

Transplant

The name under Shruti Gadre's photograph is wrong. It says Dr. Ahya instead of Dr. Gadre.

The authorship of the article at the end of the article is incorrect. It says Vivek Ahya, instead of Shruti Gadre and Marie Budev.

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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.

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