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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Bruce Jancin/Frontline Medical News

Dr. Javier Bermejo, a cardiologist at Gregorio Marañón University Hospital in Madrid.

Avoid sildenafil for PH after valvular heart disease correction

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Off-label use of the phosphodiesterase-5 inhibitor sildenafil to treat residual pulmonary hypertension after successful correction of valvular heart disease is not merely ineffective, it's counterproductive, according to the results of the randomized, placebo-controlled SIOVAC study.

"We believe based upon our results that off-label use of sildenafil in patients with left heart disease-pulmonary hypertension due to valvular disease should be discouraged," Javier Bermejo, MD, declared at the annual congress of the European Society of Cardiology.

Sildenafil is approved with a solid, evidence-based indication for treating some other types of pulmonary hypertension. Many cardiologists also prescribe the drug off label for residual pulmonary hypertension in patients with corrected valve disease, hoping that it will be of benefit, since there is currently no approved treatment for this common and serious condition associated with increased mortality. But because the anecdotal literature on sildenafil for this specific type of pulmonary hypertension is mixed, Dr. Bermejo and his coinvestigators in the Spanish Network Center for Cardiovascular Research decided to conduct a multicenter randomized trial.

CONTROLS FARED BETTER THAN TREATED // *continued on page 4*

Phrenic nerve stimulator shows benefits in heart failure patients

BY MITCHEL L. ZOLER
Frontline Medical News

DALLAS – Heart failure patients with central sleep apnea who received treatment with a transvenous phrenic nerve–stimulating device showed dramatic improvement in their global self-assessment, compared with control patients, in a subgroup analysis of 80 patients enrolled in the device's pivotal trial.

The Remede System, which consists of a battery pack and small, thin wires placed under the skin in the upper chest area, monitors respiratory signals and causes normal breathing to be restored by stimulating the phrenic nerve to communicate with the diaphragm. Among 35 patients with heart failure enrolled in the Remede System pivotal trial and treated for 6 months with the phrenic nerve stimulator, 57% reported that they had "markedly" or "moderately" improved, compared with a 9% rate for this self-rating among 44 control heart failure patients in the trial, a statistically significant difference, Lee R. Goldberg, MD, said at the annual scientific meeting of the Heart Failure Society of America.

NO SIGNAL OF HARM SEEN // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Meet Debasree Banerjee, MD, MS winner of a CHEST Foundation grant.

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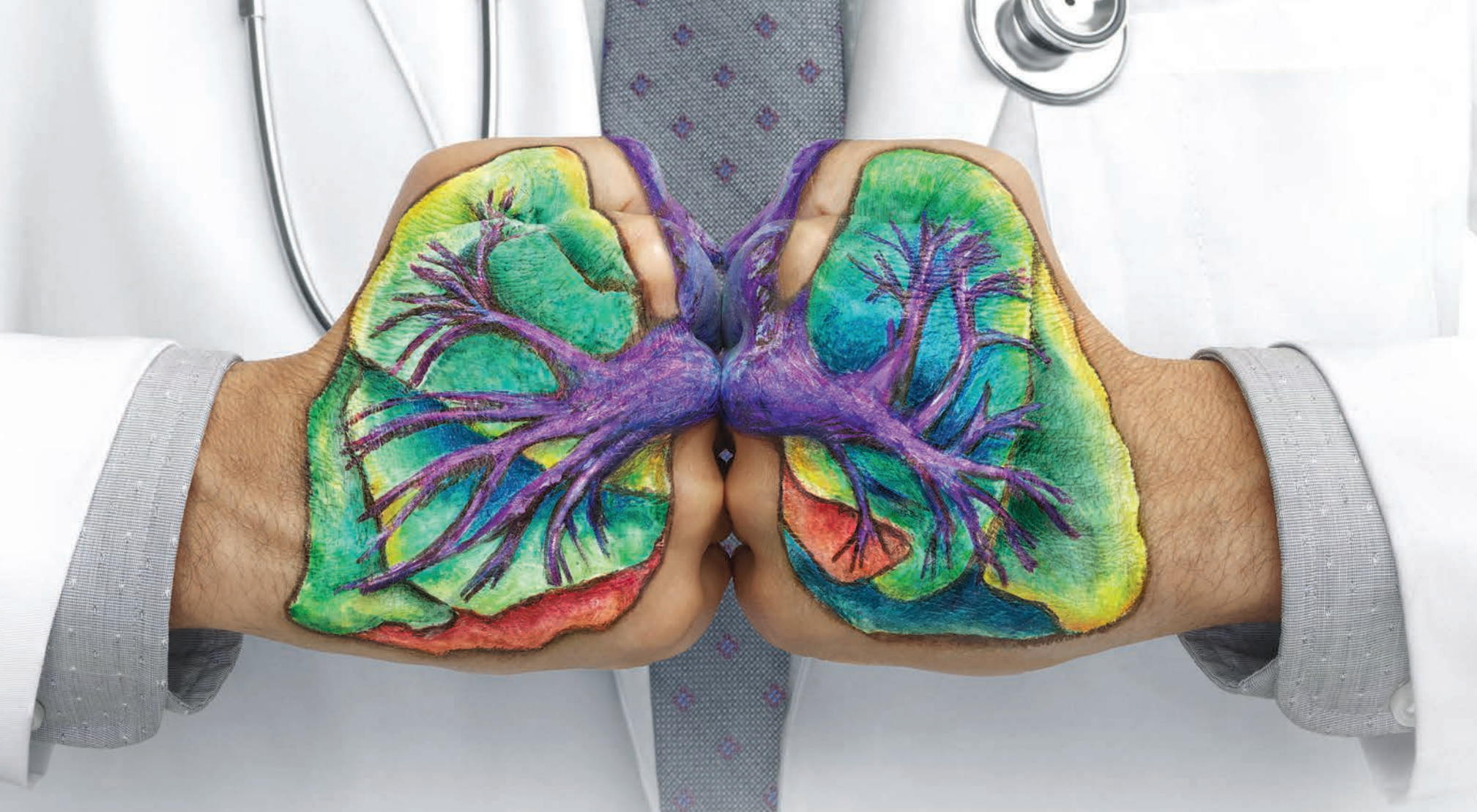

Indication

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

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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

Controls fared better than treated // *continued from page 1*

SIOVAC (Sildenafil for Improving Clinical Outcomes After Valvular Correction) comprised 200 patients with residual pulmonary hypertension after corrected valvular heart disease at 17 Spanish general hospitals. The patients were randomized to receive sildenafil at 40 mg t.i.d. or placebo for 6 months in this double-blind trial.

The primary endpoint was a standardized composite clinical score widely used in heart failure trials. It consists of all-cause mortality, hospital admission for heart failure, worsening exercise tolerance, and deterioration in a global self-assessment rating.

The shocker for the investigators – who had expected a positive study – was that 33% of patients in the sildenafil group worsened significantly on the composite clinical score at 6 months, compared with 14% of placebo-treated controls, said Dr. Bermejo, a cardiologist at Gregorio Marañón University Hospital in Madrid.

Moreover, only 27% of the sildenafil group improved, compared with 44% of controls. About one-third of patients in both groups re-

mained unchanged over the course of the 6-month trial.

Dr. Bermejo noted that valvular disease is considered the next cardiac epidemic because of its strong association with advancing age and the rapid aging of the population worldwide. Pulmonary hypertension occurs is virtually all patients with severe mitral disease and in up to two-thirds of those with asymptomatic aortic stenosis. Regression of the pulmonary hypertension is often incomplete after successful surgical or transcatheter correction of the valvular lesion.

Discussant Irene M. Lang, MD, called SIOVAC "a very clear study." It convincingly establishes that sildenafil – a vasodilator – is ineffective for the treatment of what the current ESC/European Respiratory Society guidelines on pulmonary hypertension call isolated post-capillary pulmonary hypertension, a condition defined hemodynamically by a diastolic pulmonary vascular pressure gradient of less than 7 mm Hg and/or a pulmonary vascular resistance below 3 Wood units (Eur Heart J. 2016 Jan 1;37[1]:67-119.)

The SIOVAC findings underscore the strong IIIC recommendation in the European guidelines that the use of approved therapies for pulmonary arterial hypertension is not recommended in patients with left heart disease-pulmonary hypertension, added Dr. Lang, a coauthor of the guidelines and professor of vascular biology at the Medical University of Vienna.

The Spanish government funded SIOVAC. Dr. Bermejo reported having no financial conflicts of interest.

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NEWS

Sepsis response team not beneficial

BY LUCAS FRANKI
Frontline Medical News

FROM CHEST ▪ A sepsis response team did not have a positive effect on mortality or organ dysfunction in septic patients, compared with standard treatment by a primary care team, according to a study abstract from the CHEST annual meeting.

The study, by Chhaya Patel, MD, and colleagues, covers a retrospective analysis of 517 septic patients in an inpatient ward at a tertiary care academic center from June 2014 until December 2016. Of this group, 302 were treated by a sepsis response team, while the others were treated by the normal primary care team.

Compared with the primary care team, the sepsis team was more likely to intervene on patients with a quick Sepsis-Related Organ Failure Assessment score greater than 1 (33.8% vs. 22.8%), change or initiate antibiotics within 3 hours (64.6% vs. 37.2%), and obtain blood cultures on time (66.4% vs 45.2%). An additional difference between the two groups was that the sepsis team had better compliance with the 3-hour bundle (15.2% vs 8.4%).

Despite the sepsis team's higher level of compliance with certain protocols, the combined outcome measure of mortality and organ dysfunction within 28 days was not significantly higher for patients treated by the sepsis team (11.3% vs. 9.8%; $P = .6$). In fact, there was at least one downside to being treated by the sepsis team, which was having a 14% longer hospital stay.

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No signal of harm seen

// *continued from page 1*

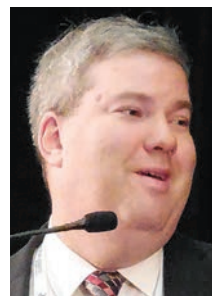
This analysis of the 80 heart failure patients enrolled in the pivotal trial, (which also included 71 patients with central sleep apnea but without heart failure) also showed that, during the first 6 months of phrenic nerve stimulation, patients had a 5% incidence of first heart failure hospitalization, compared with a 17% rate among controls who received no stimulation, a difference that fell slightly short of statistical significance. The results also showed no signal of harm – including no suggestion of increased mortality – an important observation, because a prior study of another approach for treating central sleep apnea, adaptive servo-ventilation, showed clear evidence for increased mortality in the SERVE-HF trial (N Engl J Med. 2015 Sep 17;373 [12]:1095-105).

Further analysis focused on echocardiographic examinations after 12 months in 23 of the heart failure patients who entered the study with a left ventricular ejection fraction of 45% or less and received 12 months of phrenic nerve stimulation. The average LVEF rose in these patients from 30% at baseline to 35%, a statistically significant difference, and left ventricular end systolic volume fell by an average of almost 11 mL from baseline, a difference just short of statistical significance, findings Dr. Goldberg called "a little exciting."

"It is very encouraging to see some evidence for ventricular remodeling," commented Lynne W. Stevenson, MD, professor of medicine and a heart failure specialist at Vanderbilt University in Nashville, Tenn.

"There is no treatment option right now for central sleep apnea, and during the phrenic nerve–stimulation pivotal trial we treated some patients [at our center] with fairly advanced heart failure who did fine on the treatment," noted Dr. Goldberg, medical director of the heart failure and transplantation program at the University of Pennsylvania in Philadelphia.

The FDA approved the use of this device for the treatment of moderate to severe central sleep apnea on Oct. 6 . "I think we would use it" in heart failure patients with intolerable symptoms from central sleep apnea, Dr. Goldberg said in an interview during the meeting.



'There is no treatment option right now for central sleep apnea ... we treated some patients' with fairly advanced HF who did fine.

DR. GOLDBERG

"There is a tight connection between sleep-disordered breathing, sleep apnea, heart failure, and cardiovascular disease, and we have been pretty aggressive in trying to treat the sleep apnea. Even if phrenic nerve stimulation just improves patients' quality of life and is neutral for other outcomes," it would be reasonable to offer it to patients, he said. "But many of us think there is a bigger connection that results in a therapeutic benefit [to heart failure patients] by treating their central sleep apnea."

Continued on following page

VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: Among the encountered categories of central sleep apnea, such as idiopathic CSA, treatment-emergent CSA, and Cheyne-Stokes respiration (CSR) in association with heart failure (HF), the latter has received most attention in the last decade because of its association with increased mortality in HF patients. While the role of CSR in sympathetic activation and arrhythmogenesis in heart failure patients has been debated, attempts to treat CSR with adaptive servo-ventilation have been associated with increased mortality in patients with lower left ventricular ejection fraction. Transvenous phrenic nerve pacing is a novel modality that appears to be well tolerated. Despite treating only central apneas, it appears to reduce the apnea-hypopnea index by more than 50% in HF patients with central-predominant AHI greater than 20. Other improvements were noted in global functioning and oxygen saturations without worsening of obstructive apneas. Given what we have previously seen with adaptive servo-ventilation, longer-term trials to examine mortality with this treatment will be important.

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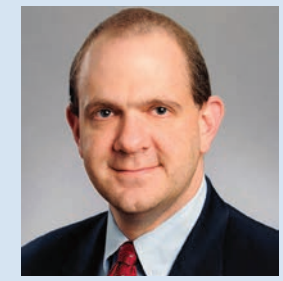

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Ideal intubation position still unknown

BY ANDREW D. BOWSER
Frontline Medical News

FROM CHEST ▪ In critically ill adults undergoing endotracheal intubation, the ramped position does not significantly improve oxygenation compared with the sniffing position, according to results of a multicenter, randomized trial of 260 patients treated in an intensive care unit.

Moreover, "[ramped] position appeared to worsen glottic view and increase the number of attempts required for successful intubation," wrote Matthew W. Semler, MD, of Vanderbilt University Medical Center, Nashville, Tenn., and his coauthors (Chest. 2017 Oct. doi: 10.1016/j.chest.2017.03.061).

The ramped and sniffing positions are the two most common patient positions used during emergent intubation, according to investigators. The sniffing position is characterized by supine torso, neck flexed forward, and head extended, while ramped position involves elevating the torso and head.

Some believe the ramped position may offer superior anatomic alignment of the upper airway; however, only a few observational studies suggest it is associated with fewer complications than the sniffing position, the authors wrote.

Accordingly, they conducted a multicenter randomized trial with a primary endpoint of lowest arterial oxygen saturation, hypothesizing that the endpoint would be higher for the ramped position: "Our primary outcome of lowest arterial oxygen saturation is an established endpoint in ICU intubation trials, and is linked to periprocedural cardiac arrest and death," they wrote.

The investigators instead found that median lowest arterial oxygen saturation was not statistically different between groups, at 93% for the ramped position, and 92% for the sniffing position ($P = 0.27$), published data show.

Further results showed that the ramped position appeared to be associated with poor glottic view and more difficult intubation. The incidence of grade III (only epiglottis) or grade IV (no visible glottis structures) views were 25.4% for ramped vs. 11.5% for sniffing ($P = .01$), while the rate of first-attempt intubation was 76.2% for ramped vs. 85.4% for sniffing ($P = .02$).

While the findings are compelling, the authors were forthcoming about the potential limitations of the study and differences compared with earlier investigations. Notably, they said, all prior controlled trials of patient positioning during endotracheal intubation were conducted in the operating room, rather than in the ICU.

Also, the operators' skill levels may further explain differences in this study's outcomes from those of similar studies, the researchers noted. Earlier studies included patients intubated by one or two senior anesthesiologists from one center, while this trial involved 30 operators across multiple centers, with the average operator having performed 60 previous intubations. "Thus, our findings may generalize to settings in which airway management is performed by trainees, but whether results would be similar among expert operators remains unknown," the investigators noted.

The authors reported no potential conflicts of interest. One coauthor reported serving on an advisory board for Avisa Pharma.

VIEW ON THE NEWS

Valuable new data amid sparse literature

Editorialists praised the multicenter, randomized design of this study, and its total recruitment of 260 patients. They also noted several limitations of the study that "could shed some light" on the group's conclusions (Chest. 2017 Oct. doi: 10.1016/j.chest.2017.06.002).

"The results diverge from [operating room] literature of the past 15 years that suggest that the ramped position is the preferred intubation position for obese patients or those with an anticipated difficult airway." This may have been caused by shortcomings of this study's design and differences between it and other research exploring the topic of patient positioning during endotracheal intubation, they wrote.

The study lacked a prespecified algorithm for preoxygenation and the operators had relatively low amounts of experience with intubations. Finally, the beds used in this study could contribute to the divergences between this intensive care unit experience and the operating room literature. The operating room table is narrower, firmer, and more stable, while by contrast, the ICU bed is wider and softer, they noted. This "may make initial positioning, maintenance of positioning, and accessing the patient's head more difficult."

Nevertheless, "[this] important study provides ideas for further study of optimal positioning in the ICU and adds valuable data to the sparse literature on the subject in the ICU setting," they concluded.

James Aaron Scott, DO, Jens Matthias Walz, MD, FCCP, and Stephen O. Heard, MD, FCCP, are in the department of anesthesiology and perioperative medicine, UMass Memorial Medical Center, Worcester, Mass. The authors reported no conflicts of interest. These comments are based on their editorial.

Continued from previous page

The pivotal trial enrolled a total of 151 patients with central sleep apnea at 31 centers in Germany, Poland, and the United States who were selected based on having an apnea-hypopnea index of at least 20 events per hour. All participants received a transvenous phrenic nerve–stimulator implant, and then randomization assigned 73 patients to have the device turned on for the first 6 months while 78 device recipients had their devices left off to serve as controls. The study's primary efficacy endpoint was the percentage of patients having at least a 50% cut in their apnea-hypopnea index, which happened in 51% of evaluable patients in the active treatment arm and in 11% of the evaluable controls. The FDA's approval of this device is based on these specific findings, according to a statement from the agency. This device is not intended for use in patients with obstructive sleep apnea. Adverse events reported in the study included concomitant device interaction, implant site infection, and swelling and local tissue damage or pocket erosion. The Remede System is contraindicated for patients with active infection or who are known to require an MRI. The primary study results were published last year (Lancet. 2016 Sep 3;388[10048]974-82).

'It is very encouraging to see some evidence for ventricular remodeling.'

DR. STEVENSON

"We hope this treatment will have the collateral effect of improving cardiovascular disease outcomes, but we don't know that yet. The initial target will be patients with apnea-hypopnea episodes that affect their quality of life," Dr. Goldberg said.

The apparent safety of this approach for treating central sleep apnea may relate to its mechanism of action, he suggested. The mortality-boosting effect of adaptive servo-ventilation may correlate with the positive pressure it creates in a patient's chest that perhaps causes myocardial stress or hemodynamic problems. In contrast, phrenic nerve stimulation produces diaphragm motion that mimics normal breathing and creates negative chest pressure. "A lot of hypothesis generation needs to happen to better understand the underlying physiology," Dr. Goldberg conceded.

At the end of the 6-month period that compared active treatment with control, the heart failure subgroup also showed statistically significant benefits from treatment for several sleep metrics, including apnea-hypopnea index, the central apnea index, and oxygen desaturation, and also for daytime sleepiness measured on the Epworth Sleepiness Scale. After 12 months on active treatment, patients also showed a significant improvement over baseline in their score on the Minnesota Living With Heart Failure Questionnaire, Dr. Goldberg reported.

The trial was sponsored by Respicardia, the company developing the Remede System. Dr. Goldberg has been a consultant to and has received research funding from Respicardia. Dr. Stevenson had no relevant disclosures.

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Cases of Legionnaires' continue to rise in U.S.

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Rates of reported Legionnaires' disease nearly quadrupled in the United States between 2000 and 2015, and it is likely underdiagnosed, said Laura A. Cooley, MD.

"Improved testing and surveillance are needed to improve understanding of disease and outbreak burden," she said at an annual scientific meeting on infectious diseases. "There is more to learn about environmental sources of *Legionella* for cases not associated with known outbreaks and about the distribution of *Legionella* in the environment."

Dr. Cooley, a medical epidemiologist at the National Center for Immunization and Respiratory Diseases at the Centers for Disease

Dr. Laura A. Cooley

Control and Prevention, Atlanta, said that between 2000 and 2015, the rate of reported cases in the United States increased by about 350%, from 0.42 cases per 100,000 people to 1.89 cases per 100,000, "and this is likely an underestimate due to underdiagnosis." Reasons for the increase are likely multifactorial, she said, including increased susceptibility of the population. "The population is aging, and there are more people in the United States on immunosuppressive medications. There also may be more *Legionella* in the environment." There also are improved diagnostic capabilities, with the urinary antigen test, improved diagnosis and reporting due to increased awareness and testing, and increased surveillance capacity.

A Gram-negative bacillus, *Legionella* is an intracellular parasite of free-living protozoa primarily found in freshwater. "It can live and grow in biofilm, and there are more than 60 species of the bacterium," she said at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

Cases are higher in the warmer months, and the rates are highest among the elderly, men, and those of black race. Currently, *L. pneumophila* accounts for about 90% of cases in the United States. "Once it's transmitted, it has to hit a susceptible population to cause disease, generally older individuals and people with underlying conditions," Dr. Cooley said.

According to a CDC analysis of

27 building-associated *Legionella* outbreaks in the United States between 2000 and 2014, common settings included hotels, long-term care facilities, and hospitals. Common sources of transmission were aerosolizing devices such as showers and faucets, cooling towers, hot tubs, and decorative fountains (MMWR 2016;65[22]:576-84). The median number of cases per outbreak ranged from 3 to 82. Cooling tower outbreaks affected a median of 22 people, while potable water outbreaks affected a median of 10 people.

A separate analysis evaluated *Legionella* cases reported among U.S. residents between 2005 and 2009 (MMWR. 2011;60[32]:1083-6). It found that only 4% were associated with outbreaks, and 96% were sporadic. "That doesn't mean that [the cases] weren't associated with the same kind of source, they just weren't identified as an outbreak," Dr. Cooley said. "It shows that there is a lot to learn about transmission of *Legionella*."

The U.S. case definition of Legionnaires' disease consists of clinical or radiologic pneumonia plus confirmatory laboratory testing, either by urinary antigen test (UAT), lower respiratory culture, or appropriate serological testing. Polymerase chain reaction can be used as a presumptive test for a suspect case. "UAT is easy and it detects *L.*

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pneumophila serogroup 1 (Lp1), but it has some gaps," Dr. Cooley said. "It isn't completely sensitive for Lp1, and it doesn't detect any other species or serogroups. That's why we also recommend that a culture of respiratory secretions on selective media be performed at the same time. That being said, in the U.S., nearly all reported cases of *Legionella* are diagnosed by UAT only."

A 2016 CDC MMWR and Vital Signs report found that almost all *Legionella* outbreaks could be prevented with effective water management, and the CDC has published a step-by-step guide to creating a water management program to reduce *Legionella* growth and spread in buildings. The 2017 MMWR Report found that definite health care–associated Legionnaires' disease is deadly for one in four people who get it. The report also found that this issue is widespread; 76% of complete reporting jurisdictions reported at least one definite case of health care–associated *Legionella* disease in 2015. More recently, the Centers for Medicare & Medicaid Services issued a requirement to reduce risk in health care facility water systems to prevent cases and outbreaks. It applies to hospitals, skilled nursing facilities, and critical access hospitals.

Dr. Cooley reported having no financial disclosures.

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Pneumococcal vaccines knock out many serotypes

BY LUCAS FRANKI
Frontline Medical News

The introduction of pneumococcal conjugate vaccines 7 (PCV7) and 13 (PCV13) has significantly reduced pneumococcal colonization of the serotypes targeted by the vaccines, but serotypes not covered by these vaccines have picked up the slack, according to an analysis of more than 6,000 young Massachusetts children tested at well child or acute care visits over 15 years.

In the past 15 years, use of pneumococcal vaccines in the United States has led to dramatic declines in invasive pneumococcal disease (IPD) in young children, reductions in pneumonia hospitalizations, and herd protection in older adults against disease that otherwise would be caused by the vaccinated serotypes, studies have found. But not all serotypes of *Streptococcus pneumoniae* are covered by the vaccines.

The data used in the Massachusetts study included results from nasopharyngeal swabs taken from 6,537 children younger than 7 years of age in various Massachusetts communities during six respiratory illness seasons during 2000-2001, 2003-2004, 2006-2007, 2008-2009, 2010-2011, and 2013-2014. The highest rate of pneumococcal colonization was in 2011 at 32%, and the lowest was in 2004 at 23%, Grace M. Lee, MD, MPH, of the Harvard Medical School and Harvard Pilgrim Health Care Institute, both in Boston, and her associates reported (Pediatrics. 2017;140[3]:e20170001).

> *"Replacement with nonincluded serotypes remains a risk with vaccines that do not cover the full range of serotype diversity. As new selective pressures are applied, such as the introduction of a vaccine into a community, the void may be filled by nontargeted serotypes," as was observed after PCV7.*

In 2001, PCV7 serotypes were the most common, but after the rapid introduction of the vaccine, infection rates for those serotypes quickly declined, nearly disappearing by 2007. Serotype 19A became the most common serotype in 2004, but after the introduction of PCV13 in 2010, it and other serotypes targeted by PCV13 also began to decline. In 2014, the most common serotypes were 15B/C, 35B, 23B, 11A, and 23A.

Non-PCV13 serotypes accounted for about a third of observed *Streptococcus pneumoniae* colonizations in 2001, but by 2014 they accounted for nearly all colonizations. In addition, the overall rate of infection did not decrease over

Continued on following page

respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, rhinitis. **Postmarketing Experience:** The following additional adverse reactions of angioedema and dysphonia have been identified during worldwide post-approval use of indacaterol/glycopyrrolate at higher than the recommended dose. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS: Adrenergic Drugs: If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of indacaterol, a component of UTIBRON NEOHALER, may be potentiated. **Xanthine Derivatives, Steroids, or Diuretics:** Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of beta$_2$-adrenergic agonists such as indacaterol, a component of UTIBRON NEOHALER. **Non-Potassium-Sparing Diuretics:** The electrocardiographic (ECG) changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as indacaterol, a component of UTIBRON NEOHALER, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the coadministration of UTIBRON NEOHALER with non-potassium-sparing diuretics. **Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc-Prolonging Drugs:** Indacaterol, one of the components of UTIBRON NEOHALER, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may have an increased risk of ventricular arrhythmias. **Beta-Blockers:** Beta-adrenergic receptor antagonists (beta-blockers) and UTIBRON NEOHALER may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution. **Anticholinergics:** There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of UTIBRON NEOHALER with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects. **Inhibitors of Cytochrome P450 3A4 and P-gp Efflux Transporter:** Drug interaction studies with indacaterol, a component of UTIBRON NEOHALER, were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil, and ritonavir). The data suggest that systemic clearance of indacaterol is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold area under the curve (AUC) increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Indacaterol was evaluated in clinical trials for up to 1 year at doses up to 600 mcg. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of indacaterol. Therefore, no dose adjustment is warranted at the recommended 27.5/15.6 mcg twice-daily dose for UTIBRON NEOHALER when administered concomitantly with inhibitors of CYP3A4 and P-gp.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies with UTIBRON NEOHALER or its individual components, indacaterol and glycopyrrolate, in pregnant women. Animal reproduction studies were conducted with individual components, indacaterol and glycopyrrolate. Because animal reproduction studies are not always predictive of human response, UTIBRON NEOHALER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physician if they become pregnant while taking UTIBRON NEOHALER. ***Indacaterol:*** Indacaterol was not teratogenic in Wistar rats and New Zealand rabbits at approximately 340 and 770 times, respectively, the MRHD in adults (on an AUC basis at maternal subcutaneous doses up to 1 mg/kg/day in rats and rabbits). ***Glycopyrrolate:*** Glycopyrrolate was not teratogenic in Wistar rats or New Zealand White rabbits at approximately 1400 and 530 times, respectively, the MRHD in adults (on an AUC basis at maternal inhaled doses up to 3.83 mg/kg/day in rats and up to 4.4 mg/kg/day in rabbits). **Non-teratogenic Effects: Indacaterol:** There were no effects on perinatal and postnatal developments in rats at approximately 110 times the MRHD in adults (on an AUC basis at maternal subcutaneous doses up to 0.3 mg/kg/day). ***Glycopyrrolate:*** There were no effects on perinatal and postnatal developments in rats at approximately 1100 times the MRHD in adults (on an AUC basis at maternal subcutaneous doses up to 1.88 mg/kg/day). **Labor and Delivery:** There are no adequate and well-controlled human trials that have investigated the effects of UTIBRON NEOHALER during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, UTIBRON NEOHALER should be used during labor only if the potential benefit justifies the potential risk. In human parturients undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrrolate, umbilical plasma concentrations were low. **Nursing Mothers:** *UTIBRON NEOHALER:* It is not known whether UTIBRON NEOHALER is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when UTIBRON NEOHALER is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of UTIBRON NEOHALER by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue UTIBRON NEOHALER, taking into account the importance of UTIBRON NEOHALER to the mother. ***Indacaterol:*** It is not known whether indacaterol is excreted in human breast milk. Indacaterol (including its metabolites) have been detected in the milk of lactating rats. ***Glycopyrrolate:*** It is not known whether glycopyrrolate is excreted in human breast milk. Glycopyrrolate (including its metabolites) have been detected in the milk of lactating rats and reached up to 10-fold higher concentrations in the milk than in the blood of the dam. **Pediatric Use:** UTIBRON NEOHALER is not indicated for use in children. The safety and efficacy of UTIBRON NEOHALER in pediatric patients have not been established. **Geriatric Use:** Based on available data, no adjustment of UTIBRON NEOHALER dosage in geriatric patients is warranted. UTIBRON NEOHALER can be used at the recommended dose in elderly patients 75 years of age and older. Of the total number of subjects in clinical studies of UTIBRON NEOHALER, 45% were aged 65 and older, while 11% were aged 75 and older. 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. **Renal Impairment:** Based on the pharmacokinetic characteristics of its monotherapy components, UTIBRON NEOHALER can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment (estimated GFR less than 30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, UTIBRON NEOHALER should be used if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrrolate may be increased in this population. **Hepatic Impairment:** Based on the pharmacokinetic characteristics of its monotherapy components, UTIBRON NEOHALER can be used at the recommended dose in patients with mild to moderate hepatic impairment. Studies in subjects with severe hepatic impairment have not been performed.

OVERDOSAGE: In COPD patients, doses of up to 600/124.8 mcg UTIBRON NEOHALER were inhaled over 2 weeks and there were no relevant effects on heart rate, QTc interval, blood glucose or serum potassium. There was an increase in ventricular ectopies after 14 days of dosing with 300/124.8 mcg and 600/124.8 mcg UTIBRON NEOHALER, but low prevalence and small patient numbers (N=49 and N=51 for 600/124.8 mcg and 300/124.8 mcg UTIBRON NEOHALER, respectively) precluded accurate analysis. In a total of four patients, non-sustained ventricular tachycardia was recorded, with the longest episode recorded being 9 beats (4 seconds). UTIBRON NEOHALER contains both indacaterol and glycopyrrolate; therefore, the risks associated with overdosage for the individual components described below apply to UTIBRON NEOHALER. Treatment of overdosage consists of discontinuation of UTIBRON NEOHALER together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage. ***Indacaterol:*** The potential signs and symptoms associated with overdosage of indacaterol are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, vomiting, drowsiness, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of indacaterol. In COPD patients, single doses of indacaterol 3000 mcg were associated with moderate increases in pulse rate, systolic blood pressure and QTc interval. ***Glycopyrrolate:*** An overdose of glycopyrrolate may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. In COPD patients, repeated orally inhaled administration of glycopyrrolate at total doses of 124.8 mcg and 249.6 mcg once-daily for 28 days were well tolerated.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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the study period. While a reduction was seen from 2011 to 2014, it remains to be seen whether this drop is transient.

"Replacement with noninclud-ed serotypes remains a risk with vaccines that do not cover the full range of serotype diversity. As new selective pressures are applied, such as the introduction of a vaccine into a community, the void may be filled by nontargeted serotypes," as was observed after PCV7, Dr. Lee and her fellow researchers noted.

Nonsusceptibility to erythromycin was most common in 2014, with 35% of pneumococcal isolates displaying either moderate susceptibility or resistance. Nonsusceptibility to ceftriaxone (12%), clindamycin (9%), and penicillin (6%) was significantly less common, and no isolates were found to have vancomycin resistance.

"First-line penicillins continue to be the most frequently prescribed antibiotic across all age groups among young children in Massachusetts, which may result in the continued success of 19A associated with penicillin resistance," the researchers said.

Risk factors associated with colonization by either PCV13 serotypes or non-PCV13 serotypes include younger age, more hours of child care exposure, and having a respiratory tract infection on the day of sampling. The presence of a smoker in the house and recent usage of antibiotics was associated with colonization by PCV13 serotypes but not by non-PCV13 serotypes.

"As newer pneumococcal vaccines are developed, there will continue to be a need for monitoring both the intended and unintended consequences of altering the nasopharyngeal niche through immunization," Dr. Lee and her associates concluded.

This work was funded by a National Institute of Allergy and Infectious Diseases grant and the National Institutes of Health. Marc Lipsitch, PhD; William P. Hanage, PhD; Ken Kleinman; Stephen Pelton, MD; and Susan S. Huang, MD, MPH, reported various conflicts of interest. Dr. Lee and the remaining investigators indicated that they had no potential conflicts of interest.

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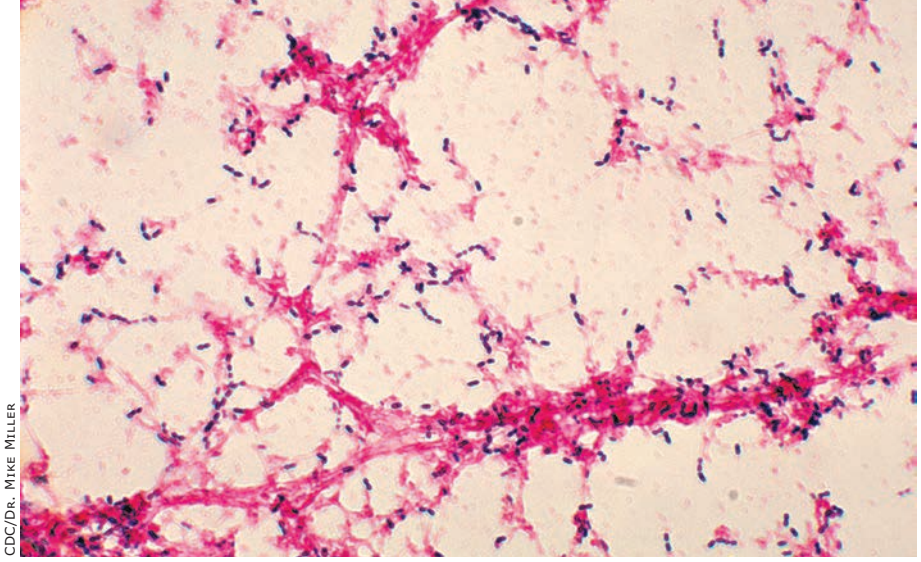

CDC/Dr. Mike Miller

Streptococcus pneumoniae

VIEW ON THE NEWS

Playing pneumococcal serotype elimination 'whack-a-mole'

"The hope that IPD and antibiotic resistance would disappear after widespread use of PCV vaccines has yet to be realized," Douglas S. Swanson, MD, and Christopher J. Harrison, MD, wrote in an accompanying editorial (Pediatrics. 2017;140[5]:e20172034).

While some invasive pneumococcal diseases, such as occult bacteremia and meningitis, have been significantly reduced due to PCV7 and PCV13, "one concern is whether some replacement serotypes could have invasive disease potential. For example, post-PCV7, there was increased severity of IPD from non-PCV7 serogroup organisms among children in the Intermountain West of the United States," the authors noted. Newly dominant strains, such as post-PCV13 serotype 35B, could cause increased IPD in vulnerable populations, becoming the equivalent of a post-PCV7 serotype 19A.

While addressing emerging serotypes in additional PCVs is possible, reformulating the vaccine and obtaining Food and Drug Administration approval would take time and resources, with no clear guarantee of ultimate success, making "this strategy seem like playing a game of whack-a-mole. To overcome the phenomenon of serotype replacement, vaccine strategies need to expand beyond serotype specificity by identifying antigens common to all *Streptococcus pneumoniae*, regardless of serotype," Dr. Swanson and Dr. Harrison said.

"Shifts back to less penicillin resistance may soon preclude the need for high dose amoxicillin for acute otitis media, and the near absence of occult *Streptococcus pneumoniae* bacteremia may drastically reduce empirical ceftriaxone for fever without a focus. To assist providers in ongoing vigilance for the now less frequent IPD, algorithms based on new epidemiologic data are in development and should decrease the number of 'sepsis work-ups' performed," they said.

On-time PCV13 vaccination would help address the risk factor of young age, and judicious antibiotic use could further reduce antibiotic resistance. Social engineering approaches, although difficult, also might help. These approaches include continued parent education to restrict secondhand smoke exposure and the risk of *S. pneumoniae* nasopharyngeal colonization, as well as having young children spend fewer hours in day care in order to reduce two other risk factors – pathogen exposure and frequency of viral upper respiratory tract infections.

Dr. Swanson and Dr. Harrison are with the division of infectious diseases at Children's Mercy Kansas City, University of Missouri-Kansas City. *Both reported conducting pneumococcal research supported by funding from Pfizer.*

Pertussis resurgence is real, but possible solutions exist

BY BRUCE JANCIN
Frontline Medical News

MADRID – The explanation for the ongoing resurgence in pertussis in adolescents and adults in the United States and other developed countries lies largely in the waning effectiveness of current acellular pertussis vaccines as early as 2-3 years post boosters, according to Stanley A. Plotkin, MD, chair of the steering committee for the Global Pertussis Initiative.

"The problem seems to lie in the lack of persistence of immunity after vaccination using the acellular pertussis vaccines. To say that this is not controversial would clearly be wrong, but that is my view," he declared at the annual meeting of the European Society for Paediatric Infectious Diseases.

It's a view supported by persuasive evidence, added Dr. Plotkin, emeritus professor of pediatrics at the University of Pennsylvania, Philadelphia.

There are other reasons for the resurgence of pertussis, he noted. Better diagnosis and improved surveillance are certainly factors. So is increased virulence of pertussis strains in response to vaccine immunity. There is intriguing preliminary evidence from a study in baboons conducted by scientists at the Food and Drug Administration that suggests acellular vaccine doesn't protect against pertussis infection and transmission, even though symptoms are prevented (Proc Natl Acad Sci USA. 2014 Jan 14;111[2]:787-92). If that work is confirmed in humans, it would mean that circulation of *Bordetella pertussis* is intensified in the United States and other countries using acellular vaccine.

In the United States, investigators at Northern California Kaiser Permanente have shown that the effectiveness of acellular pertussis in the Tdap vaccine wanes rapidly in adolescents. Indeed, it plunged from 69% effectiveness in the first year after vaccination to less than 9% by year 4 (Pediatrics. 2016 Mar;137[3]:e20153326).

In contrast, whole-cell pertussis vaccines provide roughly 6-10 years of protection against infection, and native infection provides persistent

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protection against reinfection for 7-20 years, Dr. Plotkin noted.

He was senior coauthor of a recent study that addresses why acellular pertussis vaccine immunity wanes so quickly. He and his coinvestigators demonstrated that while whole-cell pertussis vaccines promote vigorous Th1 and Th17 responses, which discourage pharyngeal colonization, acellular pertussis vaccines orient the immune system toward a less salutary Th1/Th2 response (Cold Spring Harb Perspect Biol. 2017 Mar 13. doi: 10.1101/cshperspect.a029454).

In addition, other investigators have shown that repeated booster doses of acellular pertussis vaccine generate higher levels of antigen-specific IgG4, which doesn't bind complement and results in impaired phagocytosis and a suboptimal inflammatory response. In contrast, priming of the immune system via administration of a whole-cell pertussis vaccine at birth followed by acellular pertussis boosters results in improved phagocytosis and complement-mediated microbial killing via preferential induction of IgG1(Cold Spring Harb Perspect Biol. 2017 Mar 13. doi: 10.1101/cshperspect.a029553).

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Pertussis

Possible solutions to the pertussis problem

The long-term solution is clear, Dr. Plotkin said: "I think a new vaccine for adolescents and adults is badly needed."

Infants don't need a new vaccine; that's not where the vaccine failures are occurring. "Again, I stress that the problem so far has not been in infants, it has been in adolescents and adults," he said.

A new vaccine is a daunting prospect. Given the huge investment vaccine manufacturers made in the 1990s to bring the current acellular vaccines to the market, they are hardly eager to launch development programs for new pertussis vaccines. They have other vaccine development priorities.

Moreover, the regulatory challenges are huge unless the Food and Drug Administration and other licensing authorities are willing to forgo the large, long, and expensive clinical trials that have traditionally been required. In lieu of such efficacy studies, they would need to consider studies demonstrating better immunogenicity based upon antibody titers, or animal studies.

"The possibility of a human challenge study in adults is an idea I like; I'm not sure about the FDA," the pediatrician said.

Until a new or improved vaccine becomes available, the most important strategy to control the resurgence of pertussis is acellular vaccination of pregnant women in their third trimester to provide passive protection to the newborn via transplacental antibody. That practice is already recommended in the United States and many other countries. And while it reduces the risk of pertussis in early infancy – the most serious form of the disease – that strategy won't have any real impact on the adult burden of disease, which Dr. Plotkin estimated at more than 600,000 cases annually.

Bruce Jancin/Frontline Medical News

Dr. Stanley A. Plotkin, chair of the steering committee for the Global Pertussis Initiative.

Cocooning – a strategy of vaccinating all of a newborn's family contacts – has been promoted in guidelines but has proved difficult to implement. "I think cocooning strategies by and large have been a failure," he declared.

More frequent boosters of current acellular pertussis vaccines would presumably increase effectiveness, but that would be costly and tough to put in place on a public health scale.

A return to using conventional whole-cell pertussis vaccines would be a tough sell to the public and is probably flat out unacceptable. Developing a less reactogenic whole-cell vaccine might be a work-around, but it hasn't been done yet.

The easiest way to improve acellular pertussis vaccine for adolescents and adults is to improve the pertussis toxin antigen component. Increasing the dose of pertussis toxin could generate more and longer-lasting antibodies to it. An even more exciting possibility is based upon evidence more than a decade old that genetic inactivation of pertussis toxin results in antibody levels far higher and presumably more bactericidal than the formalin-inactivated pertussis toxin included in current vaccines, according to Dr. Plotkin.

Adding stronger adjuvants to a Tdap vaccine for adolescents is another appealing strategy.

The Global Pertussis Initiative is sponsored by Sanofi Pasteur. Dr. Plotkin reported serving as a consultant to that vaccine manufacturer and numerous others but declared he had no financial conflicts regarding his presentation.

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New pertussis vaccine may solve immunogenicity problem

BY BRUCE JANCIN

Frontline Medical News

MADRID – A novel, monovalent, acellular pertussis vaccine containing a recombinant, genetically inactivated pertussis toxin displayed markedly greater sustained immunogenicity than the widely used Sanofi Pasteur Tdap, known as Adacel, which is used as a booster vaccination of adolescents and young adults, in a pivotal phase 3, randomized trial, Simonetta Viviani, MD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

A Tdap containing the same proprietary genetically detoxified pertussis toxin (PT) also outperformed the conventional, acellular pertussis–containing Adacel in the pivotal three-arm study. Both novel vaccines were similar to Adacel in terms of safety. Based on these results, the novel monovalent vaccine, known as Pertagen, and the novel Tdap, known as Boostagen, are now licensed and marketed in Thailand.

"Our interpretation of these results is that they open up a new way to approach pertussis vaccination," declared Dr. Viviani, director of clinical development at BioNet-Asia, a Bangkok-based biotech vaccine company.

DR. VIVIANI

The impetus for developing new acellular pertussis vaccines is the documented resurgence of pertussis.

"One suggested approach has been to replace chemically inactivated PT with a genetically inactivated PT," Dr. Viviani explained.

The significant phase 3 trial included 450 Thai 12- to 17-year-olds who were randomized to a single 0.5-mL dose of Pertagen, Boostagen, or Adacel. Both Pertagen and Boostagen contain 5 mcg of the genetically inactivated PT and 5 mcg of filamentous hemagglutinin.

The seroconversion rate, defined as the proportion of subjects who reached at least a fourfold increase in titers of PT and filamentous-hemagglutinin antibodies over baseline, was far superior at both 28 days and 1 year in subjects who got Pertagen or Boostagen, compared with those who received Adacel.

The fast-waning immunity that is a major limitation of conventional acellular pertussis vaccines was amply illustrated by the difference in falloff of PT-neutralizing antibody over time. The PT-neutralizing antibody titer was 278 IU/mL at 1 month and 77 IU/mL at 1 year in the Pertagen group, 216 IU/mL at 1 month and 67 IU/mL at 1 year with Boostagen, and a mere 36 IU/mL at 1 month and 12 IU/mL at 1 year with Adacel.

The study was sponsored by BioNet-Asia and Mahidol University.

Dr. Viviani is a BioNet employee.

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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
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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.

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FDA advisory committee rejects opioids in children's cough syrup

BY IAN LACY
Frontline Medical News

ROCKVILLE, MD. – The majority of a Food and Drug Administration advisory panel agreed the benefit versus risk of prescription opioid cough suppressants for pediatric patients was not favorable.

The voting was broken into multiple votes based on age range of patients and the specific opioid present in the cough syrup. Unlike other advisory committee meetings, this meeting did not focus on the treatment of a disease state, but rather on the treatment of a symptom.

On Sept. 11, 2017, the FDA's Pediatric Advisory Committee voted 21-2, with one abstention, that the benefit versus the risk of opioid cough suppressants for pediatric patients was not favorable.

This vote was preceded by two previous votes specifically questioning the use of codeine and hydrocodone in medications for pediatric patients. For codeine, the committee voted unanimously that the benefit versus risk was not favorable in pediatric patients aged 12 years to less than 18 years.

For hydrocodone, the committee asked two questions: 1) Was the benefit versus risk favorable for pediatric patients aged 6 years to less than 12 years? and 2) Was the benefit versus risk favorable for pediatric patients aged 12 years to less than 18 years? On the vote for patients aged 6 years to less than 12 years, the committee voted 23-1, with no abstention, that it was not favorable. The committee likewise voted 23-1 that it wasn't favorable in patients aged 12 to less than 18 years.

Due to the wide scope of this committee, the voting was based on presentations from pharmaceutical company representatives presenting the results of industry-led studies and independent researchers.

According to Sharon Levy, MD, MPH, adolescents are the most at-risk population for opioid misuse. This susceptibility is due to the developmental neurobiology of adolescent brains. A region of the brain associated with the reward pathway, nucleus accumbens, is developing in adolescents and plays a role in salience. Salience, or the differentiation between important versus unimportant rewards, varies widely by age group. Young children show little salience with rewards, and treat rewards equivocally. Adults have a proportional response to rewards with accurate salience. Adolescents, on the other hand, are unhappy with small rewards, but receive a massive return with large rewards. This type of neurobiological feedback makes adolescents "vulnerable to develop substance use disorders."

Dr. Levy also noted a correlation between prescribed opioid use and alcohol, marijuana, and tobacco use as contributing factors to opioid misuse. When opioids are prescribed for pain management, there is an adjusted odds ratio (AOR) of 1.33, indicating a high likelihood of misuse. Similar AORs are seen in adolescents who have used marijuana, cigarettes, and alcohol: 2.44, 1.25, and 1.23, respectively.

Sovereign pharmaceuticals representative Leonard Lawrence presented the findings of a pharmacokinetic study for hydrocodone and guaifenesin in 25-35 pediatric patients evenly divided into groups aged 6 years to less than 12 years, and 12 years to less than 18 years. According to Mr. Lawrence, codeine appears "to be a greater risk in children younger than 12 years, and should not be used" because of difficulty breathing. Mr Lawrence

Continued on following page

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Pediatric pulmonologists talk about this all the time but it is usually primary care and urgent care providers who give children cough suppressants that don't work and are potentially dangerous. I don't understand why they aren't taken off the market.

Faster multiplex PCR led to faster hospital discharges

BY AMY KARON
Frontline Medical News

SAN DIEGO – Switching to a faster, more comprehensive multiplex PCR viral respiratory assay enabled a hospital to discharge young children with acute respiratory illnesses sooner, prescribe oseltamivir more often, and curtail the use of antibiotics and thoracic radiography, Rangaraj Selvarangan, PhD, reported at an annual meeting on infectious disease.

The study shows how rapid multiplex PCR testing can facilitate antimicrobial stewardship, said Dr. Selvarangan, who is a professor at the University of Missouri Kansas City School of Medicine and director of the microbiology laboratory at Children's Mercy Kansas City. "Our antimicrobial stewardship programs monitor these test results daily, add notes, and make recommendations on antibiotic choices," he said.

Acute respiratory illness is a leading reason for pediatric hospitalization, is usually viral in nature, and continues to fuel the overuse of antibiotics. Multiplex PCR respiratory panel assays have been available in the United States for about a decade, but uptake has varied. "As one of the early adopters of the technology, we wanted to see how it might affect patient care," Dr. Selvarangan said.

For the study, the researchers compared hospital records from December 2008 through May 2012, when Children's Mercy hospital used the Luminex xTAG Respiratory Viral Panel, with records from August 2012 through June 2015, after the hospital had switched over to the BioFire FilmArray Respiratory Panel. FilmArray targets the same 17 viral pathogens as the Luminex panel, but also targets *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, seasonal influenza A, parainfluenza type 4, and four coronaviruses.

The study included children aged up to 2 years who were not on immunosuppressive medications, in the

Continued from previous page

went on to say that these effects were exacerbated in obese children with lung disease or obstructive sleep apnea.

Victor S. Sloan, MD, of UCB in Brussels, presented an internal review of Tussionex, a combination cough medicine (hydrocodone/chlorpheniramine). This review took into account modern pharmacovigilance methods, changes in clinical practice, and a literature review. "Upon annual review, UCB determined that benefit risk balance for use of Tussionex for cough in children was no longer favorable," said Dr. Sloan. Based on the results of the review, UCB has filed a label supplement to limit use of Tussionex to patients aged 18 years or older.

"Codeine, in particular, is an antiquated drug," said Kathleen Neville, MD, pediatrics and clinical pharmacology section chief of Arkansas Children's Hospital, Little Rock.

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NICU, or hospitalized for more than 7 days. For this population, the two panels yielded similar rates of positivity overall (about 60%) and for individual viruses, Dr. Selvarangan said. A total of 810 patients tested positive for at least one virus on the Luminex panel, and 2,096 patients tested positive on FilmArray. Results for FilmArray were available within a median of 4 hours, versus 29 hours for Luminex (*P* less than .001). The prevalence of empiric antibiotic therapy was 44% during the Luminex era and 28% after the hospital switched to FilmArray (*P* less than .001). Rates of antibiotic discontinuation rose from 16% with Luminex to 23% with FilmArray (*P* less than .01). Strikingly, oseltamivir prescriptions rose fivefold (from 17% to 85%; *P* less than .001) after the hospital began using FilmArray, which covers seasonal influenza. Finally, use of chest radiography fell significantly in both infants and older children after the hospital began using FilmArray instead of Luminex.

This study is one of the first to directly compare clinical outcomes

Continued on following page

AMY KARON/FRONTLINE MEDICAL NEWS

Dr. Rangaraj Selvarangan, PhD

Continued from previous page

between two assays, Dr. Selvarangan noted.

"For the individual patient, having more rapid diagnostic methods for viral infections not only allows for the prompt initiation of the correct therapy, but helps to avoid the incorrect prescription of antibiotics for viral disease," said Vera A. De Palo, MD, FCCP. "For community health in general, the authors indicate the important antimicrobial stewardship benefits of the more comprehensive multiplex PCR viral respiratory assay."

Dr. Selvarangan disclosed grant support from both Biofire Diagnostics and Luminex, and an advisory relationship with BioFire.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: I have found film arrays to be incredibly useful in certain situations. I also prefer it over ordering a mycoplasma IgM for the diagnosis of mycoplasma. The blood tests can cross-react with viral respiratory tract illnesses leading a clinician to treat with a macrolide, for example, when the illness was really precipitated by a respiratory virus.

Guidelines cut ACS hospital returns in sickle cell disease

BY HEIDI SPLETE
Frontline Medical News

Children with sickle cell disease who experience acute chest syndrome benefit from the current guideline-recommended antibiotic regimen, based on data from more than 7,000 patients.

Although acute chest syndrome (ACS) is among the most common complications of sickle cell disease (SCD), data on the effectiveness of the recommended antibiotic therapies (macrolides and cephalosporins) are lacking, wrote David G. Bundy, MD, of the Medical University of South Carolina, Charleston, and colleagues. ACS often leads to intensive hospital care and 1%-2% morbidity, they noted.

The most recent guidelines from the National Heart, Lung, and Blood Institute call for "an intravenous cephalosporin and an oral macrolide antibiotic," the researchers said.

To determine the impact of antibiotic use as directed on reducing hospital readmissions in young SCD patients, the researchers reviewed data from 14,480 hospitalizations for ACS involving 7,178 children and young adults aged 0-22 years seen at 41 hospitals in the United States (JAMA Pediatr. 2017 Sep 11. doi: 10.1001/jamapediatrics.2017.2526).

'This high level of interhospital variation also suggests possible clinician disagreement regarding the ideal antibiotic treatment for children with ACS.'

Overall, 74% of the patients were treated with antibiotics according to the guidelines, but use of guideline-recommended antibiotics ranged from 24% to 90% across the participating hospitals.

"This high level of interhospital variation also suggests possible clinician disagreement regarding the ideal antibiotic treatment for children with ACS," the researchers wrote.

Rates of all-cause readmission and 30-day ACS-related readmission were significantly lower among patients who received the recommended antibiotics (odds ratio, 0.50 and 0.71, respectively). Children aged 5-9 years were most likely to receive the recommended antibiotics (80%), while young adults aged 19-22 years were the least likely (64%).

The findings were limited by several factors, including coding errors and incomplete clinical information, the researchers noted. But the results suggest that the guideline-recommended antibiotics are effective, "so more robust dissemination and implementation of existing treatment guidelines may reduce readmissions in this high-risk population," they said.

The researchers had no financial conflicts to disclose.

Study coauthor Staci Arnold, MD, was supported in part by the Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program.

Preterm bronchopulmonary dysplasia rate maintained

BY BIANCA NOGRADY
Frontline Medical News

Inhaled nitric oxide (NO) therapy does not appear to achieve reduction in the incidence of bronchopulmonary dysplasia in preterm infants, according to data published online Sept. 25 in JAMA Pediatrics.

Shabih U. Hasan, MD, from the Cumming School of Medicine at the University of Calgary, and his coauthors wrote that inhaled nitric oxide is currently approved for the treatment of hypoxic respiratory failure in infants with pulmonary hypertension. Animal studies have prompted interest in its potential to prevent bronchopulmonary dysplasia in preterm infants, but randomized trials so far have shown mixed results (JAMA Pediatrics. 2017 Sep 25. doi: 10.1001/jamapediatrics.2017.2618).

In this study, researchers recruited 451 preterm infants of less than 30 weeks' gestation, with a birth weight below 1,250 g, and who were receiving ventilation or respiratory support. They were randomized either to inhaled NO (229 infants), starting at 20 ppm then decreasing to 10 ppm after 3-4 days and finally to 5 ppm on day 10 or 11 until day 24, or to nitrogen placebo (222 infants).

The dosage selected was higher, and the treatment was given for a longer period and initiated later than in some previous studies, which the authors hypothesized might improve outcomes.

However, there was no significant difference between the placebo and inhaled NO groups in the primary outcome of survival to 36 weeks postmenstrual age without bronchopulmonary dysplasia (31.5% vs. 34.9%).

Similarly, the rate of severe bronchopulmonary dysplasia was similar for placebo and inhaled nitric oxide (26.6% vs. 20.5%), as was the rate of postnatal corticosteroid use (41.0% vs. 41.5%), mean days of positive pressure respiratory support (55 vs. 54), mean days of oxygen therapy (88 vs. 91) and mean days of hospitalization (105 vs. 108).

The subgroup analysis revealed that characteristics such as birth weight, gestational age, sex, postnatal age at study entry, maternal race or mode of respiratory support also did not influence the outcomes.

While the rates of severe bronchopulmonary dysplasia were similar between the placebo and inhaled nitric oxide groups, the inhaled NO group had a larger number of infants whose mothers were white and a higher rate of rupture of mem-

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Nitric oxide is an expensive but sometimes important therapy for critically ill infants in the NICU and PICU. However, I don't know anyone who believes it will prevent BPD. BPD prevention is the holy grail of neonatology and as elusive as looking for a therapy for the common cold!

branes for more than 7 days. The two groups had similar incidence of prematurity complications, such as sepsis, patent ductus arteriosus, necrotizing enterocolitis, retinopathy, intraventricular hemorrhage, and pulmonary air leak.

There were also no significant differences in neurodevelopmental or respiratory outcomes at 18-24 months postmenstrual age.

The authors commented that they had hoped their results would be similar to the earlier NO CLD trial, which hinted at a substantial increase in survival without bronchopulmonary dysplasia, compared with placebo in infants aged 7-14 days at the start of treatment.

"The NO CLD trial was not powered to assess the primary outcome in the subgroup enrolled between ages 7 and 14 days, whereas our study was powered specifically for that purpose and included twice as many infants in each treatment arm," the authors wrote.

Despite this, and a lack of any obvious differences between the study populations, the authors could not identify a reason for the lack of efficacy seen in their own study, compared with this earlier study.

The study was sponsored by Mallinckrodt Pharmaceuticals. Four authors declared honorarium, speaking engagements, advisory positions or consultancies with Mallinckrodt Pharmaceuticals.

Wait two days to replace CVCs in candidemia

BY AMY KARON
Frontline Medical News

SAN DIEGO – Wait at least 2 days before replacing central venous catheters (CVC) in patients with catheter-associated candidemia, according to the results of a single-center retrospective cohort study of 228 patients.

Waiting less than 2 days to replace a CVC increased the odds of 30-day mortality nearly sixfold among patients with catheter-related bloodstream infections due to candidemia, even after controlling for potential confounders, Takahiro Matsuo, MD, said at an annual scientific meeting on infectious diseases. No other factor significantly predicted mortality in univariate or multivariate analyses, he said. "This is the first study to demonstrate the optimal timing of central venous catheter replacement in catheter-related [bloodstream infection] due to *Candida*."

Invasive candidiasis is associated with mortality rates of up to 50%, noted Dr. Matsuo, who is a fellow in infectious diseases at St. Luke's International Hospital, Tokyo. Antifungal therapy improves outcomes, and most physicians agree that removing a CVC does, too. To better pinpoint optimal timing of catheter replacement, Dr. Matsuo and his associates examined risk factors for 30-day mortality among patients with candidemia who were treated at St. Luke's between 2004 and 2015.


DR. MATSUO

Among 228 patients with candidemia, 166 had CVCs, and 144 had their CVC removed. Among 71 patients who needed their CVC replaced, 15 died within 30 days. Central venous catheters were replaced less than 2 days after removal in 87% of patients who died and in 54% of survivors ($P = .04$). The association remained statistically significant after the researchers accounted for potential confounders (adjusted odds ratio, 5.9; 95% confidence interval, 1.2-29.7; $P = .03$).

Patients who died within 30 days of CVC replacement also were more likely to have hematologic malignancies (20% versus 4%), diabetes (13% vs. 11%), to be on hemodialysis (27% vs. 16%), and to have a history of recent corticosteroid exposure (20% versus 11%) compared with survivors, but none of these associations reached statistical significance. Furthermore, 30-day mortality was not associated with gender, age, *Candida* species, endophthalmitis, or type of antifungal therapy, said Dr. Matsuo, who spoke at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

The findings ideally should be confirmed in a larger randomized controlled trial, Dr. Matsuo said.

Negative nasal swabs reliably predicted no MRSA infection

BY AMY KARON
Frontline Medical News

SAN DIEGO – Only 0.2% of intensive care unit patients developed MRSA infections after testing negative on nasal surveillance swabs, said Darunee Chotiprasitsakul, MD, of Johns Hopkins Medicine in Baltimore.

But physicians often prescribed vancomycin anyway, accumulating nearly 7,400 potentially avoidable treatment days over a 19-month period, she said during an oral presentation at an annual meeting on infectious diseases.

Current guidelines recommend empiric vancomycin to cover MRSA infection when ill patients have a history of MRSA colonization or recent hospitalization or exposure to antibiotics. Patients whose nasal screening swabs are negative for MRSA have been shown to be at low risk of subsequent infection, but guidelines don't address how to use swab results to guide decisions about empiric vancomycin, Dr. Chotiprasitsakul said.

Therefore, she and her associates studied 11,882 adults without historical MRSA infection or colonization who received nasal swabs for routine surveillance in adult ICUs at Johns Hopkins. A total of 441 patients (4%) had positive swabs, while 96% tested negative.

Among patients with negative swabs, only 25 (0.22%) developed MRSA infection requiring treatment. Thus, the negative predictive value of a nasal swab for MRSA was 99%, making the probability of infection despite a negative swab "exceedingly low," Dr. Chotiprasitsakul said.

But clinicians seemed not to use negative swab results to curtail vancomycin therapy, she found. Rates of empiric vancomycin use were 36% among patients with positive swabs and 39% among those with negative swabs. Over 19 months, ICU patients received 7,371 avoidable days of vancomycin, a median of 3 days per patient.

Matching patients by ICU and days at risk identified no significant predictors of MRSA infection, Dr. Chotiprasitsakul said. Johns Hopkins Medicine has robust infection control practices, high compliance with hand hygiene and contact precautions, and low rates of nosocomial MRSA transmission, she noted. The predictive value of a negative MRSA nasal swab could be lower at institutions where that isn't the case, she said.

Johns Hopkins is working to curtail unnecessary use of vancomycin, said senior author Sara Cosgrove, MD, professor of medicine in infectious diseases and director of the department of antimicrobial stewardship. The team has added the findings to its guidelines for antibiotic use, which are available in an app for Johns Hopkins providers, she said in an interview.

The stewardship also highlights the data when discussing starting and stopping vancomycin in patients at very low risk for MRSA infections, she said. "In general, providers have responded favorably to acting upon this new information," Dr. Cosgrove noted.

Johns Hopkins continues to track median days of vancomycin use per patient and per 1,000 days in its units. "[We] will assess if there is an impact on vancomycin use over the coming year," said Dr. Cosgrove.


Frontline Medical News

Dr. Darunee Chotiprasitsakul

The investigators had no conflicts of interest. The event marked the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

No benefit seen for routine low-dose oxygen after stroke

BY KARI OAKES
Frontline Medical News

Routine use of low-dose oxygen supplementation in the first days after stroke doesn't improve overall survival or reduce disability, according to a large new study.

The poststroke death and disability odds ratio was 0.97 for those receiving one of two continuous low-dose oxygen protocols, compared with the control group (95% confidence interval, 0.89-1.05; $P = .47$).

The Stroke Oxygen Study (SO_2S) was a single-blinded, randomized, controlled trial that recruited 8,003 adults with a diagnosis of acute stroke within 24 hours of hospital admission, drawing from 136 centers in the United Kingdom, according to an article in JAMA (2017;318[12]:1125-35). A total of 7,677 participants (96%) had data available for analysis of the primary outcome measure, a composite of death and disability 90 days post stroke.

Participants, who were not hypoxic at enrollment, were randomized 1:1:1 to receive continuous oxygen supplementation for the first 72 hours after stroke, to receive supplementation only at night, or to receive oxygen when indicated by usual care protocols. The average participant age was 72 years and 55% were men in all study arms, and all stroke severity levels were included in the study.

Patients in the two intervention arms received 2 L of oxygen by nasal cannula when their baseline oxygen saturation was greater than 93%, and 3 L when oxygen saturation at baseline was 93% or less. Participation in the study did not preclude more intensive respiratory support when clinically indicated.

Nocturnal supplementation was included as a study arm for two reasons: Poststroke hypoxia is more common at night, and night-only supplementation would avoid any interference with early rehabilitation caused by cumbersome oxygen apparatus and tubing.

Not only was no benefit seen for patients in the pooled intervention arm cohorts, but no benefit was seen for nighttime versus continuous oxygen as well. The odds ratio for a better outcome was 1.03 when comparing those receiving continuous oxygen to those who only received nocturnal supplementation (95% CI, 0.93-1.13; $P = .61$).

First author Christine Roffe, MD, and her collaborators in the Stroke Oxygen Study Collaborative Group also performed subgroup analyses and did not see benefit of oxygen supplementation for older or younger patients, or for patients with chronic obstructive pulmonary disease, heart failure, or more severe strokes.

"Supplemental oxygen could improve outcomes by preventing hypoxia and secondary brain damage but could also have adverse effects," according to Dr. Roffe, consultant at Keele (England) University and her collaborators.

A much smaller SO_2S pilot study, they said, had shown improved early neurologic recovery for patients who received supplemental oxygen after stroke, but the pilot also "suggested that oxygen might adversely affect outcome in patients with mild strokes, possibly through formation of toxic free radicals," wrote the investigators.

These were effects not seen in the larger SO_2S study, which was designed to have statistical power to detect even small differences and to do detailed subgroup analysis. For patients like those included in the study, "these findings do not support low-dose oxygen in this setting," wrote Dr. Roffe and her collaborators.

Dr. Roffe reported receiving compensation from Air Liquide. The study was funded by the United Kingdom's National Institute for Health Research.

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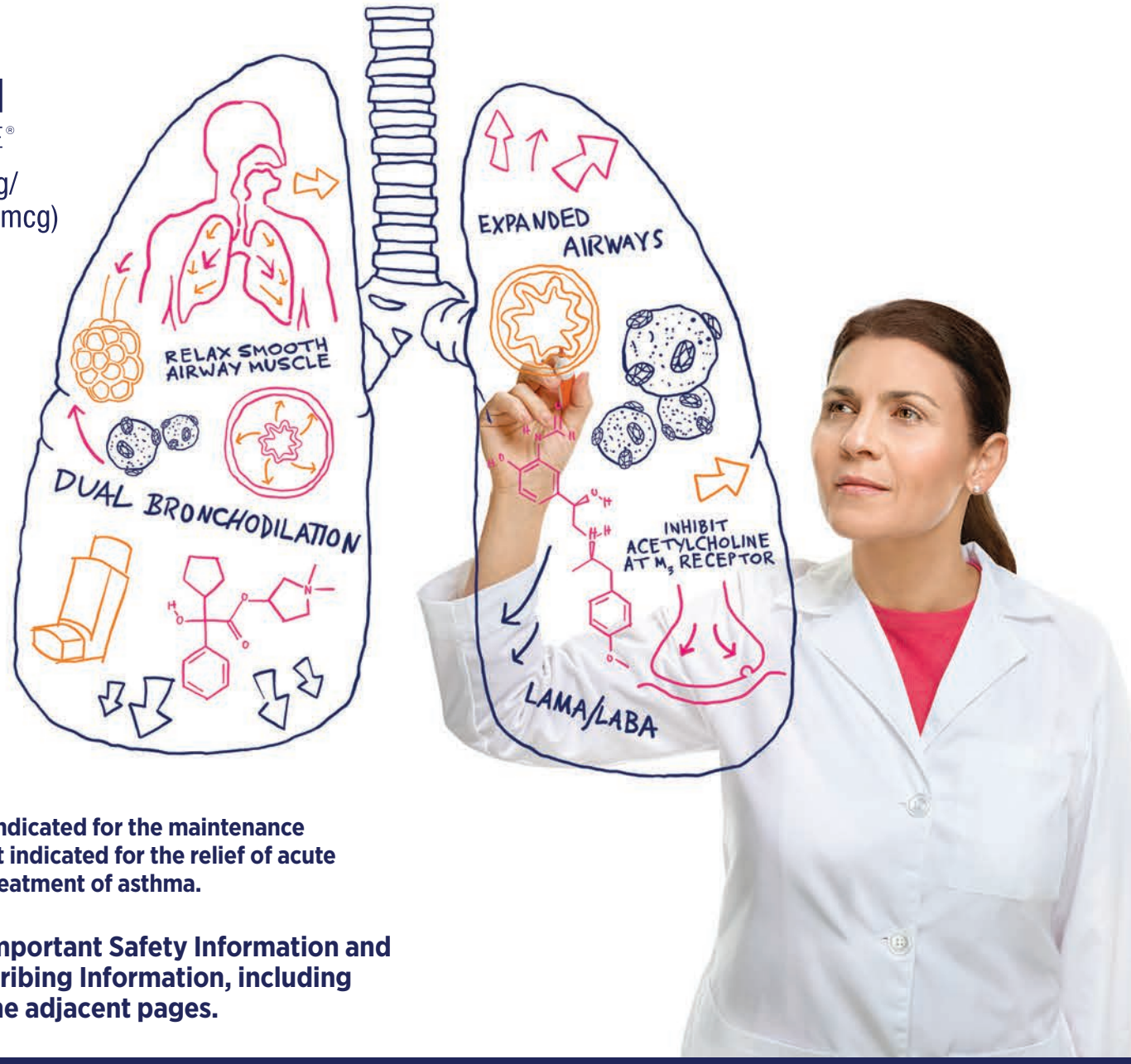
Correction

An article titled "Changes to CPT® codes coming January 2018," published in October on page 62, misidentified the CPT code that should be utilized when a therapeutic bronchoscopy procedure is performed in the nonhospital setting and later repeated. CPT code **31645** is the correct code for this scenario.

BEVESPI
AEROSPHERE®

(glycopyrrolate 9 mcg/
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting beta$_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

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

CONTRAINDICATION: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. BEVESPI is contraindicated in patients with a hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product.

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions, including angioedema, urticaria, or skin rash, occur, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI (≥2% and more common than placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant beta$_2$-agonists

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

INTELLIGENT FORMULATION*

Intelligent formulation for a pMDI using patented CO-SUSPENSION™ Delivery Technology[1]

MAXIMIZE BRONCHODILATION†

Improved lung function‡ vs placebo including[1]

- 150-mL improvement in predose FEV_1 at 24 weeks
- Nearly a 300-mL improvement in peak FEV_1 at 24 weeks
- Nearly a 200-mL improvement in FEV_1 at 5 minutes on Day 1

In a separate study vs placebo

- Achieved a 381-mL improvement in peak inspiratory capacity on Day 29[2§‖]

Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.[1]

BEVESPI AEROSPHERE is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. It is not for the treatment of asthma.

LEARN MORE AT DUALBRONCHODILATION.COM

* BEVESPI AEROSPHERE is a pMDI containing the LAMA glycopyrrolate and LABA formoterol fumarate, along with phospholipid porous particles that form the co-suspension with the micronized drug crystals.[1]

† Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials (n=3699).[1,3]

§ Results from a separate Phase IIIb trial (n=35). There was a significant mean improvement in primary endpoint FEV_1 $AUC_{0\text{-}24}$ on Day 29 vs placebo.[2¶] Peak inspiratory capacity after the evening dose on Day 29 was a secondary endpoint.[#] Similar results seen in a second Phase IIIb trial (n=75).[2‖]

- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

LIMITATION OF USE: Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

‡ Demonstrated in two 24-week efficacy and safety studies in patients with moderate to very severe COPD (n=3699). Inclusion criteria: A clinical diagnosis of COPD; between 40-80 years of age; history of smoking ≥10 pack-years; post-albuterol FEV_1 of <80% of predicted normal values, and FEV_1/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; $P<0.0001$ for all treatment comparisons.[1,3] Statistically significant results were also seen in Trial 2.[1,3]

‖ Two Phase IIIb crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI AEROSPHERE compared with placebo in subjects with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and Study B). Inclusion criteria were consistent with the two 24-week pivotal trials. Adverse events were numerically similar across treatment arms.[2]

¶ Primary endpoint, FEV_1 $AUC_{0\text{-}24}$: Study A – BEVESPI AEROSPHERE (n=35) vs placebo (n=31) = 249 mL (baseline FEV_1 1.382 L and 1.345 L, respectively); Study B – BEVESPI AEROSPHERE (n=65) vs placebo (n=65) = 265 mL (baseline FEV_1 1.328 L and 1.333 L, respectively); both $P<0.0001$.[2]

Secondary endpoint, Peak IC (evening): Study A – BEVESPI AEROSPHERE (n=34) vs placebo (n=30) = 381 mL (baseline IC [evening], 1.980 L and 1.939 L, respectively); Study B – BEVESPI AEROSPHERE (n=62) vs placebo (n=63) = 312 mL (baseline IC [evening] 1.877 L and 1.913 L, respectively); both $P<0.0001$.[2]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2016. **2.** Data on File, 3270300, AZPLP. **3.** Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357.

AstraZeneca

BEVESPI AEROSPHERE™

(glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication *[see Warnings and Precautions (5.1) in the full Prescribing Information]*. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs.

A 28-week, placebo-controlled US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

When beginning BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled medicines containing beta$_2$-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. If such effects occur, BEVESPI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

BEVESPI AEROSPHERE, 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$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta$_2$-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. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

BEVESPI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention

BEVESPI AEROSPHERE should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma *[see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information]*.

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Hypersensitivity reactions *[see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10) in the full Prescribing Information]*

Clinical Trials Experience

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

The clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

Additional Adverse Reactions**:** Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of $beta_2$ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m^2 basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m^2 basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

Pediatric Use

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

Geriatric Use

Based on available data, no adjustment of the dosage of BEVESPI AEROSPHERE in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Glycopyrrolate

High doses of glycopyrrolate, a component of BEVESPI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom

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CARDIOTHORACIC SURGERY

LVAD use soars in elderly Americans

BY MITCHEL L. ZOLER
Frontline Medical News

DALLAS – The percentage of left ventricular assist devices placed in U.S. heart failure patients at least 75 years of age jumped sharply during 2003-2014, and concurrently the short-term survival of these patients improved dramatically, according to data collected by the National Inpatient Sample.

During the 12-year period examined, the percentage of left ventricular assist devices (LVADs) placed in U.S. heart failure patients aged 75 years and older rose from 3% of all

Mitchel L. Zoler/Frontline Medical News

Dr. Aniket S. Rali

LVADs in 2003 to 11% in 2014, Aniket S. Rali, MD, said at the annual scientific meeting of the Heart Failure Society of America.

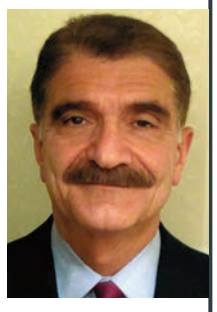
In actual numbers, LVAD placement into elderly patients jumped from 23 in 2003 to 405 in 2014, a greater than 17-fold increase. During the same period, total U.S. LVAD use rose from 726 placed in 2003 to 3,855 placed in 2014, about a fivefold increase.

The U.S. national numbers also showed that throughout the period studied, elderly U.S. patients who received an LVAD were increasingly sicker, with steadily increasing numbers of patients with a Charlson Comorbidity Index score of 4 or greater. Despite this, in-hospital mortality rates of elderly patients receiving an LVAD plummeted, dropping from 61% of elderly LVAD recipients in 2003 to 18% in 2014. During the same time, the percentage of elderly patients with a Charlson Comorbidity Index score greater than 4 doubled from 33% in 2003 to 66% in 2014, said Dr. Rali, a cardiologist at the University of Kansas Medical Center in Kansas City.

"If the Charlson Comorbidity Index score is increasing but in-hospital mortality is decreasing, then increased LVAD use is not a bad

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The success of LVAD use as a destination therapy for patients not candidates for transplantation has changed the paradigm for the treatment of patients with end stage heart failure. This report is a confirmation of this paradigm shift.



trend," Dr. Rali said in an interview. He hopes that future analysis of longitudinal data from patients could identify clinical factors that link with better patient survival and help target LVAD placement to the patients who stand to gain the most benefit.

"We may be able to give these elderly patients not just longer life but improved quality of life" by a more informed targeting of LVADs, he suggested. "I think these numbers will help convince people that all is not lost," he noted, for elderly heart failure patients who receive an LVAD as destination therapy. Patients at least 75 years old are not eligible for heart transplantation, so when these patients receive an LVAD it is, by definition, destination therapy.

The data also showed a marked sex disparity in LVAD use, with LVAD placement in men at least 75 years old rising from 1.4/1,000 patients in 2003 to 2.78/1,000 patients in 2014. In contrast, among women these rates rose from 0.8/1,000 patients in 2003 to 1.36/1,000 patients in 2014.

The average age for elderly U.S. LVAD recipients for the entire 12-year period studied was 77.6 years among a total of 2,090 recipients. For all 21,323 U.S. LVAD recipients during 2003-2014 the average age was 51.5 years old.

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Closure of left atrial appendage slashes stroke risk

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Routine surgical closure of the left atrial appendage during open heart surgery provides long-term protection against cerebral ischemic events, according to the findings of the first-ever randomized controlled trial to address the issue.

"I think we can say, based on our study, that it would be advisable to routinely add surgical closure of the left atrial appendage to planned open heart surgery," Jesper Park-Hansen, MD, said at the annual congress of the European Society of Cardiology.

New-onset atrial fibrillation is common following cardiac surgery. That's one of the reasons why 1%-3% of patients have a stroke within the first year following coronary artery bypass graft (CABG) surgery. A clot kicked loose from the left atrial appendage (LAA) is the source of most ischemic strokes.

In light of the demonstrated success of percutaneous closure of the LAA using the Watchman and other devices for stroke prevention in patients with atrial fibrillation, Dr. Park-Hansen and his coinvestigators at the University of Copenhagen organized LAACS (the Left Atrial Appendage Closure Study). The goal was to generate solid, randomized trial evidence as to whether preemptive routine surgical closure of the LAA at the time of cardiac surgery is of benefit. Some cardiac surgeons already do this routinely; many others don't because of the lack of Level 1 supporting evidence.

LAACS included 141 patients randomized to surgical LAA closure or not at the point of first-time open heart surgery. The study population included patients with and without a history of atrial fibrillation. LAA closure was accomplished via a purse string closure with a silk

Continued on following page

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: This report on prophylactic closure of left atrial appendage (LAAC) during the first heart operation in preventing subsequent cerebrovascular accident (CVA) events is the first of its kind, and, although the treated group had a lower rate of CVA compared with the control group, the difference did not reach statistical significance. Both open and closed atrial appendage groups had a high rate of perioperative atrial fibrillation, 60.5% and 50%, respectively. Only 10% of the treated group had follow-up transesophageal echocardiography for confirmation of complete appendage closure. Nonetheless, the results reported are encouraging for cardiac surgeons in considering LAAC in high-risk patients undergoing cardiac operations.

CARDIOTHORACIC SURGERY

Hearts from HCV-infected patients successfully transplanted

BY MITCHEL L. ZOLER
Frontline Medical News

GRAPEVINE, TEXAS – The heart transplant team at Vanderbilt University has successfully placed hearts from deceased, hepatitis C virus–positive patients into recipients, and then eradicated the subsequent infection that appeared in most recipients using a standard, direct-acting antiviral regimen.

So far, five of nine heart transplant recipients who developed a post-transplant hepatitis C virus (HCV) infection had the infection eradicated using one of the highly effective HCV drug regimens, and an additional three patients from the series are nearing their 12th week without detectable virus following treatment that marks a sustained response, Kelly H. Schlendorf, MD, said at the annual scientific meeting of the Heart Failure Society of America. The ninth patient died after developing a pulmonary embolism during the 7th week on antiviral therapy.

The team has also placed hearts from HCV-positive donors into an additional four patients who have not developed HCV infection, for a total of 13 heart transplants performed using hearts that until now have been routinely beyond consideration.

The recipients have been patients in a marginal clinical state and facing a long projected wait on the heart-recipient queue of the United Network for Organ Sharing (UNOS), Dr. Schlendorf said in an interview.

These have been "patients with a morbidity and mortality risk from waiting that can be mitigated by expanding the donor pool." She gave an example of a patient with a left ventricular assist device that required replacement by either a second device or transplant, "so getting the transplant quickly was a good thing," said Dr. Schlendorf, a cardiologist at Vanderbilt in Nashville.

Based on her analysis of UNOS data, "upwards of 100" and perhaps as many as 300 additional donor hearts could be available annually for U.S. transplants if the organs weren't excluded because of HCV infection.

The Vanderbilt team has so far approached 15 patients in their program wait-listed for hearts about the possibility of accepting an HCV-positive organ, and all 15 have given their consent, she said. "We spend a lot of time talking with patients and their caregivers about the risks and benefits and possible complications."

The 13 recipients, starting in September 2016, included 12 patients who were HCV naive and 1 patient with a history of HCV exposure. All 13 received the program's standard three-drug regimen for immunosuppression.

During close surveillance, 9 of the 13 developed an infection. Patients with genotype 1 HCV received 12 weeks of treatment with ledipasvir plus sofosbuvir. Those infected with genotype 3 received 12-24 weeks of treatment with sofosbuvir plus velpatasvir. Treatment with these direct-acting antivirals meant that patients had to adjust the time when they took their proton-pump inhibitors, and they needed to stop treatment with diltiazem and statins while on the antivirals.

"In the era of direct-acting antivirals, HCV-positive donors may provide a safe and effective way to expand the donor pool and reduce wait-list times," Dr. Schlendorf said. She noted that in recent years an increased number of potential organ donors have been HCV positive. She also cautioned that so far follow-up has been relatively brief, with no patient yet followed as long as 1 year after transplant.

The direct-acting HCV antivirals are expensive, and some payers established clinical criteria that patients must meet to qualify for coverage of these regimens. "We have not encountered difficulties getting insurers to pay," Dr. Schlendorf said. Despite the antivirals' cost there are significant cost savings from fewer days in the ICU waiting for heart transplantation and a reduced need for mechanical support as a bridge to transplant, she noted.

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MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS
Dr. Kelly H. Schlendorf

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: With the shortage of donor hearts, many patients on the transplant waiting list either do not survive or remain on cardiac assist devices, which may require replacement. The report from the Nashville group is an attempt to expand the donor pool for the high-risk and very ill patients on the transplant list. This is an early report on a small series of 13 patients. Longer follow-up beyond 1 year is needed to prove the viability of this strategy as an effective option for cardiac transplant candidates.

Continued from previous page

string around the neck of the appendage backed up by an additional single running suture. Transesophageal echocardiography performed in 10 patients a mean of 520 days post closure showed no signs of leakage or incomplete closure.

The primary composite outcome was comprised of clinical stroke or transient ischemic attack diagnosed by a neurologist, or a silent cerebral infarct detected on MRI performed 2-4 weeks post discharge and again at least 6 months later. At a mean follow-up of 3.7 years and a maximum of 6 years, this outcome had occurred in 6.3% of the LAAC group, significantly lower than the 18.3% rate in controls. All but one patient with a cerebral ischemic event in the control group had atrial fibrillation. The risk of an event was unrelated to whether or not a patient had a history of atrial fibrillation prior to surgery or to CHA_2DS_2-VASc score.

Dr. Park-Hansen emphasized that he and his coinvestigators don't consider LAACS to be the final word on routine prophylactic appendage closure.

"This is the first randomized study. We are eager to move on to another randomized study on a larger scale. That is the next step for us," he said.

"The challenge now – and what we will be discussing with our surgeons – is to agree on a feasible safe and effective means of left atrial appendage closure. My personal opinion is the Lariat suture delivery device or some other easily reproducible method of closure could be a good way to go," Dr. Park-Hansen added.

The research group's cardiac surgeons already have ruled out excision and stapling because of concerns about bleeding risk and the additional cost imposed by stapling.

Discussant Volkmar Falk, MD, commented that LAACS was too small, probably severely underpowered, should have included a preoperative MRI so investigators could reliably capture perioperative silent cerebral infarcts, and the double suture purse string is "probably not the best method" to occlude the LAA.

"LAACS addresses an important question, but alas, it does not provide the answer," declared Dr. Falk, professor and director of the department of cardiothoracic and vascular surgery at Charité Medical University in Berlin.

Dr. Park-Hansen and Dr. Falk reported having no financial conflicts of interest.

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BRUCE JANCIN/FRONTLINE MEDICAL NEWS
Dr. Jesper Park-Hansen

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).

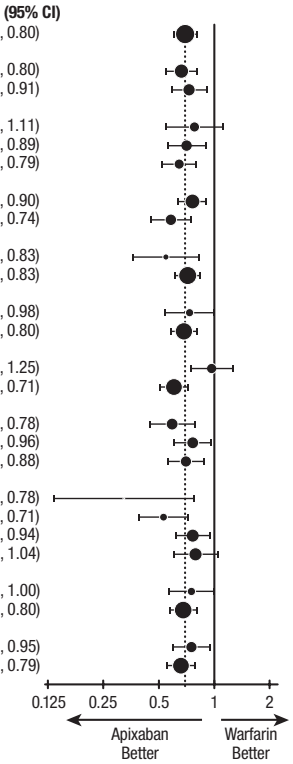
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§ 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]*.

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

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MACRA: Screening for hypertension

If you haven't started reporting quality data for the Merit-Based Incentive Payment System (MIPS), there's still time to avoid a 4% cut to your Medicare payments.

Under the Pick Your Pace approach being offered this year, the Centers for Medicare & Medicaid Services allows clinicians to test the system by reporting on one quality measure for one patient through paper-based claims. Be sure to append a Quality Data Code (QDC) to the claim form for care provided up to Dec. 31, 2017, in order to avoid a penalty in payment year 2019.

Consider this measure:

Measure #317: Preventive Care and Screening: Screening for High Blood Pressure and Follow-Up Documented

This measure is aimed at capturing the percentage of patients aged 18 years and older who were screened for high blood pressure and given a follow-up plan.

What you need to do: Check the patient's blood pressure and recommend follow-up care – lifestyle modifications, additional testing, or medication, as appropriate – and document that plan.

Eligible cases include patients aged 18 years and older on the date of the encounter and a patient encounter during the performance period. Applicable codes include (CPT or HCPCS): 90791, 90792, 90832, 90834, 90837, 90839, 90845, 90880, 92002, 92004, 92012, 92014, 96118, 99201, 99202, 99203, 99204, 99205, 99212, 99213, 99214, 99281, 99282, 99283, 99284, 99285, 99215, 99304, 99305, 99306, 99307, 99308, 99309, 99310, 99318, 99324, 99325, 99326, 99327, 99328, 99334, 99335, 99336, 99337, 99341, 99342, 99343, 99344, 99345, 99347, 99348, 99349, 99350, D7140, D7210, G0101, G0402, G0438, G0439 without telehealth modifier: GQ or GT.

To get credit under MIPS, be sure to include a QDC that shows that you successfully performed the measure or had a good reason for not doing so. For instance, code G8783 indicates that a normal blood pressure reading was documented and follow-up is not required, while code G8950 indicates that the patient had a pre-hypertensive or hypertensive blood pressure reading documented and the appropriate follow-up was documented. Exclusion code G9744 should be used if the patient is not eligible due to an active diagnosis of hypertension.

CMS has a full list measures available for claims-based reporting at qpp.cms.gov. The American Medical Association has also created a step-by-step guide for reporting on one quality measure.

Certain clinicians are exempt from reporting and do not face a penalty under MIPS:

- Those who enrolled in Medicare for the first time during a performance period.
- Those who have Medicare Part B allowed charges of $30,000 or less.
- Those who have 100 or fewer Medicare Part B patients.
- Those who are significantly participating in an Advanced Alternative Payment Model (APM).

MIPS: It's time to get started

BY GREGORY TWACHTMAN
Frontline Medical News

David O. Barbe, MD, president of the American Medical Association, is urging physicians to participate in the Medicare Quality Payment Program, even if the business case isn't quite there.

QPP is the value-based payment system created by the Medicare Access and CHIP Reauthorization Act (MACRA). It promotes high-value care through Medicare payment increases. But for some practices, the investment in personnel and technology needed to earn those increases may be more than the increases themselves, leading doctors to do just enough to avoid being penalized.

"I think that many physicians don't feel they are ever going to get a bonus but sure would like to avoid

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a penalty," Dr. Barbe, said in an exclusive interview. "I am afraid many will simply perform at the lowest level that keeps them out of the penalty. Because many of them find that making the investment it takes to perform highly, there is not a business case for that."

Full participation in QPP's Merit-based Incentive Payment System (MIPS) could run small practices an additional $10,000 to $30,000 a year, he said. "If you've got $200,000 in Medicare receipts, if you get adjusted even the maximum of 4%, that is $8,000. You can't cover $20,000 with $8,000. The math doesn't work. There is not a business case there for it."

That said, Dr. Barbe still spoke in favor of QPP and noted that the AMA is working with the Centers for Medicare & Medicaid Services as well as Congress to make the program more valuable and meaningful for physicians.

"We understand where we need to go as a profession, as an industry," he said. "How we get there is the key, it's the challenge and it requires flexibility. ... CMS has been accommodating but there are limits to how long they can go."

The AMA is urging doctors who have missed the 90-day window for full participation – which effectively closed for most on Oct. 2 – to consider the Pick Your Pace option offered by the CMS.

Pick Your Pace allows physicians and practices to submit data on one measure for one patient to avoid a reduction in Medicare pay, even though they would not be eligible for a bonus.

DR. BARBE

"AMA has put out a lot of tools to help physicians assess their readiness, assess the gap between what they are able to do in their practice now and what they need to do to be successful under [the MIPS] primarily down to and including a video that would walk a physician step-by-step through the one patient, one measure, no penalty," Dr. Barbe said.

He also encouraged doctors to pick a measure that is meaningful to their practice if only to get the ball rolling and get their feet wet in the QPP pool.

"What I tell physicians is pick something that is relevant for your practice," he said."If I see a lot of diabetes patients in my practice but I don't see many people on anticoagulants, it doesn't make sense for me to pick an anticoagulant measure."

And if all a practice can do this year is one patient, one measure, Dr. Barbe urged physicians to look toward the next reporting year with an eye to do more, as that will ultimately lead to better quality of care delivered.

"Report on one patient and one measure this year ... but look at next year to say 'that's going to be a 90-day project for me,' and get in on that. There is a pretty long laundry list of conditions and metrics that you can report on."

And if practices start capturing relevant data, it opens the door to improving their practice if they also take the time to analyze what they are collecting.

"That is the purpose," Dr. Barbe said. "As you measure yourself along the way, if the threshold for performance is here, and you find yourself working at this [lower] level for the first 30 days or whatever, then you stop and take stock of that" and react accordingly.

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Ruling: Apologies can't be used against doctors

BY ALICIA GALLEGOS
Frontline Medical News

The Ohio Supreme Court has ruled that apologies by physicians that include an admission of fault cannot be used against them in court, upholding a lower court decision that spared a doctor's comments from being heard at trial.

In a Sept. 12 decision, state Supreme Court justices concluded that Ohio's apology statute protects both expressions of regret for an unanticipated outcome and acknowledgments that the patient's treatment fell below the standard of care. The decision resolves a split among Ohio appeals courts over whether expressions of fault are admissible.

The decision declaring Ohio's apology statute "unambiguous" is an important and clarifying ruling for physicians and settles the differing opinions of some lower courts, said Reginald Fields, director of external and professional relations for the Ohio State Medical Association.

"We applaud the high court's decision," Mr. Fields said in an interview. "Even the two dissenting justices agreed that the apology law is clear; they just questioned whether it applied in this particular case. This ruling likely means pending legislation thought to be needed to clarify the law is now unnecessary. The OSMA will now focus on other aspects of tort reform, such as 'loss of chance' claims and further elimination of frivolous lawsuits."

The Ohio Association for Justice, the state's plaintiffs' bar did not respond to a request for comment.

The case of Stewart v. Vivian resulted from a lawsuit filed by Dennis Stewart against Cincinnati psychiatrist Rodney Vivian, MD, after the death of Mr. Stewart's wife by suicide. Michelle Stewart was admitted to the emergency department of Mt. Orab MediCenter in February 2010 after attempting suicide and was later transferred to the psychiatric unit at Mercy Hospital Clermont in Batavia, Ohio. After consulting with nurses, Dr. Vivian ordered that a staff member of the psychiatric unit visually observe Ms. Stewart every 15 minutes, according to court documents. The next evening, Mr. Stewart arrived at the psychiatric unit to visit his wife and found her unconscious as a result of hanging.

Two days later, Dr. Vivian went to Ms. Stewart's room in the intensive care unit to speak with family members. The content of the conversation between Dr. Vivian and family members is disputed. Family members allege that Dr. Vivian expressed that it was a "terrible situation" and that the patient had told Dr. Vivian that she "wanted to be dead" would "keep trying" to kill herself. Dr. Vivian testified that he told the family he was "sorry this has happened." Ms. Stewart was later taken off life support and died.

In 2011, Mr. Stewart sued Dr. Vivian and Mercy Hospital Clermont for medical malpractice, loss of spousal consortium, and wrongful death. Dr. Vivian argued that his statements to family members in the ICU room were inadmissible under the state's apology law because they were "intended to express commiseration, condolence, or sympathy." Mr. Stewart countered that Dr. Vivian's statements were admissible because they were not "pure expressions of apology, sympathy, commiseration, condolence, compassion, or a general sense of benevolence." The trial court sided with Dr. Vivian and his statements were kept from trial testimony. The jury returned a verdict in favor of Dr. Vivian, concluding that he was not negligent in his assessment, care, or treatment.

The 12th District Court of Appeals ruled that Dr. Vivian's statements were properly excluded, finding that the Ohio's apology law is ambiguous because according to the term's dictionary definition, "apology" may or may not include an admission of fault. But the decision conflicted with the case of Davis v. Wooster Orthopaedics & Sports Medicine, Inc. in which the Court of Appeals for the 9th District in Ohio determined Ohio's apology statute protects from admission "pure expressions of apology, sympathy, commiseration, condolence, compassion, or a general sense of benevolence," but not "admission of fault."

Resolving the split, the Ohio Supreme Court concluded that the state law is unambiguous and that its legislative intent is to shield expressions of regret for unexpected outcomes that may include acknowledgments that the patient's medical care fell below the standard of care.

Ohio Supreme Court Chief Justice Maureen O'Connor and Justice William M. O'Neill partially dissented. While they agreed with the majority's holding regarding the intent of Ohio's apology law, Justice O'Connor wrote that the Dr. Vivian's statements fell outside the law's protection.

"Dr. Vivian's statements were not an apology nor did they express regret or a type of shared sadness associated with sympathy or commiseration," she wrote in her dissent.

At least 36 states have apology laws that shield against certain statements, expressions, or other evidence related to disclosures being used against physicians in court.

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CMS alerts physicians of payment reductions for PQRS noncompliance

BY GREGORY TWACHTMAN
Frontline Medical News

Doctors who did not adequately meet Physician Quality Reporting System (PQRS) requirements in 2016 will soon be receiving notification letters alerting them that their Medicare Part B physician fee schedule payments will be reduced by 2%.

Officials from the Centers for Medicare & Medicaid Services said in a statement that "the majority" of eligible professionals "successfully reported to PQRS and avoided the downward payment adjustment," but did not state how many doctors are expected to receive letters.

Physicians who are flagged for the payment reduction, but who believe they successfully complied with PQRS requirements, will have the opportunity to challenge the finding. They must submit an informal review request online here within 60 days of the release of the 2016 PQRS feedback report.

The CMS noted that there are no hardship exemptions to avoid the payment reduction for 2018.

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CARDIOVASCULAR MEDICINE

Riociguat may benefit subset of PAH patients

BY DOUG BRUNK
Frontline Medical News

Switching to riociguat may be an effective strategy for pulmonary arterial hypertension (PAH) patients who respond inadequately to phosphodiesterase-5 inhibitors, results from a small open-label study demonstrated.

"This study represents an important step towards determining if this new treatment strategy is an effective approach to the management of patients with PAH, although additional data from larger, randomised, controlled studies are needed to further establish the safety and efficacy of this approach," researchers led by Marius M. Hoeper, MD, wrote in a study published online Sept. 9, 2017, in the European Respiratory Journal (Eur Respir J. 2017 Sep 9. doi: 10.1183/13993003.02425-2016).

Current clinical data indicate that many patients with PAH who receive phosphodiesterase-5 inhibitors do not reach treatment goals. "For example, in the AMBITION study, 73% of patients with PAH receiving tadalafil monotherapy and 61% of those receiving tadalafil in combination with ambrisentan did not achieve a satisfactory clinical response at week 24 of the study (N Engl J Med. 2015;373:834-44)," Dr. Hoeper of the Clinic for Respiratory Medicine at Hannover Medical School Germany and his associates wrote. "Furthermore, in the SERAPHIN study, event-free survival of patients receiving [phosphodiesterase-5 inhibitors] monotherapy was approximately 50% at 3 years (N Engl J Med. 2013;369:809-18)."

For the current trial, known as RESPITE, investigators from nine countries in Europe and North America enrolled 61 PAH patients in a 24-week, open-label uncontrolled analysis to investigate the safety, feasibility, and benefit of switching them from phosphodiesterase-5 inhibitors to riociguat. The patients underwent 1-3 days free of phosphodiesterase-5 inhibitors before receiving riociguat in a maximum dose of up to 2.5 mg t.i.d. Most patients (74%) were female, and 92% were Caucasian. In all, 51 patients (84%) completed all 24 weeks of treatment, while the remaining 10 discontinued treatment, 4 of whom due to adverse events.

Among those who completed all 24 weeks of the trial, their mean 6-minute walking distance had increased by a mean of 31 meters and their N-terminal pro b-type natriuretic peptide level decreased by a mean of 347 pg/mL. Additionally, 54% of the patients studied experienced an improvement in their the World Health Organization Functional Class. However, 32 patients (52%) experienced study drug–related adverse events and 10 (16%) experienced serious adverse events, two of which were related to the drug being studied. Six patients (10%) experienced clinical worsening, including death in two, though the deaths were deemed to be unrelated to the drug being studied.

"Although not mechanistically studied, the findings of RESPITE support the hypothesis that a defective [nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate] pathway might explain why some patients have no sufficient or sustained response to [phosphodiesterase-5 inhibitors] therapy," the researchers noted. "In such patients, direct stimulation of [soluble guanylate cyclase] may be more effective than inhibition of [phosphodiesterase-5], but this hypothesis is still unproven."

They acknowledged certain limitations of the study, including its prospective design and the relatively homogenous patient population. "Other limitations include the lack of a long-term continuation phase, and the absence of mechanistic data allowing identification of patients likely to respond or not respond to switching," they wrote. "Two deaths were observed in this study, which might raise concerns, although neither of the deaths (one due to pneumonia and one due to subdural haematoma) was considered by the investigators to be study drug-related or due to worsening PAH. Given the lack of a control group and the rate of study withdrawals and clinical worsening events, further evaluation to clarify the safety of switching is required."

The study was funded by Bayer AG, Berlin.

Dr. Hoeper and his coauthors disclosed having financial ties to numerous pharmaceutical companies, including Bayer, which makes riociguat.

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Risk factors for PAH identified in lupus patients

BY JEFF EVANS
Frontline Medical News

FROM CHEST ▪ The presence of specific autoantibodies may help to identify the small percentage of patients with systemic lupus erythematosus (SLE) who are at higher risk of developing pulmonary arterial hypertension after SLE diagnosis and may also detect those at lower risk of death, according to findings from a retrospective study of French patients.

Eric Hachulla, MD, of the University of Lille (France) and his coinvestigators reported that 51 SLE patients in the French Pulmonary Hypertension Registry who had a diagnosis of pulmonary arterial hypertension (PAH) confirmed by right heart catheterization were more likely to have the condition if they had anti-SSA and anti-SSB antibodies, compared with a control group of 101 SLE patients without known PAH who were selected from SLE expert centers participating in the registry. Overall, anti-SSA antibodies were present in 62% of PAH patients vs. 40% of non-PAH patients, and anti-SSB antibodies were detected in 27% with PAH, compared with 8% of those without.

Following SLE diagnosis, the 51 SLE patients had a median delay in diagnosis of PAH by about 5 years. Their survival was 89% at 3 years and 84% at 5 years. "Survival appeared to be substantially better than that still observed today in [PAH associated with systemic sclerosis], where estimated 3-year survival is about 50%. Our survival rates are comparable to those reported by Sobanski et al. in the recently published study for the U.K. SLE-PAH cohort (85% at 5 years)," the authors wrote.

In the current study, mortality during 10 years of follow-up was significantly lower among patients who had anti–U1-RNP antibodies than among those who did not (0% vs. 25%; $P = .04$). This finding of improved survival in patients with anti–U1-RNP antibodies mirrored the results reported in the British SLE-PAH cohort study and a 2016 Chinese study, indicating that "the presence of anti–U1-RNP antibodies appears to be a protective factor in terms of survival."

Treatment with hydroxychloroquine followed a trend toward increased survival, but was not statistically significant (hazard ratio, 0.31; 95% confidence interval, 0.09-1.11; $P = .07$).

"These findings must be interpreted with caution due to the small number of untreated patients and require further investigations in other cohorts," the investigators wrote.

But "based on our results on the potential effect of hydroxychloroquine, this treatment might be used in association with the immunosuppressive strategy for SLE-PAH patients."

Read more of the findings in CHEST (2017 Aug 26. doi: 10.1016/j.chest.2017.08.014).

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Prescription-strength ibuprofen worse for BP

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Prescription-strength ibuprofen has a bigger adverse effect on blood pressure than celecoxib or naproxen, a finding that suggests a likely mechanism for the worse cardiovascular event rate documented in ibuprofen-treated arthritis patients in the PRECISION trial, Frank Ruschitzka, MD, said at the annual congress of the European Society of Cardiology.

"Prescription-strength ibuprofen is under pressure – it has a high incidence of new-onset hypertension, particularly when compared to the more selective COX-2 inhibitor celecoxib. Before we did this study, many would have said it's the other way around," observed Dr. Ruschitzka, professor of cardiology at the University of Zurich.

He presented the results of PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement).

"These results will have impact on your daily practice when you go home," the cardiologist said.

PRECISION-ABPM was a prespecified double-blind, randomized, 60-center substudy of the published PRECISION trial, which included 24,081 U.S. patients who needed daily NSAIDs for arthritis and were also at increased cardiovascular risk. They were randomized to the COX-2 inhibitor celecoxib at 100-200 mg b.i.d. or the nonselective NSAIDs ibuprofen at 600-800 mg three times a day or naproxen at 375-500 mg twice daily. Participants also received a proton pump inhibitor to protect against NSAID-related GI bleeding. In the on-treatment analysis, the ibuprofen group was significantly more likely to experience cardiovascular and all-cause mortality and renal events than were those on celecoxib (N Engl J Med. 2016 Dec 29;375[26]:2519-29).

The PRECISION-ABPM substudy included 444 arthritis patients, 92% of whom had osteoarthritis. During the 4-month study, investigators amassed roughly 60,000 automated blood pressure measurements across the three study arms.

The primary outcome was change

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from baseline in mean 24-hour systolic blood pressure (SBP). It increased by 3.7 mm Hg in the ibuprofen group and declined by 0.3 mm Hg in the celecoxib group, while the naproxen group occupied the middle ground with a 1.6–mm Hg increase.

The nearly 4-mm Hg increase in mean 24-hour SBP at 4 months in the ibuprofen group is of sufficient magnitude to be clinically important, Dr. Ruschitzka noted. Fully 23.2% of ibuprofen-treated patients who had normal baseline blood pressure developed hypertension as defined by a mean 24-hour SBP of at least 130 and/or a diastolic blood pressure of at least 80 mm Hg. In contrast, incident hypertension occurred in only 10.3% of the celecoxib group and 19% of naproxen-treated patients. Thus, the likelihood of developing hypertension was 61% less with celecoxib than ibuprofen and 51% less with celecoxib than naproxen.

Not treating chronic arthritic pain to avoid the cardiovascular risk of NSAIDs is not a legitimate option.

"Pain is a cardiovascular risk factor," Dr. Ruschitzka emphasized. "It's unethical not to treat it. If you don't treat pain, the patient's blood pressure goes up, heart rate goes up, and you're driving patients into inactivity."

Although he's convinced there's no such thing as a safe NSAID from a

cardiovascular risk standpoint, the PRECISION and PRECISION-ABPM data show celecoxib is less unsafe than ibuprofen. And as for the oft-heard statement that naproxen is the safest NSAID for the heart, Dr. Ruschitzka commented, "What an urban legend."

Discussant Scott Solomon, MD, director of noninvasive cardiology at Brigham and Women's Hospital, Boston, said that, although PRECISION-ABPM doesn't support the notion that conventional NSAIDs such as naproxen or ibuprofen are any safer than celecoxib, it would be wrong to conclude from the study that celecoxib doesn't affect blood pressure and is safer than the others from a cardiovascular standpoint. That's because the three study drugs weren't compared in an equipotent way. Because of safety concerns, the Food and Drug Administration required that the daily dose of celecoxib be capped at the low end of the therapeutic range, while no such constraints were placed on the two nonselective NSAIDS.

Dr. Ruschitzka discussed his findings in a video interview on www.mdedge.com/chestphysician.

PRECISION-ABPM was sponsored by Pfizer.

Dr. Ruschitzka and Dr. Solomon, who is also a professor of medicine at Harvard Medical School, reported having no financial conflicts of interest regarding their presentations.

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Distinguished CHEST Educators

In keeping with the commitment of the American College of Chest Physicians (CHEST) to be the home of the clinician educator, and supporting CHEST's strategic vision of advancing best patient outcomes through innovative chest medicine education, a new designation intended to provide national-level recognition of excellence in continuing medical education has been established—the innovation award-winning Distinguished CHEST Educator.

Distinguished CHEST Educators are within the top 5% of CHEST's faculty and are recognized for their achievements in making significant and long-term contributions to the design and delivery of CHEST education. With more than 108 ways to educate, these faculty members have exceeded expectations by serving as CHEST committee chairs, vice-chairs, faculty, and peer reviewers for programs such as the CHEST Annual Meeting.

"The greatest achievement I can imagine is seen in the people we train—as that lives on. Real values in medicine live only by being handed down to others. Over the past decade, CHEST has afforded me the privilege to represent the organization on a national platform, and, in doing so, I have been able to refine my own skills and those of my peers, as well as adding both quality and detail to my understanding of how young physicians learn," says Nader Kamangar, MD, FCCP, of UCLA, CHEST member since 2000, and Distinguished CHEST Educator.

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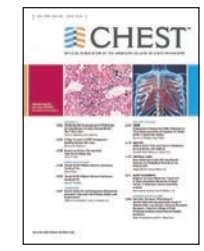
This Month in *CHEST:* Editor's Picks

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



ORIGINAL RESEARCH

Burden of Adult Community-Acquired, Healthcare-Associated, Hospital-Acquired, and Ventilator-Associated Pneumonia: New York City, 2010 to 2014. *By R. E. Corrado, et al.*

Hyperbaric Oxygen Therapy Is Associated With Lower Short- and Long-Term Mortality in Patients With Carbon Monoxide Poisoning. *By C-C Huang, et al.*

EVIDENCE-BASED MEDICINE

Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold: CHEST Expert Panel Report. *By M. A. Malesker, et al, on behalf of the CHEST Expert Cough Panel.*

Cough in Ambulatory Immunocompromised Adults: CHEST Expert Panel Report. *By M. J. Rosen, et al, on behalf of the CHEST Expert Cough Panel.*

Learn About a CHEST Foundation Research Grant Winner

In 2015, Debasree Banerjee, MD, MS, received the CHEST Foundation Research Grant in Pulmonary Arterial Hypertension. She was also a 2016 NetWorks Challenge Travel Grantee as a member of the Women's Health NetWork, allowing her to attend the 2016 CHEST Annual Meeting and network with peers and leaders in chest medicine. Read our follow-up interview with Dr. Banerjee on her research progress and how the grants she's received have impacted her and the work she is doing.

What is the project you have been working on?

I have been researching the role of the specific sodium channel in the heart, how it affects the conductance in patients with pulmonary arterial hypertension, and how it might affect RV function. We know in some sources that about 25% of patients with PAH can die of sudden cardiac death, and sudden cardiac death is more common in patients with left-sided heart disease.

Instead of dying of sudden death or end stage heart failure, we wanted a way to see, just based on a physical exam, if there's evidence of heart pump function not working well. With the funding, I've been able to more than double the sample size of the original pilot data and add in two more large objectives to complement my original aim.

What has receiving the grant meant to you?

One of the reasons I was able to stay at Brown was because of winning this grant from the CHEST Foundation. It was able to cement my interest in fully pursuing a physician scientist career, which is huge, because it is not what I had planned on doing. Because of this grant, I had an 80% protected research position in my first year. Winning the grant gave me a feeling of affirmation and validation, and that certainly motivates me to continue on this path.

Going into fellowship, if you had asked me what I had envisioned myself doing, I would have said I'd be a medical educator. I think I was surprised by my research year in fellowship when I was working on this project, because the grant created so much excitement. I felt like I could actually do this, and obtaining the grant uped the ante of investment and kept me excited. Plus, the grant allowed me to do everything, see the whole process, the full arc, and I'm not even done.

What barriers have you encountered with your research?

Not having all the control, like unplanned hospitalizations or advanced sickness in the patients. There are also things cost-wise that are needed for the research that I wouldn't have had access to without the grant. I didn't do much research in medical school and residency, since I was more focused on teaching, so I hadn't been prepared for the administrative legwork. But, it's something I'm learning.

Being able to follow up with the CHEST Foundation and attend the CHEST annual meeting are exciting ways to overcome any slumps or doubts, because you see the interest and encouragement for the work you're doing. Receiving the travel grant and coming to the annual meeting as a new faculty member, it was the most high-yield conference I've ever attended. Every day, there is something new and interactive for development.

What advice would you give to someone who hasn't received a grant before but is considering applying?

If they can get a good mentor, that's invaluable. It takes perseverance, persistence, and passion, and if you believe your work is having an impact, it's absolutely worth doing. Even if you apply and don't get it the first time, try, try again. I have so much more faith in CHEST because of the positivity I see from the investment in my own mentor, who was a past foundation grant recipient and encouraged me to apply. CHEST gives ample opportunity to network and help to be steered in the right way. As a grant recipient and being folded into the CHEST community, you start to think, "I want this feeling again. Someone thinks this is important work."

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This designation will be granted to select clinical educators each year. The inaugural class of Distinguished CHEST Educators was honored at the end of October at CHEST 2017 in Toronto, as will be the tradition for the classes that follow.

Distinguished CHEST Educator

Congratulations to the inaugural class of Distinguished CHEST Educators.

Sandra Adams, MD, MS, FCCP
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Robert Arntfield, MD, FCCP
Anthony Asciutto, RRT
Olivier Axler, MD, PhD, FCCP
Meyer Balter, MD, FCCP
Gisela Banauch, MD, MS, FCCP
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A Visit With Stephen J. Welch

CHEST Executive Vice President and CEO

Stephen J. Welch was officially appointed Executive Vice President and CEO in April after serving as the interim for both positions since May 2016. Here's a little "inside look" at what Steve is all about.

What is one major accomplishment you hope to achieve as Executive Vice President & Chief Executive Officer?

My goal as EVP/CEO is fairly simple and straightforward: to ensure the organization remains relevant and viable as a leader in providing clinically focused, innovative educational programs and content. I don't really have one accomplishment that I'm focused on, but I do want to ensure that we achieve our annual organizational goals that support CHEST's strategic plan. That may sound a little vague, but it's true. We have so many outstanding programs and initiatives that I'd be doing a disservice to identify a single goal.

How does your previous experience with CHEST help you successfully lead the organization?

With CHEST being a not-for-profit organization, which relies on volunteer leadership and faculty, I think the relationships I've built over the past 23 years within the organization and the chest medicine community are invaluable. I personally know so many of our leadership because I've been part of the organization at the executive level working with them for those 23 years. They know me and how I approach opportunities, address issues, and handle challenges, which has helped build an immediate level of mutual respect, trust, and confidence between the staff and leadership. In addition, there was no disruption from having someone come in from the outside and have to get up to speed. It made the transition pretty seamless for the staff, as well.

During my time at CHEST, I've seen how the organization operates, from the journal, to the annual meeting and board reviews, to the simulation and hands-on skills training, to operational activities like the management of our finances and new global headquarters and training center. I've also had the opportunity to meet with many of our international members and sister societies. Those experiences have allowed me to work closely with many of our faculty, authors, and educators to understand their educational and professional needs, so we can ensure that we meet them.

CHEST is only as good as the education we provide, and it's our subject matter experts who drive that content engine. In my previous role leading the Publishing Division and working on our journal *CHEST*® and programs like SEEK, I've had the honor and pleasure of working with some of the greatest minds in pulmonary, critical care, and sleep medicine. It's humbling.

What will be some of the underlying themes as you work to outline the strategic plan for the next 5 years?

We are in the final stages of planning for 2018 and beyond, and although our proposed roadmap isn't significantly different than what we have been doing, there's some greater emphasis on a few key areas. For example, we're looking at innovations in educational delivery. We've got some very forward thinking faculty educators and staff who are collaborating to develop innovations like gamification of educational and simulation programs, and augmented reality. Globalization and growth are also a key part of our strategic plan, and we are committed to the broad delivery of our educational programs and content both here and around the world. Finally, we have invested

in a data analytics project that is maturing, and we'll be leveraging that information to provide more personalized education plans – not just for the physician but for the entire health-care team. It's important for us to stay relevant and viable.

Why has CHEST shifted to an interdisciplinary, team-focused approach?

I look at it as simply an evolution that reflects how health care is changing. It's a team sport now, and our advanced practice providers (APPs) play a huge role in patient management and care. To be as effective and efficient as possible, and ensure the best patient outcomes, the whole team needs to be on the same page, and we believe that providing education for the interdisciplinary care team will help ensure that the best patient care is delivered.

There's also a need for this education, and we want to fill it. Our APPs tell us that there is no formal pulmonary training or post-masters fellowship in pulmonary medicine for them. They are often left on their own to fill any gaps in knowledge and skills. That's where our CHEST programs, such as our CHEST Annual Meeting, come in. We have an Interprofessional NetWork made up of APPs and physicians, and they were integral in working with the CHEST 2017 Program Committee to ensure plenty of relevant content was offered. Moving forward, we will continue to offer and build interdisciplinary programs designed for the entire team, as well as programs that address clinical issues across disciplines.

What are some of the critical skills CHEST physicians need to keep the population healthy during the ever-evolving field?

Educationally, we recognize that conferences like the annual CHEST meeting must provide more than just talking heads. We've invested heavily in high-fidelity medical simulation through small group, hands-on skill training in critical care techniques, airway management, EBUS, critical care ultrasound, bronchoscopy, and other chest medicine content. It's like the old adage about fishing: instead of telling people how to fish, we teach them to fish.

Any final thoughts?

I always encourage our members to get involved with CHEST and experience the camaraderie and connectivity of the CHEST family. Ask any of our leadership, and you will surely hear their story of that special person who first introduced them to the College. Reach out and tell a colleague about CHEST. We are focused on clinically relevant education that our members can take back and put into action immediately. At the end of the day, it's about providing state-of-the-art education via high fidelity medical simulation, hands-on skills training, clinically focused courses, case-based programming, and more—all intended to be immediately implemented to improve patient care and patient outcomes. That's what the CHEST organization is all about.

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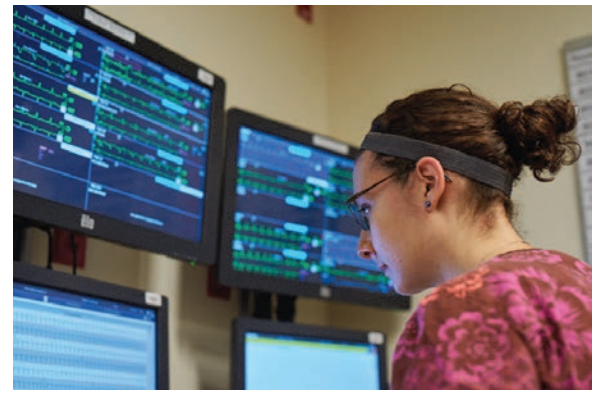

SLEEP STRATEGIES

Lessons Learned From SERVE-HF

BY JAIRO H. BARRANTES, MD

Great attention has been paid to the SERVE-HF trial ("Treatment of Sleep-disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure"), which showed increased all-cause mortality and cardiovascular mortality in the Adaptive Servo-ventilation (ASV) group compared with the control group of conventional heart failure management alone. The results of this trial led to the recommendation by multiple ASV manufacturers and medical societies to withdraw clinical use of ASV from patients with heart failure and a reduced ejection fraction (HFrEF) less than 45%.

Sleep-disordered breathing is common in patients with HFrEF with prevalence rates of 50% to 75%. Central sleep apnea (CSA) is associated with increased mortality in heart failure (HF) and is found in 25% to 40% of this subpopulation. It is estimated that the severity of CSA increases in parallel with the severity of the HF. For several years, treatment of CSA with positive pressure ventilation was believed to favor outcomes in HFrEF with a protective effect.

In the Canadian Positive Airway Pressure for Patients with CSA and HF (CANPAP) trial, subjects were randomized to treatment with CPAP or no CPAP. This trial was terminated early; it did not show an advantage of CPAP in morbidity or mortality. A post-hoc analysis suggested that mortality might be reduced if the frequency of respiratory events per hour or apnea hypopnea index (AHI) is reduced to 15/hour or less while using CPAP.

Hoping to improve the outcomes of HF, SERVE-HF was the first randomized, large scale, multinational trial directed to treat CSA in patients with HFrEF < 45% and concomitant clinically significant sleep apnea with AHI > 15/hour of central predominance (CSA index >10/hour). Treatment arms compared the addition the ASV, one of the most effective noninvasive positive pressure ventilation technologies for central apneas that offers automated inspiratory pressure support in addition to expiratory positive pressure vs conventional medical treatment alone in the control group.

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The study published in the *New England Journal of Medicine* in September 2015 was designed in an intention-to-treat basis with the primary end point of time to first event, a composite of death from any cause, lifesaving cardiovascular intervention (heart transplant, implantation of LVAD, resuscitation after sudden cardiac arrest, or defibrillation for ventricular arrhythmia), or unplanned hospitalization for heart failure. The study did not show significant differences in the primary end point between the ASV and control group (54.1% and 50.8%, respectively; hazard ratio, 1.13; 95% confidence interval, 0.97 to 1.31; P=.10).[1]

The most interesting and unexpected outcome was an increase in the all cause mortality and cardiovascular mortality in the ASV group (hazard ratio for death from any cause, 1.28; 95% CI, 1.06 to 1.55; P=.01; and hazard ratio from cardiovascular death, 1.34; 95% CI, 1.09 to 1.65; P=.006).[1] These findings led to the above recommendations from manufacturers, as well as a position statement from the American Academy of Sleep Medicine. These findings cannot be extrapolated to the obstructive sleep apnea population with concomitant HFrEF or to patients with HF with preserved ejection fraction, where positive pressure ventilation has offered an advantage[1] likely by a different physiologic mechanism not fully uncovered at this time, believed to be an overall effect of afterload reduction.

Selection and self-selection bias in this study was addressed in a new analysis by the same SERVE-HF investigator group published August 2017, where a time-dependent model of on-treatment analysis (done to tease out if the original results were related to the treatment assignment or to poor adherence) was conducted to understand potential causes of the initial findings in the original study. It showed patients randomized to ASV who crossed over to the control group were at higher risk of cardiovascular death than control subjects; also the control patients with crossover to ASV had a signal of lower risk of cardiovascular death risk compared with patients assigned to ASV.[2]

Reduced adherence to ASV treatment during SERVE-HF was a concern, since it resulted in a reduced exposure to the treatment. The on-treatment analysis showed again an increase of cardiovascular death in HFrEF patients with predominant CSA treated with ASV in addition to conventional heart failure treatment compared with the control group.[2] There was no increase in cardiovascular death risk associated with ASV use intervals (dose effect). This effect is not related to the amount of hours used per night.

The effect of the recommended withdrawal of treatment in HFrEF patients with EF<45% and moderate to severe central predominant sleep apnea is being addressed in smaller studies. A single center retrospective analysis observed the effects after ASV discontinuation in this population. Thirteen out of 126 patients treated with ASV who met SERVE-HF criteria were followed for at least a year; 93% of the subjects who met criteria had ASV removed; immediate recurrence of the central apnea was observed in most (except two patients), while adverse events were

not identified (defined as need for emergency hospitalization). Day and nighttime symptoms were reported by 61% of the group, and they were started on alternative treatments.[3] At 1 year after ASV removal, 88% of patients were still alive, overall cardiac function did not change in 1 year (P=0.17), and seven patients required adjustment of medications for heart failure. Symptomatic patients were treated with oxygen supplementation for nocturnal symptoms or CPAP if they had daytime sleepiness. None was treated with bi-level PAP, acetazolamide, or phrenic nerve stimulation. Four patients insisted on continuation of ASV despite understanding physician concerns. [3] This study helps to demonstrate that ASV discontinuation is feasible but requires close follow-up. However, larger, long-term prospective reviews are required to draw statistically meaningful conclusions about the consequences and safety of ASV removal; these studies will be difficult to conduct under the current indications for ASV in the interest group.

At this time, investigators have shifted to further understand the causes of the increase in cardiovascular mortality, overall mortality, and the understanding of the pathophysiologic processes associated with ASV use in HFrEF. It is not known whether the effect in mortality is related to the specific ASV device/algorithm used to suppress CSA or is related to the ASV principle itself. Upcoming studies will assist in clarifying these details. Currently, there is an ongoing trial looking at the effect of ASV on survival and hospital admissions in heart failure (ADVENT–HF) using a different ASV device; this study will hopefully elucidate the impact of class effect vs device effect. It may also provide better insight of the etiology of mortality and the impact of improved ASV compliance, first addressed by the on-treatment analysis of the SERVE-HF.[4]

Although the reasons for increased mortality related to ASV are unclear, proposed hypotheses include: central apnea is an adaptive mechanism to HFrEF and the reversal of central apneas might adversely affect the underlying disease process,[1] low adherence to ASV may impact outcomes, and specific devices may induce hyper-/hypoventilation generated by the algorithm designs of the specific ASV device and this may result in electrolyte abnormalities that generate arrhythmias.

The ADVENT-HF trial, although similar in design, has significant differences from SERVE-HF: different ASV devices may have a different impact on cardiac output and ventilation, recruited patients included those with less daytime sleepiness, and the potential to assess the effect of ASV in patients with OSA and low daytime sleepiness in patients with reduced EF.[5,6] This ongoing study may help us to further understand why there is increased mortality and what effect ASV has on the treatment of sleep apnea in patients with HFrEF.

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