Celebrating 10 Years
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COURTESY DR. MICHAEL J. WAXMAN

ICU patients with COPD and IPF seldom are asked about resuscitation or intensity of care, said Dr. Michael J. Waxman.

ICU palliative care falls short for COPD

BY AMY KARON
Frontline Medical News

Patients with chronic obstructive pulmonary disease or interstitial lung disease have longer stays in the intensive care unit, yet are less likely than patients with metastatic cancer to receive comprehensive palliative care.

This finding, reported in Annals of the American Thoracic Society, underscores the need to expand palliative care programs, incorporate elements of palliative care into routine ICU practices, and identify the most effective components of palliative care, said experts who were not involved in the study.

"Patients with metastatic cancer are more likely to discuss goals of therapy and code status with their inpatient physician and then receive referrals to palliative care," said Michael J. Waxman, MD, FCCP, medical director of the intensive care unit at Research Medical Center in Kansas City. "I can share many anecdotes over the years where a patient is admitted to my ICU with metastatic cancer, or severe COPD [chronic obstructive pulmonary disease] or IPF [idiopathic pulmonary fibrosis]," he added. "The cognition of these patients in some cases may have been normal, but I learned during my re-

See **Palliative care** • *page 10*

CPAP did not reduce cardiovascular events in randomized trial

CPAP duration may have been too short

BY AMY KARON
Frontline Medical News

Adults with moderate to severe sleep apnea and coronary or cerebrovascular disease had about the same frequency of cardiovascular events whether they received continuous positive airway pressure (CPAP) therapy or usual care alone, according to a large randomized trial.

But CPAP was used for only 3.3 hours per night by these patients and might have been "insufficient to provide the level of effect on cardiovascular outcomes that had been hypothesized," Dr. Doug McEvoy of the Adelaide Institute for Sleep Health, Flinders University, Adelaide, Australia and his associates reported at the annual congress of the European Society of Cardiology. Their study was simultaneously published in the New England Journal of Medicine (N Engl J Med. 2016 Aug 28. doi: 10.1056/NEJMoa1606599).

Notably, CPAP did show a trend toward significance in a prespecified subgroup analysis that matched 561 patients who used CPAP for a longer period – more than 4 hours a night – with the same number of controls

See **CPAP** • *page 16*

No renal advantage for vasopressin

BY MARY ANN MOON
Frontline Medical News

Vasopressin was no better than norepinephrine in preventing kidney failure when used as a first-line treatment for septic shock, according to a report published online in JAMA.

In a multicenter, double-blind, randomized trial comparing the two approaches in 408 ICU patients with septic shock, the early use of vasopressin didn't reduce the number of days free of kidney failure, compared with standard norepinephrine.

However, "the 95% confidence intervals of the difference between [study] groups has an upper limit of 5 days in favor of vasopressin, which could be clinically important," said Anthony C. Gordon, MD, of Charing Cross Hospital and Imperial College London, and his associates. "Therefore, these results are still consistent with a potentially clinically important benefit for vasopressin; but a larger

See **Kidney failure** • *page 4*

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- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[2,3]**
- **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]**
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ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{co}$ (percent predicted diffusing capacity of lung for carbon monoxide) between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52. 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%. The primary endpoint was change in %FVC from baseline to week 72.

†Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.

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

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

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

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

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

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

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

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

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

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References: 1. Data on file. Genentech, Inc. 2015. **2.** Esbriet Prescribing Information. Genentech, Inc. September 2015. **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. **5.** Raghu G, Rochwerg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline [published correction appears in *Am J Respir Crit Care Med.* 2015;192(5):644]. *Am J Respir Crit Care Med.* 2015;192(2):e3-e19.

Esbriet®
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Norepinephrine vs vasopressin

Kidney failure *from page 1*

trial would be needed to confirm or refute this."

Norepinephrine is the recommended first-line vasopressor for septic shock, but "there has been a growing interest in the use of vasopressin" ever since researchers described a relative deficiency of vasopressin in the disorder, Dr. Gordon and his associates noted.

"Preclinical and small clinical studies have suggested that vasopressin may be better able to maintain glomerular filtration rate and improve creatinine clearance, compared with norepinephrine," the investigators said, and other studies have suggested that combining vasopressin with corticosteroids may prevent deterioration in organ function and reduce the duration of shock, thereby improving survival.

To examine those possibilities, they performed the VANISH (Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock) trial, assessing patients age 16 years and older at 18 general adult ICUs in the United

Kingdom during a 2-year period.

The study participants were randomly assigned to receive vasopressin plus hydrocortisone (100 patients), vasopressin plus matching placebo (104 patients), norepinephrine plus hydrocortisone (101 patients), or norepinephrine plus matching placebo (103 patients).

The primary outcome measure was the number of days alive and free of kidney failure during the 28 days following randomization.

There was no significant difference among the four study groups in the number or the distribution of kidney-failure–free days, the investigators said (JAMA. 2016 Aug 2. doi: 10.1001/jama.2016.10485).

In addition, the percentage of survivors who never developed kidney failure was not significantly different between the two groups who received vasopressin (57.0%) and the two who received norepinephrine (59.2%).

The median number of days free of kidney failure in the subgroup of patients who died or developed kidney failure was not significantly different between those receiving vasopressin (9 days) and those receiving norepinephrine (13 days).

The quantities of IV fluids administered, the total fluid balance, serum lactate levels, and heart rate were all similar across the four study groups. There also was no significant difference in 28-day mortality between patients who received vasopressin (30.9%) and those who received norepinephrine (27.5%).

Adverse event profiles also were comparable.

However, the rate of renal replacement therapy was 25.4% with vasopressin, significantly lower than the 35.3% rate in the norepinephrine group.

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The use of such therapy was not controlled in the trial and was initiated according to the treating physicians' preference. "It is therefore not possible to know why renal replacement therapy was or was not started," Dr. Gordon and his associates noted.

The use of renal replacement therapy wasn't a primary outcome of the trial. Nevertheless, it is an important patient-centered outcome and may be a factor to consider when treating adults who have septic shock, the researchers added.

The study was supported by the U.K. National Institute for Health Research and the U.K. Intensive Care Foundation.

Dr. Gordon reported ties to Ferring, HCA International, Orion, and Tenax Therapeutics; his associates reported having no relevant financial disclosures.

Intensified rifampicin boosts outcomes in TB/HIV

BY BRUCE JANCIN
Frontline Medical News

DURBAN, SOUTH AFRICA – Prescribing high-dose rifampicin in addition to antiretroviral therapy reduces 12-month all-cause mortality in patients who are coinfected with tuberculosis and HIV and who have a low CD4 cell count, Corinne S. Merle, MD, reported at the 21st International AIDS Conference.

"Current strategies to reduce TB/HIV mortality rely largely on optimal management of HIV disease with early ART [antiretroviral therapy]. We wanted to look at whether there is value in focusing on the TB side of the problem. This is the first study to look at more intensive TB therapy for reducing mortality; and we think that, at least in patients who are immunosuppressed, there might be some benefit in a more aggressive TB treatment from the start," said Dr. Merle of the London School of Hygiene and Tropical Medicine.

She presented the results of the open-label, multicenter trial of 747 ART-naive adults from West Africa. All were coinfected with TB/HIV and had a CD4 count of at least 50 cells/mm^3 at enrollment. They were randomized to one of three treatment arms: ART starting at 2 weeks combined with standard TB treatment; ART starting at 8 weeks plus standard TB therapy; or ART initiation at 8 weeks coupled with 2 months of high-dose rifampicin (Rifadin) at 15 mg/kg daily, followed by standard TB therapy. None of the participants had multidrug-resistant TB. More than one-quarter of them were undernourished as evidenced by a baseline body mass index below 16 kg/m^2. The primary outcome was all-cause mortality at 12 months.

There was no significant difference between the study arms, with a 10% rate in the intensified TB treatment arm and mortality rates of 11% and 14% with standard TB therapy and ART starting after 2 and 8 weeks, respectively. However, a prespecified secondary analysis restricted to the 159 subjects with a baseline CD4 count below 100 cells/mm^3 struck gold. Overall 12-month mortality was 4% in the intensified TB treatment subgroup, compared with 19% in patients on standard TB therapy with ART starting at 2 weeks and 28% with ART starting at 8 weeks. In a Cox regression analysis, severely immunosuppressed patients in the high-dose rifampicin group were an adjusted 88% less likely to die within 12 months than those on standard TB treatment with ART starting at 8 weeks and 80% less likely to die than those starting ART at 2 weeks. At 18 months after randomization, roughly three-quarters of patients in each study arm had undetectable HIV viral loads. There was no evidence of an increased risk of hepatotoxicity with 2 months of high-dose rifampicin. Only 4 of nearly 3,800 aspartate aminotransferase measurements obtained during the trial showed grade 3 or 4 hepatotoxicity, Dr. Merle noted.

In a plenary lecture on TB/HIV coinfection at the AIDS 2016 conference, Anton Pozniak, MD, singled out the trial as a sterling example of how to optimize available clinical management tools while awaiting a desperately needed new TB vaccine and better drugs.

More than 1 million new TB cases occur annually in HIV-infected persons, roughly 80% of them in sub-Saharan Africa. There are now 400,000 deaths per year worldwide in coinfected TB/HIV patients. Indeed, TB has become the No. 1 cause of death among people living with HIV infection, said Dr. Pozniak, director of HIV services at Chelsea and Westminster Hospital in London.

He offered a road map to eliminating TB by the year 2035. At present, the global trend is a 2% per year decline in new cases. Optimizing TB case finding, treatment, and preventive therapy could achieve a 10% per

Continued on following page

FRONTLINE MEDICAL NEWS

Dr. Anton Pozniak

IN THIS ISSUE

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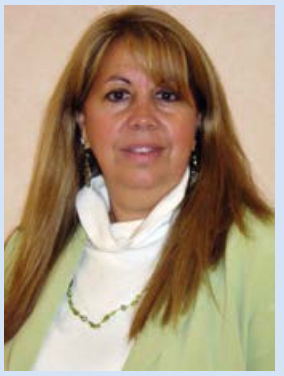

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CMV viremia not culprit in high mortality of TB/HIV

BY BRUCE JANCIN
Frontline Medical News

DURBAN, SOUTH AFRICA – Cytomegalovirus viremia is common among patients hospitalized for HIV-associated tuberculosis, but it appears to be a bystander rather than a contributor to the high mortality seen in this population, Amy Ward, MD, said at the 21st International AIDS Conference.

"CMV [cytomegalovirus] viremia is likely a marker of more severe immunodeficiency rather than a direct contributor to mortality," she concluded based upon the findings of her prospective cohort study. The finding means therapies for CMV viremia will not open up a new avenue of potentially life-saving treatments for these patients.

In other severe immunodeficiency conditions, such as after organ transplant, CMV viremia is directly related to increased mortality, and ganciclovir therapy can prevent progression to clinical disease and death, explained Dr. Ward of the University of Cape Town, South Africa.

She presented a prospective cohort study of 256 HIV-infected South African adults, median age 36 years, who were hospitalized with a new diagnosis of TB. At enrollment, their median CD4 count was 64 cells/mm^3. Only 35% were on antiretroviral therapy (ART); 44% had previously been on ART, 21% were ART-naive, and 41% had a positive TB blood culture.

CMV viremia was present in 31%, and CMV viral load was 1,000 copies/mL or more in half of them. None had CMV retinitis, based on panoptic fundoscopy at enrollment. HIV-related retinal pathologies at enrollment included disseminated cryptococcal disease, ocular TB granules, and HIV retinitis.

CMV [cytomegalovirus] viremia is likely a marker of more severe immunodeficiency rather than a direct contributor to mortality. Therapies for CMV viremia will not open up a new avenue of potentially life-saving treatments for these patients, Dr. Merle said.

The primary endpoint of the study was mortality at 12 weeks on anti-TB therapy. The mortality rate was 38% in the CMV viremic group, significantly higher than the 17.8% mortality rate seen in the CMV-negative patients.

In a univariate Cox proportional hazards regression analysis, CMV viremia was associated with a 2.1-fold increased risk for 12-week mortality. But advancing age, a low CD4 count, and decreasing serum albumin were also risk factors.

When these variables were incorporated in a multivariate regression analysis along with HIV viral load, tuberculosis blood culture results, and gender, CMV viremia was no longer a significant risk factor for 12-week mortality. Age was the sole significant predictor of death. Patients who were at least 36 years old had a 32.8% mortality rate, compared with a 14.1% rate in those who were younger. The CD4 count didn't differ significantly by age; however, the prevalence of CMV viremia was 38% in the older group and 26.3% in patients under age 36.

"Those patients who were 36 years old and above had a higher mortality and were more likely to have CMV viremia, both findings perhaps reflecting premature aging of the immune system," Dr. Ward said.

Also, no dose-response was seen between CMV viral load and mortality risk. The 12-week mortality rate was 33.3% in patients with a CMV viral load below 1,000 copies/mL and similar at 34.1% in those with a viral load above that cutpoint, she noted.

The study was funded by the Wellcome Trust and the South African Medical Research Council. Dr. Ward reported having no financial conflicts of interest.

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Continued from previous page

year decrease in new cases. That rate still wouldn't reach the goal by 2035. But more than a dozen candidate TB vaccines are in the developmental pipeline, including a mycobacterial whole cell extract in phase III testing in China. If a new vaccine can be introduced by 2025, that would be a game changer.

"A new vaccine that could prevent adolescents and adults from developing and transmitting TB would be the single most cost-effective tool in mitigating the epidemic," he said. "Even if we had only a 60% efficacious vaccine and delivered it to 20% of the target population, it could potentially avert 30-50 million incident cases of TB by 2050."

A new vaccine plus effective alternatives to the standard 6 months of isoniazid for latency prophylaxis by 2025 are estimated to reduce new cases of TB by an average of 17% per year. That circumstance would mean the end of TB by 2035, Dr. Pozniak declared.

The trial was funded by the European and Developing Countries Clinical Trials Partnership. Dr. Merle reported having no financial conflicts of interest.

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Flu vaccine prevented hospitalizations in patients age 50 and older

BY MARY ANN MOON
Frontline Medical News

The seasonal influenza vaccination reduced flu-related hospitalizations by 56.8% among people aged 50 and older during a recent flu season, according to a report published in Clinical Infectious Diseases.

Even in the oldest age group – the population with the highest risk of developing flu complications and perhaps the weakest immune response – influenza vaccination prevented serious complications, said Fiona P. Havers, MD, of the influenza division, Centers for Disease Control and Prevention, Atlanta, and her associates.

Data on vaccine efficacy in older adults are sparse, and randomized, placebo-controlled trials would be unethical. Dr. Havers and her colleagues studied the issue using a case-control design, focusing on community-dwelling adults aged 50 years and older during the 2010-2011 flu season. They identified 368 patients across 10 states who were hospitalized for polymerase chain reaction–confirmed influenza and matched them for age and county of residence with 773 control subjects.

Dr. Fiona Havers

Hospitalized case-patients were less likely to have been vaccinated (55%) than were control subjects (63%). Thus, the flu vaccine reduced the risk of hospitalization for influenza by 56.8% overall.

Vaccination reduced hospitalization for influenza by 63.9% in the youngest age group (50-64 years), by 61.0% in the intermediate age group (65-74 years), and by 57.3% in the oldest age group (75 years and older).

These results are similar to those reported in other studies of adults in the United States and Europe assessing the same time period. They also are consistent with the results of observational studies performed during different flu seasons, the investigators said (Clin Infect Dis. 2016 Aug 2. doi: 10.1093/cid/ciw512).

Compared with control subjects, case-patients were more likely to be of nonwhite race, to be of Hispanic ethnicity, to have a lower income, to have had fewer years of education, to have two or more chronic health conditions, to have required recent hospitalization for respiratory problems, to have impaired mobility, and to have lower functional status.

"These findings support current U.S. recommendations for annual influenza vaccination in older adults, especially in adults aged 65 and older who are at higher risk of influenza-associated complications," Dr. Havers and her associates said.

The Centers for Disease Control and Prevention supported the study.

Dr. Havers reported having no relevant financial disclosures. One of her associates reported ties to Genentech, Merck, Novavax, and Pfizer.

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References: 1. ProAir RespiClick Prescribing Information. Horsham, PA: Teva Respiratory, LLC; April 2016. **2.** ProAir RespiClick Patient Information Leaflet. Horsham, PA: Teva Respiratory, LLC; April 2016.

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COPD, ILD patients underserved

Palliative care *from page 1*

view that they did not receive a good discussion of desires regarding resuscitation or intensity of care. It was regularly assumed that there would be no limits on intensity of care."

Palliative care historically has focused on patients with cancer, even though mortality rates can be high in noncancer lung disease, Crystal Brown, MD, and her associates at the University of Washington in Seattle wrote in their article (Ann Am Thorac Soc. 2016;13:684-9.). Their secondary analysis of the randomized Integrating Palliative and Critical Care trial examined medical chart data for 592 patients with COPD, 158 patients with metastatic cancer, and 79 patients with interstitial lung disease (ILD) who died in the ICUs of 15 Seattle-area hospitals between 2003 and 2008. The investigators performed regression modeling to test associations between diagnosis and eight elements of palliative care – avoidance of cardiopulmonary resuscitation during the hour before death, pain assessment during the 24

hours before death, the presence of a do-not-resuscitate order at the time of death, discussion of prognosis within 72 hours of ICU admission, withdrawal of life support measures before death, involvement of a spiritual care provider, consultation with a palliative care specialist, and the presence of an advance directive. The statistical models controlled for many potential confounders, including age, sex, race and ethnicity, education level, hospital, and whether patients died before or after hospitals implemented a palliative care quality improvement intervention.

Even though median lengths of ICU stay were significantly longer for ILD patients (4.2 days) and COPD patients (2.9 days) than for metastatic cancer patients (2.3 days), patients with COPD were significantly less likely to avoid CPR in the hour before death (adjusted odds ratio, 0.43; 95% confidence interval, 0.20-0.90), while ILD patients were less likely to have a documented pain assessment in the 24 hours before death (OR, 0.43; 95% CI, 0.19-0.97), compared with metastatic cancer patients. Patients with ILD or COPD also were significantly less likely to have a do-not-resuscitate order in place or documentation of a discussion of their prognosis, Dr. Brown and her associates reported.

The findings raise several concerns. "Clearly, this points to both intensivists and palliative care consultants needing to do more to target patients with nonmalignant end-stage chronic lung diseases, such as some patients with COPD and ILD," said Robert Hyzy, MD, FCCP, director of the critical care medicine unit at the University of Michigan Hospital, Ann Arbor.

The difference in length of stay also suggests a need to recognize earlier when critically ill patients have not responded to an appropriate time period of treatment (sometimes called a "time-limited trial"), "which signals the transition from cure to comfort," he added.

Vera De Palo, MD, MBA, FCCP, who is chief of medicine at Signature Healthcare Brockton (Mass.) Hospital, agreed.

"While treatment plans for patients with end-stage ILD and COPD do at times include palliative care, the study points out what is often the experience for most patients," she said. "Our oncology colleagues have better understood the time line of transition between curative care and palliative care than those of us who also manage noncancer chronic diseases. They are more likely to participate in the development of palliative care programs, ensuring that this avenue of care is also available to their patients."

This is not the only study to reveal gaps in palliative care for advanced nonmalignant lung disease. In a recent analysis of the Nationwide Inpatient Sample, only 2.6% of COPD patients who were home on oxygen and then were hospitalized with an exacerbation received a palliative care referral (CHEST. 2016 Jul 4. doi:10.1016/j.chest.2016.06.023). Such findings belie the most recent palliative care guidelines from the American Thoracic Society for patients with respiratory diseases and critical illnesses, which not only emphasize most of the same palliative care elements as the study by Dr. Brown and her colleagues, but also recommend "early consultation" with palliative care experts to help manage difficult end-of-life discussions (Am J Respir Crit Care Med. 2008;177:912-27).

Continued on following page

Continued from previous page

Oncology palliative care includes both primary and secondary (specialty-level) services, Arif Kamal, MD, of Duke Cancer Institute at Duke University Medical Center, Durham, N.C., and his associates wrote in a viewpoint published in JAMA. Primary services, such as assessing and managing symptoms, discussing priorities and what to expect, and ensuring continuity of care, are usually left to the oncology team. Secondary services are reserved for more complex or time-consuming cases and are provided by palliative care consultants. "This 'manage first, refer second' practice reflects the ethos of the oncology profession – the notion that 'this is our job' – while also reflecting a practical humility – 'It's hard to be everything to everyone all the time,'" Dr. Kamal and his associates wrote.

When it comes to palliative care for advanced nonmalignant lung disease, Dr. De Palo said, patients and families may not feel ready to discuss end-of-life issues, and providers may find it difficult to initiate these conversations. "From the moment of diagnosis, the focus of a patient's care for providers is curative care." Including a palliative focus can be difficult.

Nonmalignant pulmonary diseases often carry an "uncertain short-term prognosis," the ATS guidelines stated, and experts echoed that point. "I believe our confidence in determination of prognosis is a key factor in hesitation or delay in engaging palliative care," said David Bowton, MD, FCCP, a professor specializing in critical care at Wake Forest School of Medicine, Winston-Salem, N.C. Oncology patients needing ICU care usually have "considerably higher" mortality than the rates of 20%-45% and 15%-30% that are cited for ILD and COPD patients, respectively, he said. Furthermore, there are seemingly accurate scoring systems for predicting short-term mortality in critically ill cancer patients, which is not the case for ILD or COPD, he added.

Such factors point to differences in disease trajectory. "In this study, it is likely that the patients with cancer diagnoses more often received the elements of palliative care in the ICU because it was clearly communicated to the intensive care providers that the opportunities for curative care were exhausted," Dr. De Palo said. "With care for end-stage chronic respiratory diseases, ICU care can usually optimize breathing enough to get the patient off the vent and stabilized at their previous functional plateau or, more often, at a lower functional plateau, until the next shortness of breath episode."

Given these challenges and uncertainties, how can clinicians improve palliative care for patients with advanced nonmalignant lung diseases? "Simple. Have a discussion with everyone about what their expectations are," said Dr. Waxman. "Find out what is important to them and what their goals of therapy are. Help them understand the reality of what actually will be possible to accomplish in a hospitalization, a surgery, or a therapy."

Dr. De Palo agreed. "For my patients with end-stage respiratory disease, we often discuss whether a sustaining therapy of mechanical ventilation would offer any benefit, and what role cardiopulmonary resuscitation should play in the context of their wishes for care as their disease progresses," she said. "I believe that providers and health care organizations should offer patients the spectrum of curative and palliative

care, and work together to develop a palliative care program where one does not exist," she stressed. Access to "the full spectrum of care – from curative to palliative – will provide the compassion and quality of life at each stage of their chronic disease."

Intensivists should also ensure that all ICU patients receive consultations with providers "who can look more at the big picture of their health care, not just at their admission diagnosis and the specific treatment they are receiving," Dr. Waxman said. Dr. Bowton offered the final caveat: "While it appears obvious that providing palliative care consultation or integrating elements of palliative care into our routine ICU care will improve the experience for our patients and their families, this has been difficult to demonstrate in well-designed studies. Thus, rather than focusing solely on our apparent shortcomings in providing palliative care to our ICU patients with ILD and COPD, we should vigorously support efforts to ascertain what components of palliative care and what 'dose' are most effective in alleviating physical and emotional distress." The National Institute of Nursing Research funded the study by Dr. Brown and her associates, who reported no relevant financial conflicts of interest.

Formoterol addition not tied to more asthma events

BY MARY ANN MOON
Frontline Medical News

Adding formoterol to budesonide in a fixed-dosecombination does not increase serous asthma-related events in adolescents and adults, according to a report published online in the New England Journal of Medicine.

This finding from a multicenter randomized double-blind clinical trial involving 11,693 patients should allay safety concerns about adding long-acting beta-agonists to inhaled glucocorticoids in moderate to severe asthma.

Previously, two large studies linked such additive therapy to increased asthma-related deaths and other serious outcomes, but other clinical trials and numerous meta-analyses found no such increase.

In 2009, the Food and Drug Administration mandated that the four manufacturers of long-acting beta-agonists available in the United States conduct postmarketing safety analyses of these agents. The current trial is AstraZeneca's response to the mandate, said Stephen P. Peters, MD, PhD, FCCP, of Wake Forest University, Winston-Salem N.C., and his associates.

They assessed patients aged 12 years and older who had taken daily asthma medication for at least 1 year before enrollment and had a history of at least one exacerbation during that year. These participants were enrolled at 534 medical centers in 25 countries during 2011-2015 and randomly assigned to receive either budesonide plus formoterol (5,846 patients) or budesonide alone (5,847 patients) through an inhaler twice daily for 26 weeks. The primary endpoint was a composite of asthma-related death, intubation, and hospitalization.

A total of 43 patients in the combined-therapy group had 49 serious asthma-related events, while 40 patients in the budesonide-only group had 45 such events. This is a nonsignificant difference and establishes the noninferiority of the combined treatment regarding this outcome, the investigators said (N Engl J Med. 2016 Sept 1. doi: 10.1056/NEJMoa1511190).

In addition, 539 (9.2%) of the patients in the combined-therapy group reported 637 asthma exacerbations, while 633 in the budesonide-only group had 762 exacerbations. Thus, the risk of having an asthma exacerbation was 16.5% lower with combined therapy (HR, 0.84).

Both study groups had a clinically relevant improvement in asthma control as measured by the ACQ-6, and the combined therapy yielded a significantly greater benefit. The percentage of patients who had a clinically relevant improvement in asthma control at the conclusion of treatment also favored budesonide plus formoterol (58.7% vs. 54.4%). And the combined-therapy group also had a greater mean number of symptom-free days, had fewer nighttime awakenings, and used fewer doses of rescue medications, Dr. Peters and his associates said.

Dr. Peters and his associates reported ties to numerous industry sources.

SLEEP STRATEGIES: Sleep apnea and myocardial preconditioning: A paradigm shift?

BY NEOMI SHAH, MD, MPH

COURTESY DR. SHAH

"Despite the convincing cardioprotective discoveries from ischemic and hypoxic preconditioning, translation into clinical practice as a therapeutic modality is absent," Dr. Shah said.

The phenomenon of preconditioning reflects complex adaptive responses by living organisms to stimuli such as ischemia, hypoxia, hypothermia, or starvation. Acute ischemic preconditioning, initially described by Murry in 1986 (*Circulation*. 1986;74[5]:1124) occurs when multiple brief episodes of ischemia followed by reperfusion elicit a protective effect on the heart from a subsequent prolonged period of ischemia, such as a heart attack. This protective effect from ischemic preconditioning can be in the form of a smaller heart attack, lower chance of cardiac arrhythmias, less myocardial cell death, and lower risk of heart muscle failure. The cardioprotective effect of ischemic preconditioning is dependent on the duration and strength of the preconditioning stimulus. If the preconditioning stimulus is too strong or prolonged, detrimental effects on the heart may be observed.

Like ischemic preconditioning, hypoxic preconditioning represents a complex adaptive response that organisms have developed to offset damage inflicted by oxygen deprivation. The concept of hypoxic preconditioning is familiar to humans; for years, athletes have been using hypoxic training (high altitude and other newer technologies) to boost their performance in sporting events. Additionally, there is evidence dating back to before the breakthrough findings of Murry and colleagues who confirm the cardioprotective effects of hypoxia. In 1973, Meerson and colleagues (*Am J Cardiol*. 1973;31[1]:30) reported that mice exposed to high-altitude hypoxia have reduced mortality and smaller areas of necrotic myocardium after coronary artery occlusion.

Both of the ischemic and hypoxic preconditioning animal experiments mentioned above involve acute exposure to the preconditioning stimuli, resulting in a cardioprotective response for a limited time period. In order to afford a sustained period of cardioprotection, recurrent hypoxic exposure may be necessary. Indeed, recent studies have concentrated on just that; repeated exposure to intermittent hypoxia over a few weeks (Manukhina et al. *Exp Biol Med*. 2013;238[12]:1413) resulted in robust cardioprotection after coronary artery occlusion and reperfusion.

Like ischemic preconditioning, hypoxic preconditioning represents a complex adaptive response that organisms have developed to offset damage inflicted by oxygen deprivation. For years, athletes have been using hypoxic training (high altitude and other newer technologies) to boost their performance.

Despite the convincing cardioprotective discoveries from ischemic and hypoxic preconditioning, translation into clinical practice as a therapeutic modality is absent. This is partly because human beings are more complex than animals. They have comorbidities and are affected by aging, both of which may alter the milieu for preconditioning stimuli. Furthermore, the therapeutic range for any given preconditioning stimulus is unknown.

Sleep apnea (SA) is exceedingly prevalent in the United States. In SA, an individual stops breathing either completely (apnea) or partially (hypopnea) during sleep, resulting in intermittent hypoxia, with arousal from sleep and resumption of breathing leading to reoxygenation. Hence, SA is characterized by intermittent hypoxia followed by reoxygenation. So, one can speculate that SA could exert cardioprotective effects as seen in hypoxic preconditioning and ischemic preconditioning. It is important to note, however, that SA is associated with hypercapnic intermittent hypoxia, whereas most of the investigations on ischemic preconditioning and intermittent hypoxia are with eucapnia or hypocapnia.

The potentially cardioprotective role of SA is supported by a growing body of complementary research that indicates that coronary collateral flow is higher in patients with SA vs control subjects (Steiner. *Chest*. 2010;137[3]:516) and that there is an increased mobilization, proliferation, and angiogenic capacity of endothelial progenitor cells from patients with myocardial infarction and SA as compared with cells from control subjects without SA (Berger. *Am J Respir Crit Care Med*. 2013;187[1]:90). Some epidemiologic data support a weaker relationship between SA and coronary ischemic events compared with other cardiovascular events (Gottlieb. *Circulation*. 2010;122[4]:352). Hypoxic preconditioning may explain the relatively decreased pro-thrombotic influence of SA in the coronary vascular bed. Nevertheless, more research is needed to determine if SA is cardioprotective. If, however, cardioprotection from SA is confirmed, it may contribute to a paradigm shift in how SA is considered in relation to coronary heart disease. Furthermore, future investigations would need to focus on what dose and duration of SA is needed for cardioprotection to occur. Prospective studies may also provide an opportunity for investigating interindividual variability in the susceptibility of the myocardium to the hypoxic preconditioning stimulus from SA.

This article highlights how complex the relationship between hypoxia and myocardial response is. This is further supported by results from a recent clinical trial, AVOID (Air Versus Oxygen In ST-elevation MyocarDial Infarction) (Stub. *Circulation*. 2015;131[24]:2143). Results from the AVOID trial report that routine oxygen use in normoxic patients hospitalized with a heart attack was not beneficial and, in fact, was harmful. Patients who received oxygen had more myocardial injury than those who did not.

Therefore, even though for decades we thought that oxygen therapy helps hospitalized heart attack patients, results from the AVOID trial have initiated a paradigm shift. It remains to be determined whether such a paradigm shift will follow for sleep apnea.

Dr. Shah is with the department of epidemiology and population health, Albert Einstein College of Medicine, N.Y.

No decrease in cardiac events

CPAP *from page 1*

(hazard ratio, 0.8; 95% CI, 0.6 to 1.1; $P = .1$). Dr. McEvoy discussed the implications of prolonged CPAP use in a video interview with Bruce Jancin, our reporter at the ESC Congress in Rome.

Obstructive sleep apnea causes episodic hypoxemia, sympathetic nervous system activation; intrathoracic pressure swings strain the heart and great vessels, and increases markers of oxidative stress, hypercoagulation, and inflammation.

Randomized trials have linked CPAP therapy to lower systolic blood pressure measures and improved endothelial function and insulin sensitivity.

Observational studies suggest that CPAP might help prevent cardiovascular events and death if used consistently, the investigators noted.

Because cardiovascular disease and obstructive sleep apnea often co-occur, the researchers carried out a secondary prevention trial, Sleep Apnea Cardiovascular Endpoints (SAVE), to quantify rates of major cardiovascular events among 2,717 adults aged 45-75 years with obstructive sleep apnea and established coronary or cerebrovascular disease. Patients were randomly assigned to receive CPAP therapy plus usual care, or usual care alone. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization from unstable angina, transient ischemic attack, or heart failure.

The researchers also looked at other cardiovascular outcomes, snoring symptoms, mood, daytime sleepiness, and health-related quality of life. They used a 1-week run-in period of sham CPAP (administered at subtherapeutic pressure) to ensure what they considered an adequate level of adherence.

The average apnea-hypopnea index (that is, the average number of apnea or hypopnea events recorded per hour) was 29 at baseline and 3.7 after initiating CPAP, the investigators said.

At a mean of 3.7 years of follow-up, 17% of CPAP users (220 patients) and 15.4% of controls had a cardiovascular event, for a hazard ratio of 1.1 (95% confidence interval, 0.9 to 1.3; $P = 0.3$).

Not only did CPAP fail to meet the composite primary endpoint, but it did not significantly affect any cause-specific cardiovascular outcome, the researchers said.

However, CPAP users did improve significantly more than controls on measures of daytime sleepiness (the Epworth Sleepiness Scale), anxiety and depression (Hospital Anxiety and Depression Scale), self-reported physical and mental health (Short-Form Health Survey), and quality of life (European Quality of Life-5 Dimensions questionnaire). They also missed fewer days of work than did controls.

Study funders included the National Health and Medical Research Council of Australia, Respironics Sleep and Respiratory Research Foundation, and Phillips Respironics.

Dr. McEvoy reported receiving research equipment for the study from AirLiquide.

Several coinvestigators reported other ties to industry.

VIEW ON THE NEWS

CPAP might not have been used long enough

This trial raises several issues. One major issue is whether the results were negative because obstructive sleep apnea does not have clinically significant adverse cardiovascular effects or because the patients did not use CPAP for a long enough duration each night to derive cardiovascular benefits. Given the substantial human and animal data that have consistently documented links between obstructive sleep apnea and cardiovascular health, we suspect that mean CPAP duration may have been inadequate at 3.3 hours per night, which is probably less than half the time the patient was asleep.

What do these results mean for clinical practice? We believe that symptomatic patients with obstructive sleep apnea should be offered a trial of CPAP therapy. However, on the basis of results from the SAVE trial, prescribing CPAP with the sole purpose of reducing future cardiovascular events in asymptomatic patients with obstructive sleep apnea and established cardiovascular disease cannot be recommended. Ongoing clinical trials will shed further light on the effects of CPAP therapy in nonsleepy patients with obstructive sleep apnea and acute coronary syndromes.

Babak Mokhlesi, MD, is with the Sleep Disorders Center at the University of Chicago. Najib Ayas, MD, is with the Sleep Disorders Program at the University of British Columbia, Vancouver. The remarks are excerpted from their editorial (N Engl J Med. 2016 Aug 28. doi: 10.1056/NEJMe1609704).

CHICA addresses shortfall of OSA screening in children

BY BRUCE JANCIN
Frontline Medical News

DENVER – Screening practices vary widely and frequently diverge from practice guidelines for children with suspected obstructive sleep apnea, Sarah M. Honaker, PhD, said at the annual meeting of the Associated Professional Sleep Societies.

The American Academy of Pediatrics and American Academy of Sleep Medicine recommend that children with frequent snoring be referred for a sleep study or to a sleep specialist or otolaryngologist. But the identification rate of suspected OSA was abysmally low in Dr. Honaker's study of 8,135 1-12 year olds seen at five university-affiliated urban primary care pediatric clinics.

To assist primary care providers in following evidence-based practice for pediatric OSA, Dr. Honaker, of Indiana University in Indianapolis, and her coinvestigators have developed a computer decision support system called CHICA (Child Health Improvement through Computer Automation). While in the clinic waiting room, the child's parent uses a tablet ot complete 20 yes/no items designed to identify priority areas to address during the visit. The items are individually tailored to the child's age, past medical history, and previous responses.

One item asks if the child snores three or more nights per week. If the answer is yes, CHICA instantly sends a prompt to the child's electronic medical record noting that the parent reports the child is a frequent snorer and this might indicate OSA.

Parental cooperation with CHICA was high: 98.5% of parents addressed the snoring question. They reported that 28.5% of the children snored at least 3 nights per week, generating a total of 1,094 CHICA prompts to the primary care providers. Nearly half (44%) of providers didn't respond to the prompt, which Dr. Honaker said is a typical rate for this sort of computerized assist intervention. Of those who did respond, 16% suspected OSA, 63% didn't suspect OSA, and the remainder said the parent in the examining room didn't report frequent snoring.

A 16% rate of suspected OSA is a low figure for frequent snorers. Moreover, 31% of children who got the CHICA frequent snoring prompt were overweight or obese, and 17% had attention-deficit hyperactivity disorder symptoms, both known risk factors for OSA. Some of the kids had both risk factors, but 39% had at least one in addition to their frequent snoring, Dr. Honaker noted.

The investigators carried out multivariate logistic regression analyses of child, provider, and clinic characteristics in search of predictors associated with physician concern that a child might have OSA. It turned out that none of the provider characteristics, such as specialty or years in practice, had any bearing on the rate of identifying possible pediatric OSA. Some physicians never suspected OSA, others did so in nearly 50% of children flagged by the CHICA prompt.

The only relevant patient factor was age: children aged 1-2.5 years were 73% less likely to generate physician suspicion of OSA.

"Surprisingly, none of the patient health factors were predictive. So having ADHD symptoms or being overweight or obese did not make it more likely that a child would elicit concern for OSA," Dr. Honaker observed. However, which of the five clinics the child attended turned out to make a big difference. Rates of suspected OSA in children with a CHICA snoring prompt ranged from a low of 5% at one clinic to a high of 27% at another.

Dr. Honaker said the Indiana University experience is hardly unique. Despite documented high rates of pediatric sleep disorders in primary care settings, screening and treatment rates are low. Primary care physicians receive little training in sleep medicine (Sleep Med Rev. 2016;25:31-9). Her study was funded by the American Sleep Medicine Foundation. She reported having no financial conflicts.

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Sleep apnea increases subsequent Alzheimer's risk

BY BRUCE JANCIN
Frontline Medical News


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DENVER – Obstructive sleep apnea diagnosed later in life is associated with an increased likelihood of subsequent Alzheimer's disease, Dr. Omonigho Bubu reported at the annual meeting of the Associated Professional Sleep Societies.

He presented a retrospective cohort study in which a dose-reponse relationship was apparent. The more severe an individual's obstructive sleep apnea (OSA) as reflected in a higher apnea-hypopnea index on polysomnography, the greater the risk of later being diagnosed with Alzheimer's disease, compared with matched controls during up to 13 years of follow-up.

The study also identified several possible contributing factors for the observed OSA/Alzheimer's relationship. Those OSA patients with more severe sleep fragmentation, nocturnal hypoxia, and abnormal sleep duration were significantly more likely to subsequently develop Alzheimer's disease than were OSA patients with less severely disrupted sleep measures, added Dr. Bubu of the University of South Florida, Tampa.

The study included 756 patients aged 65 years and older with no history of cognitive decline when diagnosed with OSA by polysomnography at Tampa General Hospital during 2001-2005. They were matched by age, race, sex, body mass index, and zip code to two control groups totaling 3,780 subjects. The controls, drawn from outpatient medical clinics at the hospital, had a variety of medical problems but no sleep disorders or cognitive impairment.

During a mean 10.5-year follow-up period, 513 subjects were diagnosed with Alzheimer's disease, according to Medicare data. In a Cox proportional hazards analysis adjusted for age, sex, race, body mass index, and education level, OSA was independently associated with a 2.2-fold increased risk. Further adjustment for alcohol intake, smoking, use of sleep medications, and chronic medical conditions didn't substantially change the results.

However, the investigators were not able to control for apolipoprotein E (APOE)–epsilon 4 allele status, which is a known risk factor for both OSA and Alzheimer's disease, so it makes one wonder whether the association is "all related to APOE," said Dr. Richard J. Caselli, professor of neurology at the Mayo Clinic, Scottsdale, Ariz., when asked to comment on the study.

Our results definitely show that OSA precedes the onset of Alzheimer's disease.

DR. BUBU

Time to onset of Alzheimer's disease was shorter in the OSA patients: The mean time to diagnosis was 60.8 months after diagnosis of OSA, compared with 73 and 78 months in members of the two control groups who developed the dementia.

When the risk of developing Alzheimer's disease was stratified according to baseline OSA severity, a dose-response effect was seen. Mild OSA, defined as 5-14 apnea-hypopnea events per hour of sleep, was associated with a 1.67-fold greater risk than in controls. The moderate OSA group, who had 15-29 events per hour, had a 1.81-fold increased risk. Patients with severe OSA, with 30 or more events per hour, had a 2.63-fold increased risk.

Gender, race, and education modified the relationship between OSA and Alzheimer's disease, Dr. Bubu said. Women with OSA had a 2.28-fold greater risk of later developing the disease, compared with controls; men had a 1.42-fold increased risk. African-Americans with OSA were at 2.56-fold greater risk than were controls, while Hispanics with OSA were at 1.8-fold increased risk and non-Hispanic whites were at 1.87-fold increased risk. OSA patients with a high school education or less were at 2.73 times greater risk of Alzheimer's disease than were controls, those with at least some college or technical school were at 1.82-fold risk, and OSA patients who'd been to graduate school had a 1.31-fold increased risk.

"Our results definitely show that OSA precedes the onset of Alzheimer's disease. But we cannot say that's causation. That will be left to future research examining the potential mechanisms we've identified," Dr. Bubu said in an interview.

A key missing link in establishing a causal relationship is the lack of data on how many of the older patients diagnosed with OSA accepted treatment for the condition, and what their response rates were. In other words, it remains to be seen whether OSA occurring later in life is a modifiable risk factor for Alzheimer's disease as opposed to an early expression of the dementing disease process whereby treatment of the sleep disorder doesn't affect the progressive cognitive decline.

Both short sleep duration of less than 6 hours as well as a mean total sleep time greater than 9 hours in patients with OSA were associated with significantly increased risk of Alzheimer's disease, compared with a sleep time of 6-9 hours. Patients with a high sleep-onset latency in the sleep lab, a high REM latency from sleep onset, a low percentage of time spent in REM, an oxygen saturation level of less than 90% for at least 1% of sleep time, and/or a high number of arousals per hour of sleep were also at increased risk of subsequent Alzheimer's disease.

The study was supported by the Byrd Alzheimer's Institute.

Dr. Bubu reported having no financial conflicts.

Sleep lab findings associated with subsequent Alzheimer's disease

	Hazard ratio for Alzheimer's
Measures of sleep duration and continuity	
Sleep efficiency <85% vs. 85% or greater	1.48
Total sleep time <6 hr vs. 6-9 hr	1.87
Total sleep time >9 hr vs. 6-9 hr	2.02
<10% time in REM vs. 10-24.9%	1.72
High sleep latency (median, 66 min) vs. low (0.9 min)	1.23
High REM latency from sleep onset (median, 126 min) vs. low (median, 30.9 min)	1.72
Sleep fragmentation measures	
High arousals per hour of sleep (median, 76.4) vs. low (11.9)	1.43
Wake after sleep onset, high (median, 182.3 min) vs. low (46.8 min)	1.74
Hypoxia measures	
Oxygen saturation index of 15 or more vs. less than 15	2.16
Oxygen saturation level below 90% for 1% or more of sleep time	1.14
High percentage of sleep time spent in apnea or hypopnea (median, 22.7%) vs. low (0.4%)	2.21
Mid-range percentage of sleep time spent in apnea or hypopnea (median, 7.8%) vs. low (0.4%)	1.32

Note: The study involved 756 patients aged 65 years and older and 3,780 control subjects.
Source: Dr. Bubu

FRONTLINE MEDICAL NEWS

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Sleep apnea in pregnancy linked to preterm birth

BY BRUCE JANCIN
Frontline Medical News

DENVER – Pregnant women with sleep apnea are more likely to have planned obstetric interventions, results of an Australian population-based cohort study suggest.

The study included all 636,227 in-hospital births during 2002-2012 in New South Wales, Australia's most populous state. Maternal sleep apnea was also associated with increased rates of planned preterm birth, even though preterm birth is widely considered the greatest contributor to neonatal morbidity and mortality, Yu Sun Bin, PhD, said at the annual meeting of the Associated Professional Sleep Societies.

"Somewhere along the line, clinicians decided that the risks of preterm birth to the baby were outweighed by the risks to the mother of delivering at term," said Dr. Bin of the University of Sydney.

The investigators compared maternal and infant outcomes for mothers with a documented diagnosis of sleep apnea – either central or obstructive – in the year before or during pregnancy with outcomes for mothers without that diagnosis. There were 519 mothers with diagnosed sleep apnea, for a prevalence of 0.08%. That figure is low in light of other evidence, making it likely that the 635,708 women in the no-sleep-apnea group actually included a substantial number of mothers with undiagnosed sleep apnea. Thus, the investigators' estimates of the adverse impacts of sleep apnea in pregnancy are "rather conservative," according to Dr. Bin.

Australian women with sleep apnea were older and less healthy than mothers without sleep apnea were. They had higher baseline rates of obesity, preexisting diabetes, chronic hypertension, and were more likely to be smokers.

The incidence of pregnancy hypertension was 19.7% in the sleep apnea group and 8.7% in controls. In a multivariate regression analysis adjusted for potential confounders, the maternal sleep apnea group had a 40% greater risk of developing hypertension than did controls. However, contrary to previous smaller studies, they did not have a significantly increased rate of gestational diabetes. Even after controlling for both pregnancy hypertension and gestational diabetes, the sleep apnea group still had a significant 15% increase in the relative likelihood of a planned delivery.

The rate of preterm birth at 36 weeks or earlier was 14.5% in the maternal sleep apnea group, compared with 6.9% in controls, for an adjusted 1.5-fold increased relative risk. Perinatal death occurred in 1.9% of the sleep apnea group and 0.9% of controls; however, the resultant adjusted 1.73-fold increased risk didn't attain statistical significance because of the small number of deaths in the study.

The incidence of 5-minute Apgar scores below 7 was 4.6% in the sleep apnea group, compared with 2.4% in controls, for an adjusted 1.6-fold increased risk.

The rate of neonatal intensive care unit admission in the sleep apnea group was 27.9%, versus 16% in controls, for a 1.61-fold increased relative risk. For the term babies in the sleep apnea group, the NICU admission rate was 20.3%, compared with 12.1% for the control group. The NICU admission rate for the two groups did not differ among preterm babies.

"This suggests that maternal sleep apnea is contributing to some condition in the baby that requires additional support," Dr. Bin observed. The nature of that condition, however, remains unclear, since all patient data available to the investigators was deidentified.

The incidence of small-for-gestational-age babies was similar in the sleep apnea and control groups. In contrast, the large-for-gestational-age rate was 15.2% in the sleep apnea group, compared with 9.1% in controls, for an adjusted 1.27-fold increased risk.

The two main limitations of the Australian study were the likely underdiagnosis of sleep apnea and the lack of any information on treatment of affected patients, according to Dr. Bin. A key unresolved question, she added, is whether interventions for maternal sleep apnea reduce the risks identified in the New South Wales study.

The Australian National Health and Medical Research Council supported the study. Dr. Bin reported having no financial conflicts.

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Andexanet effective antidote for factor Xa

BY AMY KARON
Frontline Medical News

The factor Xa antidote andexanet achieved effective hemostasis 12 hours after infusion in 79% of patients who had developed serious acute bleeding on factor Xa inhibitor therapy, according to a preliminary analysis of an ongoing study of how reducing anti–factor Xa activity affects clinical hemostatic outcomes.

"The site of bleeding was most often gastrointestinal or intracranial; anti–factor Xa activity was considerably elevated in most patients and, as such, was likely to be a major impediment to clinical hemostasis. The administration of an andexanet bolus and infusion resulted in rapid and substantial reversal of anti–factor Xa activity," Stuart Connolly, MD, of McMaster University, Hamilton, Ont., and his associates reported at the ESC Congress and in a simultaneously published study (N Engl J Med. 2016 Aug 30. doi: 10.1056/NEJMoa1607887).

Andexanet alfa is a recombinant modified human factor Xa decoy protein that "sharply" reduced plasma levels of unbound factor Xa inhibitors as well as anti-factor Xa activity in healthy older volunteers receiving apixaban or rivaroxaban, the researchers noted. Based on those findings, they designed a prospective, multicenter, single-group, open-label study (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors; ANNEXA-4) of andexanet in patients with potentially life-threatening acute major bleeding related to anticoagulation with a factor Xa inhibitor.

This interim report from the ongoing study included 67 patients with data available by June 17, 2016. Participants averaged 77 years of age and were receiving a factor Xa inhibtor because of atrial fibrillation, venous thromboembolism, or both. All patients received a bolus of andexanet for 15 to 30 minutes followed by a 2-hour infusion.

Based on previous studies, the researchers used a 400-mg bolus of andexanet followed by a 480-mg infusion when patients had last taken their factor Xa inhibitor more than 7 hours before, and a higher 800-mg bolus followed by a 960-mg infusion when patients had taken their anticoagulant more recently. Bleeding and hemostasis were evaluated based on serial CT or MRI scans of patients with intracranial hemorrhage and corrected hemoglobin and hematocrit levels at 12 hours for patients with gastrointestinal and other non-visible bleeding.

Excellent or good efficacy rates were 84% for gastrointestinal bleeding and 80% for intracranial bleeding.

DR. CONNOLLY

Among 47 patients in the primary efficacy analysis, 37 (79%) achieved excellent or good hemostasis (95% confidence interval, 64% to 89%), including 81% of patients on rivaroxaban and 75% of patients on enoxaparin, the researchers reported.

"The rates of excellent or good efficacy were 84% for gastrointestinal bleeding and 80% for intracranial bleeding, rates that were consistent for other subgroups that were examined," they said. Among the five patients (10%) with the most residual anti–factor Xa activity, all had received the lower andexanet dose. Four had received rivaroxaban while one had received apixaban.

The safety population included all 67 patients, none of whom developed infusion reactions or antibodies to factors X, Xa, or andexanet.

After 30 days of follow-up, 12 patients (18%) had experienced one or more thrombotic events, including deep vein thrombosis (seven patients), stroke (five patients), myocardial infarction (one patient), and pulmonary embolism (one patient). One-third of these events occurred within 3 days of receiving andexanet, while the rest occurred by day 30. A total of 10 patients (15%) died, and six deaths were from cardiovascular causes.

"A controlled study would be required to assess whether the frequency of these events exceeded that expected in patients at increased risk for thrombotic events," the researchers commented.

Portola Pharmaceuticals makes andexanet alfa and funded the study.

Dr. Connolly disclosed ties to Bayer, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, CSL Behring, Octapharma, and Boehringer Ingelheim outside the submitted work.

NOACs cut intracranial bleeds in atrial fib patients

BY MITCHEL L. ZOLER
Frontline Medical News

ROME – The new oral anticoagulants performed as advertised in a real-world, Danish registry of more than 40,000 patients with atrial fibrillation.

During the first year on anticoagulant treatment, patients who received a new oral anticoagulant (NOAC) had an ischemic stroke rate similar to that of patients who received the traditional oral anticoagulant, warfarin, but a significantly reduced rate of intracranial hemorrhage, Laila Stærk, MD, reported at the annual congress of the European Society of Cardiology.

These results "reinforce what we have seen in the clinical trials, but with the strength of looking in the entire Danish population," said Dan Atar, MD, a cardiologist and professor of medicine at the University of Oslo.

"It is enlightening and very reassuring to have these real-world, unselected, registry data. They provide reassurance about safety and efficacy" when prescribing a NOAC, Dr. Atar said in an interview.

The study reported by Dr. Stærk and her associates included 43,299 Danish patients who were recently diagnosed with nonvalvular atrial fibrillation and started on treatment with an oral anticoagulant during the period August 2011 (when the first NOAC, dabigatran, became available for routine use in Denmark) through December 2015. During this period, 42% of these patients received warfarin, 29% received dabigatran (Pradaxa), 16% received apixaban (Eliquis) and 13% received rivaroxaban (Xarelto).

Dr. Laila Stærk

Dr. Dan Atar

PHOTOS MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

In a propensity-score type of analysis that controlled for baseline differences in clinical and demographic parameters, the results showed that the rate of ischemic stroke during the first year on treatment ranged from 2.0% to 2.5% in the four subgroups based on the anticoagulant received with no statistically-significant differences among the four subgroups. In other words, all three NOACs had efficacy profiles similar to those of warfarin, said Dr. Stærk, a cardiology researcher at Herlev and Gentofte University Hospitals in Hellerup, Denmark.

But on the safety side, all three NOACs were linked with lower rates of intracranial hemorrhages during the 1-year follow-up compared with the patients who received warfarin. In the cases of dabigatran and apixaban, the reduced intracranial hemorrhage rates were statistically significant, with a 0.6% rate among the patients on warfarin and rates that were reduced by a relative 34% for patients who received dabigatran and by a relative 20% among those on apixaban. Rivaroxaban linked with a 13% relative risk reduction in intracranial hemorrhage that was not statistically significant.

Dr. Atar said he interpreted the finding as showing that collectively, the three NOACs assessed had comparable efficacy but better safety compared with warfarin.

Dr. Stærk has received research funding from Boehringer Ingelheim, the company that markets dabigatran (Pradaxa).

Dr. Atar said that he has been a consultant to and has received research funding from several drug companies.

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PCSK9 inhibitors flunk cost-effectiveness test

BY HEIDI SPLETE
Frontline Medical News

At current prices, PCSK9 inhibitors are not cost-effective for patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease, according to an analysis published Aug. 16 in JAMA. The costs of the cholesterol-lowering drugs would have to be reduced by at least two-thirds to reach cost-effectiveness, on the basis of data from the simulation model of atherosclerotic cardiovascular disease in the United States and the 2015 annual PCSK9 inhibitor costs of $14,350.

The high cost of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition remains a challenge because it is meant for lifelong use, and "the potential increase in health care expenditures at current or even moderately discounted prices could be staggering," wrote Dr. Kirsten Bibbins-Domingo of the University of California, San Francisco, and her colleagues (JAMA 2016 Aug 16;316[7]:743-53).

The researchers used the Cardiovascular Disease Policy Model. This model included adults aged 35-94 years and compared the cost-effectiveness of PCSK9 inhibitors and ezetimibe in treating two of the three indications for the drugs, which were heterozygous familial hypercholesterolemia (FH) and atherosclerotic cardiovascular disease (ASCVD). The third indication, homozygous FH, was not included in the analysis.

The researchers assumed that statins, ezetimibe, and the two approved PCSK9 inhibitors (evolocumab and alirocumab) each would reduce the risk of cardiovascular events by an identical amount per mg/dL of LDL cholesterol reduction.

They found that, for PCSK9 inhibitors to be cost-effective at less than $100,000 per quality-adjusted life-year (QALY), the annual cost would need to drop from its current cost of roughly $14,000 per patient to $4,536 or less per patient, the researchers said.

Overall, the model showed that adding PCSK9 to statins for patients with heterozygous FH or ASCVD prevented 316,300 major adverse cardiovascular events (defined as cardiovascular death, nonfatal MI, or stroke), compared with adding ezetimibe. The cost was $503,000 per QALY.

Adding PCSK9 inhibitors to statins for patients with ASCVD prevented about 4.3 million major cardiac adverse events, compared with adding ezetimibe; the cost was $414,000 per QALY.

In addition, the researchers found that PCSK9 inhibitor use would cut cardiovascular care costs by $29 billion over 5 years.

However, the model projected an increase of about $592 in annual drug costs from 2015, as well as a 4% annual increase in U.S. health care costs overall.

The results were limited by several factors including the lack of long-term data on outcomes in patients taking PCSK9 inhibitors, the researchers noted.

However, the findings suggest that the best way to improve the value of PCSK9 is to cut the price, they added.

In the meantime, "payers must consider the potential trade-off between paying for new drug treatments like PCSK9 inhibitors and investing in interventions known to improve access, physician prescription rates, and patient adherence to statin therapy among those at high ASCVD risk," the researchers said.

Dr. Bibbins-Domingo is the chair of the U.S. Preventive Services Task Force, but the study does not represent a recommendation from the USPSTF. She had no personal financial conflicts to disclose.

The study was funded in part by the New England Comparative Effectiveness Public Advisory Council, which receives grants from several nonprofit organizations.

Turn the page to discover clinical data and formulary coverage for **BREO**

Reach with Confidence for **24-hour BREO**

For adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA. BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**
- **When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.**

CONTRAINDICATIONS

- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required.
- BREO is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

Please see additional Important Safety Information on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the pages following this advertisement.

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BREO® ELLIPTA®
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

BREO offers patients proven efficacy with just one daily dose

In patients uncontrolled on an ICS,
BREO has been proven to:

Deliver 24-hour lung function improvement

with one inhalation, once daily*

Reduce asthma exacerbations

in patients with a history of exacerbations†

Supporting Clinical Study Information

*In a randomized, double-blind (RDB) study of 1039 patients‡ symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=312) demonstrated a 108 mL improvement from baseline in weighted mean (wm) FEV_1 (0-24 hours) at the end of the 12-week treatment period vs fluticasone furoate (FF) 100 mcg once daily (n=288) (P<0.001).[1] (In an RDB, placebo-controlled study of 609 patients‡ symptomatic on a low- to mid-dose ICS, in a subset of patients, BREO 100/25 once daily [n=108] demonstrated a change from baseline in wm FEV_1 [0-24 hours] at the end of the 12-week treatment period vs FF 100 mcg once daily [n=106] of 116 mL [95% CI: −5, 236; P=0.06].[2])

†In a 24- to 76-week RDB study of 2019 patients‡ with ≥1 exacerbations in the prior year, BREO 100/25 once daily (n=1009) reduced the risk of experiencing an exacerbation by 20% (hazard ratio=0.795, P=0.036) vs FF 100 mcg once daily (n=1010).[3] An exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

‡Studies included patients with asthma ≥12 years of age; BREO is only approved for use in patients ≥18 years of age.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.

WARNINGS AND PRECAUTIONS (cont'd)

- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO immediately and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

BREO ELLIPTA was developed in collaboration with Theravance

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Have confidence in access

Nationwide, BREO is now **covered without restriction**[§] on:

Individual patient access may vary by geography and plan benefit design.
SOURCE: Managed Markets Insight & Technology, LLC, database as of July 2016.

For local formulary information about BREO, please contact your GSK sales professional.

What you need to know about this formulary information:

[§]Covered without restriction means reimbursement from a health plan with no accompanying step edits or prior authorizations.

Formulary status may vary and is subject to change. Formulary coverage does not imply clinical efficacy or safety. Benefits designs offered by plans may vary. Actual benefits and out-of-pocket costs are determined by each plan administrator in accordance with its respective policy and procedures. Consumers may be responsible for some out-of-pocket costs based on an individual's plan.

The information provided is not a guarantee of coverage or payment (partial or full). Please verify coverage with and obtain most current information from plan sponsors. GSK does not endorse individual plans.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- 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.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS

- In a 12-week trial, adverse reactions (≥2% incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis, 10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% (<1%); and cough, 1% (2%).
- In addition to the adverse reactions reported in the two 12-week trials, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 once daily in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia, and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

ADVERSE REACTIONS (cont'd)

- In a 24- to 76-week trial of subjects with a history of 1 or more asthma exacerbations within the previous 12 months, asthma-related hospitalizations occurred in 1% of subjects treated with BREO 100/25. There were no asthma-related deaths or asthma-related intubations observed in this trial.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

- BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.
- Use BREO with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the following pages.

References: 1. Bernstein DI et al. *J Asthma.* 2015;52(10):1073-1083. **2.** Bleecker ER et al. *J Allergy Clin Immunol Pract.* 2014;2(5):553-561. **3.** Bateman ED et al. *Thorax.* 2014;69(4):312-319.

Visit BREOhcp.com for more information, including Patient Assistance Programs.

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BREO® ELLIPTA®
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder

BRIEF SUMMARY

BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation
BREO® ELLIPTA® 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

The following is a brief summary only and is focused on the asthma indication. See full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, 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 LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.2 Treatment of Asthma BREO is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 18 years and older. LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1), Adverse Reactions (6.2), Use in Specific Populations (8.4)]*. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.
Important Limitation of Use: BREO is NOT indicated for the relief of acute bronchospasm.

4 CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions: Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*; Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS. A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted.

5.2 Deterioration of Disease and Acute Episodes BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate. Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO. BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta$_2$-Agonists BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of ICS In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.6 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients from Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*. Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

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

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

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

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

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

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

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

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

6 ADVERSE REACTIONS

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

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

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

In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis,

10% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dysphonia, 2% (1%, 0%). Oral candidiasis includes oral candidiasis and oropharyngeal candidiasis.
Trial 2 was a 12-week trial that evaluated the efficacy of BREO 100/25, BREO 200/25, and fluticasone furoate 100 mcg in adolescent and adult subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years.
In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/25 (n=346) (BREO 100/25 [n=346] or fluticasone furoate 100 mcg [n=347]) were: headache, 8% (8%, 9%); nasopharyngitis, 7% (6%, 7%); influenza, 3% (3%, 1%); upper respiratory tract infection, 2% (2%, 3%); oropharyngeal pain, 2% (2%, 1%); sinusitis, 2% (1%, <1%); bronchitis, 2% (<1%, 2%); and cough, 1% (2%, 1%).
24-Week Trial Trial 3 was a 24-week trial that evaluated the efficacy of BREO 200/25 once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in adolescent and adult subjects with asthma. Of the 586 subjects, 59% were female and 84% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO 200/25 included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.
12-Month Trial Long-term safety data is based on a 12-month trial that evaluated the safety of BREO 100/25 once daily (n = 201), BREO 200/25 once daily (n = 202), and fluticasone propionate 500 mcg twice daily (n = 100) in adolescent and adult subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO 100/25 or BREO 200/25 for 12 months included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.
Exacerbation Trial In a 24- to 76-week trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010) (Trial 5). Subjects participating in this trial had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. Asthma-related hospitalizations occurred in 10 subjects (1%) treated with BREO 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 (n = 151) compared with 0 subjects treated with fluticasone furoate 100 mcg (n = 130). There were no asthma-related deaths or asthma-related intubations observed in this trial.
6.3 Postmarketing Experience In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.
Cardiac Disorders Palpitations, tachycardia.
Immune System Disorders Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.
Musculoskeletal and Connective Tissue Disorders Muscle spasms.
Nervous System Disorders Tremor.
Psychiatric Disorders Nervousness.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.
7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.
7.3 Beta-Adrenergic Receptor Blocking Agents Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.
7.4 Non–Potassium-Sparing Diuretics The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects Pregnancy Category C. There are no adequate and well-controlled trials with BREO in pregnant women. Corticosteroids and beta$_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO 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 BREO. *Fluticasone Furoate and Vilanterol:* There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day). *Fluticasone Furoate:* There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day). *Vilanterol:* There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).
Nonteratogenic Effects Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.
8.2 Labor and Delivery There are no adequate and well-controlled human trials that have investigated the effects of BREO during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO should be used during labor only if the potential benefit justifies the potential risk.
8.3 Nursing Mothers It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and beta$_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.
8.4 Pediatric Use BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established. In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. *[See Clinical Studies (14.2) of full prescribing information.]* Adolescents aged 12 to 17 years made up 14% of the study population (n = 281), with a mean exposure of 352 days for subjects in this age-group treated with BREO 100/25 (n = 151) and 355 days for subjects in this age-group treated with fluticasone furoate 100 mcg (n = 130). In this age-group, 10% of subjects treated with BREO 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age-group.
Effects on Growth Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of children and adolescents with ICS, including fluticasone furoate, on final adult height are not known. *[See Warnings and Precautions (5.17); Use in Special Populations (8.4) of full prescribing information.]*
8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO for asthma included 854 subjects aged 65 years 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 subjects.
8.6 Hepatic Impairment Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.
8.7 Renal Impairment There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No human overdosage data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO 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.
10.1 Fluticasone Furoate Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.
10.2 Vilanterol The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).
Asthma-Related Death **Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Also inform them that currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.**
Not for Acute Symptoms Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used. Instruct patients to seek medical attention immediately if they experience any of the following: Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists; Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists; Significant decrease in lung function as outlined by the physician. Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.
Do Not Use Additional Long-Acting Beta$_2$-Agonists Instruct patients not to use other LABA for COPD and asthma.
Local Effects Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.
Immunosuppression Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
Hypercorticism and Adrenal Suppression Advise patients that BREO may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO.
Reduction in Bone Mineral Density Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.
Ocular Effects Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.
Risks Associated with Beta-Agonist Therapy Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
Hypersensitivity Reactions, Including Anaphylaxis Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

BREO was developed in collaboration with Theravance.

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Infant bronchiolitis risk tied to gut flora

BY TARA HAELLE
Frontline Medical News

Infants with gut flora dominated by the genus *Bacteroides* have more than four times greater odds of developing bronchiolitis than those with microbiota dominated by *Enterobacter* and *Veillonella* combined, according to results of a recent study. Two other bacterial profiles, one dominated by *Bifidobacterium* and another by *Escherichia*, were not associated with any higher or lower risk of bronchiolitis.

"Our observations, in conjunction with earlier studies, suggest a causal pathway linking the gut microbiota in early infancy to the respiratory tract immune response against viral infection," wrote Dr. Kohei Hasegawa of Harvard Medical School in Boston, and his associates (Pediatrics. 2016 June 27. doi: 10.1542/peds.2016-0218). "That is, the *Bacteroides*-dominant gut microbiota in early infancy attenuates the development of immune function in the respiratory tract and thereby leads to an increased susceptibility to bronchiolitis."

The researchers collected stool samples from 115 healthy infants from a Massachusetts General Hospital primary care group practice, and from 40 infants who were hospitalized with bronchiolitis from November 2013 through April 2014 at one of three children's hospitals in Wilmington, Del.; Boston; and Louisville, Ky. The groups were age matched, and the infants overall were a median 3 months old. Just over half were male, and just over half were white. Of those with bronchiolitis, 65% had respiratory syncytial virus and 23% had rhinovirus.

Further, "compared with healthy controls, infants with bronchiolitis were [significantly] more likely to have a parental history of asthma, maternal antibiotic use during pregnancy, a history of premature birth, a sibling at home, and corticosteroid use before the enrollment, but they were less likely to be breastfed," the authors reported.

The researchers used a 16S rRNA gene-sequencing method similar to the one used by the Human Microbiome Project to identify the composition of the fecal samples' microbiota. Four different bacterial profiles emerged. The most common was an *Escherichia*-dominant profile, occurring in 30% of the infants overall. Microbiota dominated by *Bacteroides* followed next, occurring in 28% of infants, while 22% of infants had a *Enterobacter/Veillonella*–dominant profile, and 21% had a *Bifidobacterium*-dominant profile.

Those with a *Bacteroides*-dominant profile were older, more likely to be born vaginally, and more likely to be prenatally exposed to maternal smoking.

In infants with bronchiolitis, however, flora dominated by *Bacteroides* was most common, occurring in 44% of the ill infants. *Enterobacter/Veillonella*–dominant microbiota occurred in only 15% of the infants with bronchiolitis. Infants' risk of bronchiolitis was not significantly different among those with *Bifidobacterium*-dominant or *Escherichia*-dominant profiles, compared with the *Enterobacter/Veillonella*–dominant profile.

Patients with *Bacteroides*-dominant microflora had 4.59 greater odds of severe bronchiolitis than those with *Enterobacter/Veillonella*–dominant microbiota ($P = .008$). These odds dropped only to 3.89 after adjustments for age, sex, prematurity, mode of birth, and a history of systemic antibiotic use ($P = .03$). Similarly, adjusting for age, sex, parental history of asthma, maternal antibiotic use during pregnancy, and systemic corticosteroid use before enrollment resulted in 4.12 greater odds of bronchiolitis in those with a *Bacteroides*-dominant profile ($P = .02$).

The research was funded by the National Institutes of Health. Dr. Hasegawa reported no disclosures. Two authors reported owning shares at a microbiome research company. One had consulted on bronchiolitis. The others reported no disclosures.

VIEW ON THE NEWS

Microbiota profiles need further study

This cross-sectional, case-control study raises multiple hypotheses about the relationship between different gut microbiota compositions and the presence of bronchiolitis while also exposing limitations in the study. For instance, polysaccharide A of *Bacteroides* suppresses T-cell responses to inflammatory stimuli. Inappropriate suppression of "cellular learning" in infancy may alter subsequent mucosal immunity upon infection, resulting in exacerbated inflammatory responses to environmental challenges. Thus, an increased abundance of enteric *Bacteroides* before a viral challenge may be hypothesized to increase the likelihood of reduced viral immunity and an inappropriate response to an infection.

However, in the study by Hasegawa et al., the gut microbiota was sampled only at the time of hospitalization for infection and once in age-matched controls. Any of the observed microbiota profiles may not reflect earlier states of the microbiota and critical windows of early immune priming. Therefore, prospective longitudinal studies will be essential to determine whether the observed microbiota profiles at the time of bronchiolitis preceded symptoms, were concurrent with the disease onset, or occurred after the disease was well under way. Only through these types of studies, coupled with preclinical mechanistic models of bronchiolitis, can causality be established.

The associations identified by Hasegawa et al., if upheld by the necessary prospective and causal studies, may yield new insights into the failures of antibiotic therapy and suggest alternative approaches to therapeutically modify the microbiota and thus reduce the risk and severity of viral bronchiolitis in infants.

Respiratory tract research has entered a new era. Through a combination of clinical and preclinical models, genomics, immunology, and metabolomics, investigations into the gut-lung axis are expected to drive a paradigm shift in which pulmonary health is viewed through a wider lens of multisystem interactions that includes the microbiota, and through which new preventive strategies, diagnostics and therapeutics may be envisioned for common respiratory diseases.

These comments were condensed from an editorial by Dr. Patrick C. Seed that was published in Pediatrics (doi: 10.1542/peds.2016-1377) alongside the original research. Dr. Seed is supported by the National Institutes of Health, and he reported having no disclosures.

Portable device may underestimate FEV_1 in children

BY LORI LAUBACH
Frontline Medical News

The PiKo-1 device (nSpire Health) has limited utility in determining forced expiratory volume in 1 second (FEV_1) in children with asthma, according to Jonathan M. Gaffin, MD, and his associates.

In a study of 242 children, spirometry and PiKo-1 devices were used to test FEV1. In the Bland-Altman analysis, it reported a mean difference between FEV_1 measured by spirometry and PiKo-1 of 0.14 L. The PiKo-1 FEV_1 was found to be moderately biased to underestimate FEV_1 with increasing volumes, for every 1-liter increase in spirometry FEV_1, having the difference between spirometry and PiKo-1 increased by 0.19 L ($P < .001$).

Researchers also used the pulmonary function test (PFT) and t showed variability was 0.4 L for spirometry at 2 SDs, a significant smaller range than seen in the PFT-PiKo confidence intervals (1.1 L). It is noted that this indicates that differences are credited to distinctions in the devices themselves and not within the techniques of the person using them. There was no effect on the order of PFT or PiKo-1 performance ($P = .88$).

"The findings from this study suggest that the PiKo-1 device has limited utility in assessing FEV_1 in clinical or research settings in children with asthma," researchers concluded. "Further investigation of its use in this respect and with different populations may prove the device more valuable." The full study is in the Annals of Allergy, Asthma and Immunology (doi: 10.1016/j.anai.2016.06.022).

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Acetaminophen doesn't exacerbate pediatric asthma

BY MARY ANN MOON
Frontline Medical News

As-needed use of acetaminophen for fever or pain does not exacerbate mild persistent asthma in young children, according to a report published online in the New England Journal of Medicine.

In a prospective, randomized, double-blind clinical trial performed at 18 U.S. medical centers, neither acetaminophen nor ibuprofen raised the rate of exacerbations or impaired asthma control among 300 children aged 1-5 years. This result refutes those of observational and post hoc data that linked acetaminophen to increased asthma exacerbations, daily symptoms, and need for bronchodilators in children and adults. Those findings "have led to much controversy and even alarm," with some physicians recommending that acetaminophen be completely avoided in children with asthma until more safety data became available, said William J. Sheehan, MD, of the division of allergy and immunology, Boston Children's Hospital and Harvard Medical School, Boston, and his associates.

The investigators performed this 2-year study to obtain such safety data. The children (median age, 40 months) were randomly assigned to receive either liquid acetaminophen (150 patients) or matching liquid ibuprofen (150 patients) as needed for pain, fever, or discomfort and were followed for 46 weeks. All the participants received standard asthma-control therapies including inhaled glucocorticoids, oral leukotriene-receptor antagonists, and as-needed inhaled glucocorticoids.

The primary outcome – the mean number of asthma exacerbations – was 0.81 in the acetaminophen group and 0.87 in the ibuprofen group, a nonsignificant difference. The rate

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VIEW ON THE NEWS

Reassurance for parents, clinicians

The findings of Sheehan et al. should reassure clinicians and parents who care for young children taking asthma-controlling medications that the use of acetaminophen in usual, as-needed doses will not worsen the condition.

Acetaminophen and ibuprofen can be used similarly in situations for which they are indicated.

Augusto A. Litonjua, MD, is in the Channing Division of Network Medicine, Brigham and Women's Hospital, and at Harvard Medical School, both in Boston. Dr. Litonjua made these remarks in an editorial accompanying Dr. Sheehan's report (N Engl J Med. 2016 Aug 18. doi: 10.1056/NEJMe1607629). He reported receiving personal fees from UpToDate, Springer Humana Press, and AstraZeneca outside this editorial.

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of exacerbations also did not differ between acetaminophen and ibuprofen in the subgroup of 226 children who completed the entire trial or in the subgroup of 200 who received a study medication for pain or fever at least once during follow-up, Dr. Sheehan and his associates said (N Engl J Med. 2016 Aug 18. doi: 10.1056/NEJMoa1515990).

There also were no significant differences between the two study groups in time to first asthma exacerbation, percentage of days of good asthma control (85.8% vs. 86.8% of days), use of rescue albuterol (2.8 vs. 3.0 inhalations per week), or unscheduled health care visits for asthma (0.75 vs. 0.76 visits). No between-group differences occurred regarding adverse events or serious adverse events.

Some experts have suggested that the observational studies reporting a link between acetaminophen and asthma exacerbations may have been flawed by "confounding by indication," because children with asthma have more symptomatic respiratory infections than do those without asthma and use more acetaminophen for fever and malaise. "We [also] observed that greater use of antipyretic, analgesic medications was associated

with more apparent respiratory illnesses and that the reported respiratory illnesses were associated with asthma exacerbations.

"However, we found no evidence that acetaminophen, when used during periods of respiratory illness, was associated with a higher risk of asthma exacerbations or other asthma-related complications than was ibuprofen," Dr. Sheehan and his associates wrote.

The primary outcome – the mean number of asthma exacerbations – was 0.81 in the acetaminophen group and 0.87 in the ibuprofen group, a nonsignificant difference.

This study was funded by the National Institutes of Health and the National Heart, Lung, and Blood Institute.

Dr. Sheehan reported no relevant financial disclosures. His associates, including Dr. Leonard Bacharier, reported numerous ties to industry sources. Dr. Barcharier received grant support from the NIH/NHLBI AsthmaNet and personal fees from many companies.

Adapting PCV13 schedule boosts seroprotection

BY KARI OAKES

Frontline Medical News

A randomized clinical trial evaluating three dosing strategies for 13-valent pneumococcal vaccine (PCV13) in preterm infants found that more widely spaced priming vaccinations resulted in higher immunoglobulin G (IgG) during the first 12 months of life, but reduced the immune response seen after the 12-month booster was given.

After the primary schedule, the percent of infants lacking seroprotection for more than one half of the serotypes in the PCV13 formulation was 25% on a reduced two-dose schedule, 12% on an accelerated schedule, and 3% on an extended schedule (*P* less than .001).

Conversely, "A reduced priming schedule of PCV13 resulted in higher post-booster IgG concentrations but

lower post-primary concentrations," wrote Alison Kent, MBChB, and her coinvestigators in the PUNS (Prems Under New Schedule) Study Group (Pediatrics. 2016;138[3]:e20153945).

"Infants who received the extended schedule had lower fold increases in concentrations after booster vaccination than the other groups," wrote Dr. Kent, of the Pediatric Infectious Diseases Research Group and Vaccine Institute, St. George's, University of London, and her collaborators. Participants receiving the extended schedule had lower geometric mean concentrations (GMCs) of antibodies than did those on the reduced schedule for nine serotypes and those on the accelerated schedule for four serotypes.

The study enrolled 210 premature infants in a phase IV, controlled, open-label trial at 12 sites in the United Kingdom. Infants of less than 35 weeks gestation, and between 7 and 12 weeks of age, were randomly assigned to receive PCV13 on one of three schedules. The reduced schedule gave two priming doses at 2 and 4 months of age; the accelerated schedule gave the doses at 2, 3, and 4 months of age; and the extended schedule gave doses at 2, 4, and 6 months of age. All infants received a booster vaccination at 12 or 13

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months of age, and all received a standard suite of childhood immunizations for other diseases. The entire study was completed by 194 patients.

Serotype-specific IgG concentrations were obtained pre-vaccination, 1 month after the primary vaccination, and before and 1 month after the booster vaccination was given. IgG levels were reported for each PCV serotype; "there was considerable variation between serotypes," ranging from 0.16 ng/mL for serotype 6b on the reduced schedule to 8.49 ng/mL for serotype 14 on the extended schedule, the investigators said.

Dr. Kent and her collaborators also used logistic regression analysis to explore how the vaccine's effectiveness was affected by a number of factors. These included gestational length, the receipt of blood transfusions or pre- or post-natal steroids, BCG vaccination, early postvaccination acetaminophen, and the presence of chronic lung disease.

Later gestation was associated with increased seroprotection for four serotypes at 2 months of age, and with an increase in post-primary vaccination IgG concentrations for three others (*P*-values ranging from *P* less than .001 to $P = .021$).

No other factors were associated with protective IgG levels at any point, except that receipt of prenatal steroids had a negative association with seroprotection for several serotypes. "At no time points were antenatal steroids associated with higher antibody concentrations," wrote the investigators.

The receipt of prenatal steroids had a negative association with seroprotection for several serotypes. Antenatal steroids were not associated with higher antibody concentrations.

Most studies of immunogenicity of infant vaccination schedules have been completed using term infants, with limited knowledge about efficacy in preterm infants. Previous work had shown that preterm infants had lower IgG concentrations after the primary and booster vaccinations for eight serotypes of PCV, compared with term infants. "The lower immunogenicity ... is concerning because premature infants are also less likely to benefit from the protective maternal antibodies transferred during late pregnancy," Dr. Kent and her coauthors wrote.

The lower booster immunogenicity after the extended schedule is an effect that has been previously observed with other vaccinations and may be related to the formation of immune complexes with previously existing antibodies with the vaccine antigen, said Dr. Kent and her coauthors. The variation in immunogenicity timing for the various priming schedules, they said, will be helpful for those caring for preterm infants, enabling them "to consider this finding in the context of their own immunization programs and epidemiologic situations."

The study was funded by Pfizer as an investigator-led study, without Pfizer's input on the conduct of the trial, analysis of data, interpretation of results, or the preparation of this manuscript. Pfizer manufactures Prevnar 13.

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Dual Y-shaped stent helps treat airway fistulas

BY RICHARD MARK KIRKNER
Frontline Medical News

Airway fistula is a rare but life-threatening complication of esophageal surgery, but an innovative technique using two custom-made, Y-shaped metallic stents can preserve airway patency, researchers at Zhengzhou University in China reported in the August issue of the Journal of Thoracic and Cardiovascular Surgery (J Thorac Cardiovasc Surg. 2016;152:557-63).

The study involved 10 patients who received Y-shaped stents to treat gastrotracheal or gastrobronchial fistulas after esophageal surgery from 2010 through 2014. "Our patients tolerated the stents well and had good palliation of their symptoms," wrote Teng-Fei Li, MD, and colleagues.

Six patients died within 8 months for unrelated reasons – either tumors (four patients), or hemoptysis or pul-

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VIEW ON THE NEWS

Two stents are better than one

The Zhengzhou University investigators provide an opportunity to "think outside the box" when managing complex airway fistulas, Waël C. Hanna, MDCM, of McMaster University and St. Joseph's Healthcare in Hamilton, Ontario, said in his invited commentary (J Thorac Cardiovasc Surg. 2016;152:564).

Dr. Hanna credited a couple of innovations in their technique to overcome the challenge of Y stents that "remain notoriously difficult to position": eliminating rigid bronchoscopy and using angiography-guided oral delivery; and developing the hybrid deployment mechanism.

Dr. Hanna also noted two "important nuances" of the technique: The stents are custom-made based on the length and location of the fistula; and the routine placement of two stents, with a limb of the smaller Y stent projecting through a limb of the larger Y stent to seal the entire airway. "This Y-en-Y technique using perfectly fitted stents is likely what caused the excellent outcomes that are reported in this series," Dr. Hanna said.

But their approach may not be a practical solution to complex airway fistulas soon, he said. "Most of us who see the occasional case are unlikely to be able to commission custom-made Y stents," he said. What's more, the deployment mechanism is complicated, and the effect on patient quality of life is unclear.

Dr. Hanna had no financial relationships to disclose.

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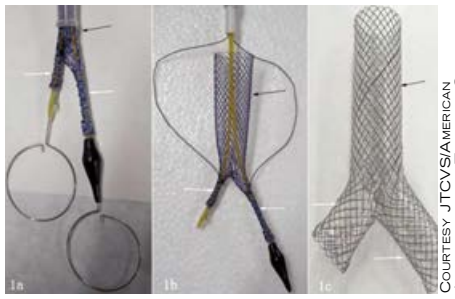
monary infection (one each). In one patient, the carinal fistula enlarged 4 months after stenting, but the researchers successfully placed an additional small Y-shaped stent. At the publication of the paper, this patient and three others had survived, Dr. Li and colleagues said.



COURTESY JTCVS/AMERICAN ASSOCIATION FOR THORACIC SURGERY

After esophagectomy, fistulas can form between the tracheobronchial tree and stomach for a variety of reasons. A metallic stent would seem the logical choice after fistula formation, but it can be problematic, Dr. Li and colleagues pointed out.

"Most often the clinician faces a situation in which the esophageal stent should have a larger diameter on the gastric side, making stenting the alimentary side of the fistula insufficient," they said. The risk of stent migration is high, and the bifurcated structure of the trachea and main bronchi can cause leakage and stent displacement.

The researchers noted that Y-shaped self-expanding stents have been used for sealing airway fistulas. These stents, however, do not always fully seal large gastrotracheal fistulas or gastrobronchial fistulas.

Their primary objective in studying the combined-type Y-shaped covered metallic stent was to determine the safety and feasibility of the technique. The researchers' secondary purpose for studying the combined-type Y-shaped stent was to evaluate its long-term patency and complication rates.

Speed and agility are important. "The operation should be performed as rapidly and gently as possible to avoid irritation to the airway." said Dr. Li and colleagues.

They designed a Y-shaped stent delivery system (Micro-Tech) and used a combined bundle-and-push to insert the main body of the stent. In all, they inserted 20 Y-shaped stents in the 10 patients, although two stents did not fully expand and were dilated with a balloon. The research-

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ers reported resolution of coughing during eating, toleration of liquid or semiliquid diet, and no complications after insertion.

Dr. Li and colleagues also developed strategies to avoid complications of Y-shaped stents, which have been known to retain secretions because they hinder cilia function.

"To avoid this, we provided sputum suction and administered continuous high-concentration oxygen during the procedure," they noted.

Also, speed and agility in placement are important. "The operation should be performed as rapidly and gently as possible to avoid irritation to the airway," Dr. Li and colleagues wrote.

The postoperative course involved IV expectorants and antiasthma agents and aerosol inhalation of terbutaline.

Surveillance bronchoscopes and debridement of granulation tissue helped avoid stent obstruction.

Nonetheless, the researchers acknowledged limitations of the retrospective study, namely the study's small sample size and lack of a control group.

Dr. Li and colleagues reported that they had no financial relationships to disclose.

Model estimates risk of pneumonia after CABG

BY MARY ANN MOON
Frontline Medical News

A model incorporating 17 easily obtainable preoperative variables may help clinicians estimate patients' risk of developing pneumonia after undergoing coronary artery bypass graft surgery, according to a report published in Annals of Thoracic Surgery.

"This model may be used to inform clinician-patient decision making and to identify opportunities for mitigating a patient's risk," said Raymond J. Strobel, a medical student at the University of Michigan, Ann Arbor, and his associates.

Postoperative pneumonia is the most common hospital-acquired infection following CABG, and it raises mortality risk fourfold and increases length of stay threefold. But reliable

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[PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

Hypercorticism and Adrenal Suppression

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

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

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

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

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

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

Reduction in Bone Mineral Density

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

Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

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

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.1) and Use in Specific Populations (8.4) in full Prescribing Information]*.

Glaucoma and Cataracts

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

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

Eosinophilic Conditions and Churg-Strauss Syndrome

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol *[see Warnings and Precautions (5.1) in full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

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

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

Clinical Trials Experience in Asthma Patients 12 years and older

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

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

Table 1 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 mcg N = 277 %**	**160/4.5 mcg N = 124 %**	**80 mcg N = 121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3

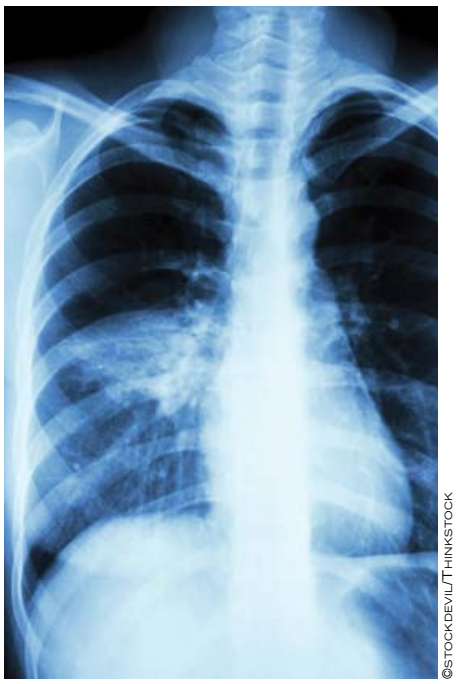
Continued from previous page

estimation of patient risk of post-CABG pneumonia has been difficult because of its low relative incidence – roughly 3% – and because most studies of the disorder are nearly a decade out of date.

To devise a predictive model using current data, Mr. Strobel and his associates assessed numerous potential risk factors and outcomes for 16,084 consecutive patients undergoing CABG at all 33 cardiac centers across Michigan during a 3-year period. They identified 531 cases of post-CABG pneumonia (3.3%) in this cohort.

The investigators performed a univariate analysis to test the associations between pneumonia and numerous factors related to patient demographics, medical history, comorbid diseases, laboratory values, cardiac anatomy, cardiac function, pulmonary function, the CABG procedure, and the institution where the procedure was performed. Variables that were found to be significantly associated with pneumonia (though usually with small absolute magnitudes) were then assessed in a multivariate analysis, which was further refined to create the final model.

The final model includes 17 factors that clearly raise the risk of post-CABG pneumonia. These include an elevated leukocyte count; a decreased hematocrit; older patient age; comorbidities such as peripheral vascular disease, diabetes, and liver disease;



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markers of pulmonary impairment such as cigarette smoking, the need for home oxygen therapy, and chronic lung disease; markers of cardiac dysfunction such as a recent history of arrhythmia and decreased ejection fraction; and emergency or urgent rather than elective operative status.

"This model performs well and demonstrates robustness across important clinical subgroups and centers," the investigators said (Ann Thorac Surg. 2016 Jun 1; doi: 10.1016/j.athoracsur.2016.03.074).

In particular, this study identified preoperative leukocytosis to be a significant predictor of post-CABG pneumonia across several subgroups of patients. "We speculate that patients presenting with an elevated white blood cell count before surgery may be mounting an immune response against a pathogen and that the insult of CABG significantly increases their odds of postoperative pneumonia. In the absence of more thorough understanding of this relationship, and unless surgery cannot be postponed, it may be prudent to delay surgery until the source of leukocytosis is satisfactorily investigated, if not identified and treated, or the leukocytosis has otherwise resolved," Mr. Strobel and his associates noted.

Challenging allografts in infectious endocarditis

BY RICHARD MARK KIRKNER
Frontline Medical News

When a patient undergoes aortic valve replacement for infective endocarditis, conventional thinking holds that cardiac surgeons should use homografts because they have greater resistance to infection, but a recent study of more than 300 cases at two academic medical centers concluded that homografts may not necessarily offer such a benefit.

The study, published in the June issue of the Journal of Thoracic and Cardiovascular Surgery (2016;151:1239-48), involved 304 consecutive adult patients on whom 30-40 different surgeons performed operations for active infective endocarditis (IE) in the aortic valve from 2002 to 2014.

"Our findings suggest that patient-specific factors, such as age and implant preference, as well as technical reconstructive considerations, should drive prosthetic choice, rather than surgical dogma," said Joon Bum Kim, Ph.D., of Massachusetts General Hospital, Harvard Medical School, both in Boston, and Asan Medical Center in Seoul, Korea, and his colleagues.

The study found that cardiac surgeons favored homografts over conventional prostheses when the patient had prosthetic valve endocarditis (58.1% vs. 28.8%) and methicillin-resistant *Staphylococcus aureus* (25.6% vs. 12.1%), both significant differences.

"No significant benefit to the use of homografts was demonstrable with regard to resistance to reinfection in the setting of IE," Dr. Kim and his colleagues said.

Because reinfection after valve replacement for IE is such a strong concern, the debate over which prosthesis is best has ensued for decades. The researchers pointed out that the evidence favoring autologous or allogeneic tissue over synthetic material in the infective field is weak, mostly built on single-armed observational studies without comparison to conventional prosthesis.

With that in mind, the researchers pooled data from two institutions to compare short- and long-term results for homograft vs. conventional prosthetic valves in patients with IE. In this study group, 86 (28.3%) had homografts, 139 (45.7%) had xenograft prostheses, and 79 (26%) mechanical prostheses.

The homograft group had more than twice the rate of early death than did the conventional group – 19.8% vs. 9.2%, a significant difference ($P = .019$).

During follow-up, which ranged from 4.7 to 72.6 months, 60 patients (19.7%) of the total group died and 23 (7.7%) experienced reinfection, but rates did not vary between the homograft and conventional prosthesis groups, Dr. Kim and his colleagues reported.

Demographics were similar between the three groups with a few exceptions Those who received the mechanical prostheses were younger (mean age, 47.2 years vs. 55.6 and 59.8 for the homograft and xenograft groups, respectively), had lower rates of diabetes (5.1% vs. 10.5% and 12.2%) and had less-severe disease based on New York Heart Association functional class III or IV scores (34.2% vs. 54.7% and 53.2%).

The types of IE pathogens also differed among the three groups; methicillin-resistant staphylococci was most common in the homograft group (25.6%), whereas the viridans group streptococci was the leading cause of IE in the mechanical (38%) and xenograft groups (25.2%).

The use of homografts involves a highly complex operation, typically requiring a complete aortic root replacement, which "may be the major drawback in recommending it to patients already at high risk of operative mortality," the investigators wrote. The durability of homografts makes their use limited for younger patients, and such grafts are somewhat scarce and require cryopreservation. "Therefore, the notion that homografts are required may in practice present an obstacle to appropriate surgical management of patients who have IE," Dr. Kim and his coauthors wrote.

All patients but one in the homograft group received aortic arch replacement (98.8%) whereas 30 of the patients in the conventional group did so (13.8%).

The study findings are consistent with an earlier comparative study (Ann. Thorac. Surg. 2012;93:480-07), according to Dr. Kim and his colleagues. "These findings suggest that patient-specific factors, such as patient preferences and technical considerations, should be the principal drivers of choices of valve prostheses," they said. "Furthermore, lack of access to homografts should not be considered an obstacle to surgical therapy for this serious condition."

Coauthor Dr. Sundt disclosed that he is a consultant for Thrasos Therapeutics. Dr. Kim and the other coauthors had no financial disclosures.

VIEW ON THE NEWS

Two commentaries: 'Reasonable' conclusions, but questions remain

The study by Dr. Kim and his colleagues joins a series of reports questioning conventional thinking on the use of homografts to prevent recurrent infective endocarditis (IE), but their propensity matching does not account for surgeon bias in selecting a prosthesis, Dr. James K. Kirklin of the University of Alabama at Birmingham said in his invited commentary (J Thorac. Cardiovasc Surg. 2016 May;151:1230-1).

For example, surgeon preference may account for the wide disparity in full root replacements, depending on the type of prosthesis, Dr. Kirklin said. "Some experienced homograft surgeons have preferred the intra-aortic cylinder technique or infracoronary implantation, which avoids the short-term and longer-term complexities of full root replacement and has demonstrated long-term structural durability equivalent to that of the full root replacement," he said.

Also, experienced homograft surgeons may prefer the homograft for its resistance to infection and adaptability to severe root infection in individual patients, particularly in those with severe infection with an abscess. And he cautioned against the study's implication that conventional prostheses are equivocal in the setting of IE.

"Of considerable importance, however, is the evidence-based conclusion that surgical referral of routine surgical aortic valve endocarditis to a center experienced with aortic homograft surgery is *not* necessary, and a justifiable expectation is that aortic valve endocarditis requiring operation can be safely and appropriately managed in centers with standard aortic valve surgery experience who do not have access to or experience with aortic valve homografts," Dr. Kirklin concluded.

Dr. Kirklin had no financial relationships to disclose.

The series by Dr. Kim and his colleagues, one of the largest of acute infective endocarditis to date, provides further evidence that the type of prosthesis used in surgery for IE involving the aortic valve probably does not affect long-term outcomes or reinfection rates, Dr. Christopher M. Feindel of the University of Toronto said in his invited commentary (J Thorac Cardiovasc Surg. 2016 May;151:1249-50).

However, Dr. Feindel said, "numerous confounding factors" inherent in any observational study could raise questions about the conclusion.

"This article delivers an important message, although not all surgeons will agree with the statistical approach taken by Dr. Kim and his colleagues," Dr. Feindel said. The propensity scoring method the study used lacked all baseline variables that affect treatment choice and outcomes, "a crucial assumption for effective use of the propensity score," he said. However, given the multitude of variables in patients with acute and complex IE, he said most surgeons would be hard pressed to accept that's even possible in the model the study used.


DR. FEINDEL

Dr. Feindel also said a close examination of the 115 patients who underwent root replacement would have been "very instructional," and the lack of follow-up on valve-related complications in almost 25% of the patients is another limitation of the study.

Nonetheless, the conclusions of Dr. Kim and his colleagues are "reasonable," Dr. Feindel said. "Clearly, this article contributes important additional information to the surgical management of IE that will help guide surgeons, especially when it comes to prosthesis of choice," he concluded. "It is up to the reader to decide whether this report finally puts to rest the "dogma" that homografts should preferentially be used in the setting of IE."

Dr. Feindel had no relationships to disclose.

Getting to know our incoming CHEST President

Gerard Silvestri, MD, MS, FCCP, will be inaugurated as the new President of CHEST next month in Los Angeles during CHEST 2016. He is the Hillenbrand Professor of Thoracic Oncology and Vice Chair of Medicine for Faculty Development at the Medical University of South Carolina, Charleston. Dr. Silvestri completed his fellowship training in pulmonary and critical care at Dartmouth, Hanover, NH. He has an advanced degree in the evaluative clinical sciences, also from Dartmouth. He is a lung cancer and interventional pulmonologist with an interest in health services research, lung cancer screening, nodule evaluation and management, and staging of lung cancer.

After becoming a Fellow of the American College of Chest Physicians in 1998, Dr. Silvestri became active with the NetWorks, serving on the Steering Committees of the Thoracic Oncology and the Interventional Chest/Diagnostic Procedures NetWorks, eventually chairing the Thoracic Oncology NetWork. Dr. Silvestri has also served on the Nominating Committee, the CHEST Scientific Program Committee, the CHEST Foundation Development Committee, as Treasurer and Trustee on the foundation's Board of Trustees, and as a Regent-at-Large for the American College of Chest Physicians for 3 years. At CHEST 2012, Dr. Silvestri was awarded the Pasquale Ciaglia Memorial Lecture in Interventional Pulmonary Medicine, and at CHEST 2014, he received the Edward C. Rosenow III, MD, Master FCCP/Master Teacher Honor Lecture award. Dr. Silvestri has authored more than 200 scientific articles, book chapters, and editorials, and he currently serves on the editorial board of the journal *CHEST*.

We asked Dr. Silvestri for some thoughts on his upcoming CHEST presidency.

1. What would you like to accomplish as President of CHEST?

As boring as this may sound, the role of the President is to oversee and carry out the strategic plan set forth by a very capable Board of Regents. It is an ambitious undertaking and among other things, it includes increasing the output of clinical practice guidelines to better serve pulmonologists and their patients, and educating as many physicians as possible through our national meeting, board review courses, our journal *CHEST*, our SEEK Library app and publication, and the CHEST headquarters, which has a state-of-the art education and simulation center. Our strategic vision aims to provide education to our global colleagues, as well as evidenced by our commitment to regional meetings on different continents and our efforts at collaborating with our Chinese colleagues to establish the first pulmonary and critical care fellowships in that populous nation.

Dr. Gerard Silvestri

Because education is our core mission, CHEST has a goal of helping to increase our faculty development offerings, culminating in a master educator certification for those who are interested and qualify. We also will be piloting an app for practice guidelines, which will help with the implementation and dissemination of our valuable clinical practice guidelines.

2. What do you consider to be the greatest strength of CHEST, and how will you build upon this during your presidency?

The greatest strength of the College is the amazing staff and physician volunteers who give tirelessly to support its mission, and ultimately, the membership. We already have begun to take measures to ensure that our most precious resources, our people, are supported to better do their work. In the next year, it is my commitment that we continue to provide the resources and recognition so that our faculty and staff can deliver the best educational content to our membership.

Our CHEST Foundation continues to champion lung health by supporting clinical research grants, community service grants, and patient education. CHEST members, their patients, and many others have benefited from the various clinical research and humanitarian projects that the Foundation has supported. Last year alone, the CHEST Foundation funded $430,000 in grants and awards for clinical research and community service projects. This year, we celebrate the 20th anniversary of the CHEST Foundation, and I am sure that the innovative initiatives of our charitable foundation will continue to move forward, making a difference for people throughout the world.

3. What are some challenges facing CHEST, and how will you address these challenges?

In a day in which physicians have limited resources, decisions about which medical society, if any, they should belong to have become increasingly real. Our members are using electronic media to find the tools they need to care for patients and may be less likely to follow the traditional medical association path. The challenge facing CHEST is to provide value, and it is the job of CHEST leadership to be certain that all of our members find that value in this organization. To do that, we must find or expand in creative ways a means to deliver our content in ways that resonate with our membership.

4. And finally, what is your charge to the members and new Fellows of CHEST?

The simple and overused answer would be to get involved. Without question, I believe that, and my start with the American College of Chest Physicians began as a member of the Thoracic Oncology NetWork, but I want to be a bit more specific. I challenge our members to find a niche within the College that they have a passion for, and in turn, they should challenge us to do better for our members and patients within that chosen area of expertise. There are so many ways to get involved, whether it be our NetWorks, CHEST social media, practice guidelines, or helping to teach in our simulation center. CHEST is an extremely welcoming organization, and your passion will find a home here and will be nurtured and supported by other like members and the CHEST staff.

NAMDRC and partners focus on CMS threat to rehab

BY PHIL PORTE
Executive Director, NAMDRC

In a genuine very good news, very bad news proposal included in the 2017 hospital outpatient regulations, the Centers for Medicare & Medicaid Services (CMS) has proposed a major payment boost for pulmonary rehab services billed through hospital outpatient departments, but, simultaneously, the Agency proposes to preclude certain programs from utilizing that long-standing payment mechanism.

In November 2015, Congress authorized CMS to take action on the growing trend of hospitals purchasing certain physician practices so that the hospital can bill for certain services at a notably higher rate than the same service when provided in the physician office setting. CMS Section 603 pf P.L. 114-74 authorizes such action, and "These proposals are made in accordance with our belief that section 603… is intended to curb the practice of hospital acquisition of physician practices that result in receiving additional Medicare payment for similar services." While we recognize that the congressional intent has some level of legitimacy, as is often the case, the CMS approach is too inclusive, especially as it applies to pulmonary rehabilitation services billed through HCPCS code G0424.

This problem has evolved because of two distinctly different formulas for determining payment. The physician fee schedule is based on the concept of RVUs, practice expense, and malpractice expense. Hospital outpatient services that may be virtually identical are based on a formula that includes charge data from Medicare claims forms and the annual hospital cost report identifying overhead.

If adopted as proposed, hospital outpatient programs in place on the date of enactment of P.L. 114-74 (early November 2015) are grandfathered into the hospital outpatient methodology. However, new programs that are not part of the main hospital campus (or within 250 yards of the campus) will only be able to bill at the physician office setting rate. Likewise, an existing program that

Continued on page 45

The power of flexibility is yours with **REVATIO Oral Suspension**

With REVATIO you have 3 dosage forms to treat pulmonary arterial hypertension (PAH): oral suspension, tablet, and injection.

Choose your dosage form based on each patient's needs.

To learn more, please visit REVATIOHCP.com

Indication

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

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No dose adjustment required for renal impaired.

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

REVATIO is available in the following dosage forms:

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

The Revatio® Family

Available in OS, tablet, and injection forms.

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

Revatio® sildenafil

Revatio®
sildenafil
20 mg tablets

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

INDICATION AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

Rx only Rev. June 2015

Continued from page 42

moves to a new location that is beyond the 250-yard threshold will lose its "grandfather" status and be forced to bill at the physician office setting payment rate.

For practical purposes, the 2017 proposed rate for G0424 in the hospital setting is $160+, while the same service in the physician office setting is $30+.

While there is certainly understandable logic in the Congressional mandate, the CMS approach that includes pulmonary rehab is fraught with basic flaws in logic, strongly supported by CMS data. For example, in 2014 only 231 distinct providers billed for a total of 22,603 services. That translates into an outlay of approximately $535,000. Compare that outlay for 2014 with the outlay for hospital outpatient pulmonary rehab at just under $120 million, billed by 1350 distinct providers.

Those data alone strongly support the contention that a business model of pulmonary rehab in a physician office setting is rarely viable. Space, capital investment, and staffing, coupled with low payment, hardly create an incentive for a hospital to purchase a pulmonary practice because of lucrative pulmonary rehab services.

Other Medicare data also work in our favor. An examination of the physician specialties that actually bill G0424 through the physician fee schedule also punches a large hole in the CMS argument. The top five physician specialties that billed G0424 through the physician office setting include:

TOTAL	**$688,489**	**$589,116**	**$535,512**
Pulmonary	**$340,805**	**$310,065**	**$229,832**
Family Practice	**$175,788**	**$116,681**	**$183,499**
Internal Medicine	**$79,053**	**$78,211**	**$52,943**
Crit Care (intensivists)	**$29,964**	**$29,139**	**$18,723**
Cardiology	**$31,947**	**$17,729**	**$17,242**

Source: *Physician Supplier Procedure Summary File (PSPS), 2012-2014*

These data speak volumes, or perhaps an absolute lack of volume. How does one support the concept that this proposed action is necessary to stem the tide of hospital acquisition of pulmonary practices when the total volume, notably declining over the past 3 years, of actual billings for pulmonary rehab is valued at under $230,000? The comparison with actual hospital billing in 2014 of just under $120 million is critical. There is no rhyme or reason to the CMS proposal *as it applies to pulmonary rehabilitation services*.

Unintended consequences are not difficult to imagine. With the new payment rates, hospitals may choose to expand their programs but cannot do so unless that physical location in on the main campus or within 250 yards of the campus. An off-site program that must move to accommodate larger space would be precluded from such a move. Likewise, hospitals that may want to open a new program must do so within the confines of the hospital campus/250-yard perimeter. Otherwise, these programs would be required to bill at the physician fee schedule rate.

In Memoriam

Steven A. Sahn, MD, FCCP, died on August 16 after an illustrious academic career. Born in Brooklyn, NY, he attended Duke University as an undergraduate and graduated from the University of Louisville School of Medicine. He completed a pulmonary–critical care fellowship at the University of Colorado, where he served the first 12 years of his academic career. Steve's early pioneering work in weaning from mechanical ventilation and in pleural physiology set the stage for almost all subsequent research in these fields. He was recruited in 1983 to the Medical University of South Carolina as Director of the Division of Pulmonary and Critical Care Medicine. During the next 30 years, he built the Division from three physicians to an internationally prominent team of clinicians and investigators. His passion for teaching blended his mentoring style with a love for sports and positive coaching. He was a master clinician who attracted patients from around the world who valued his exceptional warmth and compassion. Steve's contributions to the literature resulted in numerous awards, which included *CHEST*'s Alfred Soffer Award for Editorial Excellence, ATS Trudeau Medal, CHEST Distinguished Lecturer for Pleural Disease, Colorado Trudeau Society Pulmonary Hall of Fame, and Distinguished University Professor of Medicine at MUSC. Throughout his career he served on editorial boards of *CHEST* and *PCCSU* (Editor in Chief), on numerous committees, as co-editor of the *CHEST* "Pearls" section, and on the Council of Governors representing South Carolina. We extend our heartfelt condolences to his wife, Claire, and the entire Sahn family.

Dr. Sahn

FROM THE CEO: CHEST strengths include its spirit of innovation

BY STEPHEN J. WELCH
Interim EVP/CEO, CHEST

As a 22-year member of the senior staff of the American College of Chest Physicians, I am absolutely *thrilled* to have the opportunity to serve as its interim EVP/CEO for the current 2016-2017 fiscal year. Over the course of the years, I've been fortunate to oversee a number of CHEST's business units and divisions, including Publications, Marketing, Communications, Membership, International Development, and Information Technology (IT). This background has provided a stable foundation for a smooth transition and ensured that the organization continues to move forward to achieve its strategic plan and operational goals. That plan and those goals ensure that we will fulfill CHEST's mission and vision: "To champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research" and to be "the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care," respectively.


MR. STEPHEN J. WELCH

To this end, we are executing well as an organization. Our state-of-the-art Innovation, Simulation, and Training Center at the CHEST Global Headquarters in Glenview, Illinois, continues to provide outstanding hands-on educational events and opportunities, and our Education Calendar has something for just about everyone. Our annual Board Review courses continue to provide excellent content. The CHEST Annual Meeting 2016 in LA this October will showcase all that CHEST has to offer. And the list goes on.

One of CHEST's strengths is its spirit of innovation. Whether it's revamping the highly successful SEEK app into an easily accessible online library, adding more simulation and procedure-based training to our educational offerings, or providing our live courses as captured online "on-demand" programs, we are committed to finding ways to package and deliver meaningful education to our members and community. Our for-profit subsidiary, CHEST Enterprises, is providing professional education to industry through the PREP disease-state immersion program, and developing a data analytics product line that will provide insights into physician behavior. Our charitable foundation, the CHEST Foundation, gives nearly $500,000 in research and community service grants each year, to champion lung health. It has also expanded the number of available patient education resources in partnership with the ALA.

And in the past year, we have fully implemented CHEST's new innovative membership model to welcome more nonphysician health-care providers and give them opportunities to engage, learn, and participate. All of these things are incredibly exciting to me, and I'm grateful to be part of them.

But what I'm most excited and grateful for are the people who impact our organization. We have a diverse and passionate membership of physician and nonphysician health-care providers who want to provide the best care possible and positively impact outcomes.

Our dedicated faculty and volunteers generously give their time to the organization's work groups and programs so that they can give back to others in the field. Our hard-working leaders take responsibility and ownership of our programs and content. And, our outstanding staff operationalizes the strategic plan and goals of the organization hand-in-hand with those leaders, volunteers, faculty, and members. Together, it all results in the excellent programs you have come to expect from CHEST.

Thank you for participating and supporting this robust, dynamic organization. I am excited for the future for CHEST, and I look forward to seeing you at CHEST 2016 in Los Angeles!

If you have thoughts or ideas about how we can enhance our work to be a global leader in chest medicine, connect with me anytime. I invite you to follow and connect with me on Twitter (@RocketSurgery99), or look for me at upcoming CHEST events.

Los Angeles Inspires With Arts, Culture

Los Angeles has a flare for the dramatic, and we're not just talking about Hollywood's fast-paced, larger-than-life movie industry. When you visit Los Angeles, October 22 – 26, for CHEST 2016, be sure to check out the assortment of arts and culture venues located nearby your home base at CHEST 2016.

CHEST Annual Meeting 2016

Los Angeles has more museums and theaters than any other US city, and we'll highlight a few local favorites. For more information on LA's thriving arts and culture scene, check out discoverlosangeles.com.

• The Dorothy Chandler Pavilion – (7-minute drive) – This hall is part of the Los Angeles music center. On October 22 – 23, watch three major US ballet companies share the stage in *Celebrate Forsythe*. Or, take in *The Source*, a music-theater production about Chelsea (formerly Bradley) Manning and WikiLeaks.

• The Ahmanson Theatre – (7-minute drive) – This theater is also part of the Los Angeles music center. Be captivated by a 2016 Tony Award–winning play, *A View from the Bridge*.

• Walt Disney Concert Hall – (6-minute drive) – Home to the Los Angeles Philharmonic Orchestra and the Los Angeles Master Chorale, it is also part of the Los Angeles music center. Listen to the beautiful sounds of Mahler's Ninth or Hilary Hahn on violin.

• MOCA Grand – (5-minute drive) – The Museum of Contemporary Art has three locations in Los Angeles. The main branch, located on Grand Avenue, is the closest to the convention center. Check out the museum's main galleries at this location.

• The Getty Center – (30-minute drive) – See spectacular art and architecture at the top of Los Angeles.

Note: all estimated times assume you are starting at the Los Angeles Convention Center.

Los Angeles' arts and culture are sure to inspire you, and CHEST 2016 will move you with the latest clinical information in chest medicine.

Connect with the CHEST Foundation at CHEST 2016

At this year's annual meeting, the CHEST Foundation will have several new and exciting events, including three networking happy hours for women in lung health, international members, and nonphysician providers, and two educational sessions developed by CHEST Foundation leaders and volunteers, Chris Carroll, MD, FCCP, and Muhammad Adrish, MD, FCCP.

The new sessions will focus on conducting effective research and a panel discussion with past CHEST Foundation grant winners on creating successful community service programs. Also, we will be hosting a "Young Professionals Reception" Monday evening.

Be sure to stop by the Donor Lounge to network with leadership, meet the foundation staff, grab a coffee, and learn how you can engage with the CHEST Foundation. If you arrive early on Saturday, October 22, don't miss out on our afternoon "Champions for Lung Health Event," where CHEST Foundation leadership will be giving back to the Los Angeles community by volunteering at a COPD screening.

CHEST FOUNDATION

We are also proud to introduce our 2016 CHEST Foundation grantees at Monday's Opening Session. This year, we will be awarding nearly a half-million dollars in funding to the next generation of lung health champions.

Our grants and programs have made a difference in the lives of our members and their patients through the impactful clinical research and impressive humanitarian projects our grantees have created. Since 1996, we've provided over $10 million in funding for clinical research and community service, with a reach that spans from Texas to Tanzania.

The foundation is a go-to resource for young investigators seeking research funding, and the projects we support lead to treatment and patient care breakthroughs.

We hope to see you at one of our open invitation activities to learn more about how the CHEST Foundation can support you in your efforts to champion lung health.

Our staff matters

The CHEST staff's monthly e-newsletter, *Staff Matters*, recently highlighted two examples that demonstrate the passion, talent, and cooperation exhibited by CHEST staff as colleagues working together to advance CHEST's mission. As the name of the newsletter indicates, our staff really does matter and continually provides opportunities fostering our mission.

Chad Jackson with an official welcome letter and FCCP certificate. Left to right: Nicki Augustyn, SVP, Education; Chad Jackson, MS, RRT, FCCP, Senior Director, Simulation, e-Learning and Innovation; Sue Reimbold, SVP, Marketing and Communications, Executive Director, CHEST Foundation.

CHEST staff working together packaged enough food for 76 Haitian children for 1 year.

Celebrating a CHEST first

Chad Jackson recently earned a designation as Fellow of the American College of Chest Physicians (FCCP). He's the first nonphysician member of CHEST staff to earn this designation. In light of this great honor, Chad was asked some questions about what this means to him.

Q: What does this honor mean to you?
A: It means a lot. More than I think I can eloquently describe in a few words ...

I think it is important for the employees to know that CHEST is a HUGE name in the medical space of hospitals and health systems. CHEST also has an excellent reputation with advanced practice professionals who work with our CHEST physicians. When I told people at Florida State College of Medicine that I was coming to work for CHEST, they literally were giving me high fives in the hallways of the college.

I think this is an important perspective for employees to realize. We come to work day in and day out, and it is just a job to a lot of folks. But outside of these walls, CHEST is well-known as a leader in the pulmonary, critical care, and sleep space. It was and still is an honor for me to work here, and I am truly blessed by being able to obtain my FCCP.

Q: Why did you choose to pursue obtaining an FCCP?
A: This is a realization of a dream that I had since coming to CHEST more than 8 years ago. Previously, as a nonphysician advanced professional practitioner, registered respiratory therapists (RRTs) like me could apply for membership only after you obtained a PhD. I was working on my PhD studies and had to take a break from my studies when life "intervened" and I had too much going on. At that point, I thought my dream of obtaining my FCCP was out of reach. When the membership model changed, I don't think anyone was as excited as I was when the board discussed these changes.

I am the perfect use-case for this new membership model. I wanted a "home" for my practice. For years, I have been a member of the American Association of Respiratory Care (AARC), which many hospital-based RRTs call their home. I have also been a member of the Society of Critical Care Medicine (SCCM) and was even a Fundamentals of Critical Care Skills (FCCS) course instructor. But, my passion was educating physicians and other health care practitioners in pulmonary, critical care, and sleep medicine.

Obtaining my FCCP is the ultimate recognition for me and the work I have been doing in this medical education space.

Q: What does it mean, as a nonphysician, to have the opportunity to be recognized for your commitment to advancing chest medicine?
A: It is HUGE! I think that there are many more folks who would like to receive recognition for their work in this field, who don't feel that their current "home" organizations appreciate their efforts. For me, again, it was a dream now realized, to be able to be recognized for my efforts along with my physician friends who work so hard to provide the best possible education for our members and attendees.

* * *

CHEST staff in action

In July, as part of our annual staff appreciation day, CHEST staff members were offered the opportunity to visit the "Feed My Starving Children" facility for a few hours in the morning to prepare food portions for needy children in different parts of the world. The staff's response was tremendous, and our incoming President, Dr. Gerard Silvestri, joined us, as we took to different stations portioning out dry ingredients for individual food packets. We soon learned that our packets were destined for Haiti's children! This community outreach event brought our staff together, volunteering time toward a mutual goal of helping others and advancing CHEST's mission in our own personal way.

Here is what we achieved that morning:

- Large cartons packed: 129
- Individual meals filled and packed: 27,864
- Children fed for 1 year: 76

In the words of our interim CEO, Steve Welch, "As I looked around at everyone at the event, I was so touched by the enthusiasm that you all showed, and the comments I heard afterward, that I've asked HR to look into setting up similar things as a regular opportunity for those staff who wish to participate, in order to continue fostering an environment of volunteerism and giving back. What we do every day is incumbent on our volunteers giving their time for CHEST, and it sets a great example when we are also volunteering for causes that are important to us individually."

This Month in *CHEST:* Editor's Picks

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

A Novel PF4-Dependent Platelet Activation Assay Identifies Patients Likely to Have Heparin-Induced Thrombocytopenia/Thrombosis. *By Dr. A Padmanabhan et al.*

Safety and Tolerability of Alveolar Type II Cell Transplantation in Idiopathic Pulmonary Fibrosis. *By Dr. A. Serrano-Mollar et al.*

Hypertension Is Associated With Undiagnosed OSA During Rapid Eye Movement Sleep. *By Dr. S. L. Appleton et al.*

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PROFESSIONAL OPPORTUNITIES

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Interested physicians should contact:
Kimberly Salvail
Huntsville Hospital
kimberly.salvail@hhsys.org
256-265-7073

NEBRASKA

BC/BE PULMONARY/ CRITICAL CARE

Opportunity for BC/BE Pulmonary/Critical Care Specialist with Mary Lanning Healthcare in Hastings Nebraska in a highly reputable hospital-employed practice.

Inpatient care would be provided infull service regional referral center that includes 161 beds and a modern 10 bed ICU staffed by excellent nurses and respiratory therapist.

Outpatient care would be provided in an office conveniently located adjacent to the hospital and a well-established outreach network.

This position offers competitive salary and benefits including CME, paid vacation, student loan repayment and relocation fees. J1 and H1B are encouraged to apply.

For complete information regarding this opportunity, please contact Brad Lindblad, Director of Physician Development at 402-460-5615 or via email at **blindblad@marylanning.org**

NETWORKS: Incident sarcoidosis, AHF, Sleep research

Occupational and Environmental Health

Incident sarcoidosis

The history of sarcoidosis dates back to 1869, when Dr. Jonathan Hutchinson described symmetrical purple skin plaques on the legs and hands of a coal-wharf worker (James and Sharma. *Curr Opin Pulm Med*. 2002;8[5]:416). However, despite its distant beginning, much remains unknown. It has been hypothesized that environmental factors play a pivotal role in disease onset and course, as is evidenced by the notable exposure in the first historical case.

DR. HENA

Research has shown environmental factors, such as wood smoke, tree pollen, insecticides, and mold; as well as occupational exposures, such as flight deck work on aircraft carriers, metalworking, construction, and firefighting, carry increased risk of sarcoidosis (Newman et al. *Am J Respir Crit Care Med*. 2004;170[12]:1324; Newman and Newman. *Curr Opin Allergy Clin Immunol*. 2012;12[2]:145). A significantly high annual incidence of sarcoidosis was first demonstrated in FDNY firefighters between 1985 and 1998; 12.9/100,000, as compared with 2.5 to 7.6/100,000 for US white men (Prezant et al. *Chest*. 1999;116[5]:1183).

Following the attack on the World Trade Center (WTC) on September 11, 2001, a further increase in sarcoidosis incidence was found in FDNY firefighters exposed to WTC "dust" during the collapse and rescue/recovery effort (Izbicki et al. *Chest*. 2007;131[5]:1414). As of 2015, a total of 75 FDNY firefighters have been identified as having new post-9/11 sarcoidosis.

Since the WTC-exposed FDNY firefighters with new-onset sarcoidosis since September 11, 2001 can be considered to have had a WTC "trigger," we have a unique opportunity to define the clinical patterns and outcomes of incident sarcoidosis following a distinct exposure. Members of the Occupational and Environmental NetWork Steering Committee are currently investigating this aim and others in a National Institute of Occupational Safety and Health (NIOSH)-granted cohort study. We hypothesize that the patterns of organ involvement, and time course of disease progression or resolution, may significantly differ in this group as compared with the general population. Preliminary results of our study of WTC-exposed FDNY firefighters will be presented at CHEST 2016 in Los Angeles.

Kerry Hena, MD
Physician-in-Training Member

Palliative and End-of-Life Care

Integrated palliative care for mechanical circulatory support

Patients with advanced heart failure (AHF) have well-documented needs for comprehensive supportive care services in the critical care setting. Notable symptom burden, high morbidity and mortality, prognostic uncertainty, and need for care coordination across hospital settings pave the way for palliative care (PC) teams to work symbiotically with advanced heart failure specialists and intensivists.

Furthermore, the expanded availability of mechanical circulatory support (MCS) technology

extends these clinical and ethical challenges to balancing longevity, quality of life, and resource utilization, most prominently in the ICU.

To date, collaborations between PC, AHF specialists, and critical care have tended to be reactive, not proactive – palliative consultation usually occurs after a medical or surgical crisis (for example, the massive stroke, MCS thrombus, sepsis, and multiorgan failure) or after a prolonged ICU stay without clear improvement in patient function or prognosis.

This reactive consult may be misperceived by patient and family as "giving up."

At our institution, we have worked to develop a model of seamless integration of interdisciplinary palliative care consultation upstream in advanced heart failure patient care that aims to preempt many dilemmas in the ICU around complex medical decision making and end-of-life care.

Through development of therapeutic supportive care relationships, preparedness planning, and discussions of goals of care early in treatment pathways involving critical care resources – including MCS evaluation and cardiac transplantation – this model purports to strengthen appropriate critical care delivery for patients with advanced heart failure.

This model has evolved to where PC consultation becomes a structured part of the preoperative evaluation of all candidates for left-ventricular assist device as destination therapy (LVAD-DT). The result is a collaborative approach where patients and families see PC as part of the continuum of whole-person AHF care, rather than a negative alternative.

MCS implantation is on the rise. While MCS technology continues to evolve, its recipients remain seriously ill.

Normalizing and integrating PC consultation as part of high quality AHF and critical care sends an important message to patients and families: regardless of clinical outcome, relief from suffering matters throughout the trajectory of the illness experience.

Hunter Groninger, MD
Steering Committee Member

Respiratory Care

Professional relationships in RC

At the 2015 meeting of the American Association for Respiratory Care (AARC) in Tampa, there were more than 20 presentations given by FCCPs! Also, a majority of CHEST's Respiratory Care NetWork's steering committee was in attendance.


DR. FUHRMAN

To other members of CHEST, that might seem rather unusual. However, many CHEST members have connections with the field of respiratory care. In addition, CHEST as an organization has a professional relationship with the respiratory care field. CHEST has more than 10 official liaisons to respiratory care professional organizations.

Those organizations include: The Commission for Accreditation for Respiratory Care, which credentials all RC educational programs; The National Board for Respiratory Care, which provides the credentialing examinations for all RC practitioners in the United States; The National Association for Medical Direction for Respiratory Care (NAMDRC); the Board of Medical Advisors to the AARC; and the Respiratory Compromise Institute.

The Respiratory Care NetWork has the responsibility of identifying and nominating CHEST members for these liaison positions. These volunteer positions do involve work, yet past and present liaisons have enthusiastically fulfilled their respective roles. As one recently noted, "This work has been some of the most important endeavors of my professional career."

We are always seeking volunteers for these positions, which vary in time commitment and type of work involved. Please contact the Respiratory Care NetWork (mkosinski@chestnet.org) for further information. These organizations accomplish the type of things that made us all want to get into medicine. Be a part of those important efforts!

Thomas Fuhrman, MD, FCCP
Steering Committee Member

Sleep Medicine

Listening to patient voices: Sleep Apnea Patient-Centered Outcomes Network (MyApnea.org)

The US Department of Transportation's (DOT) Federal Motor Carrier Safety Administration (FMCSA) and Federal Railroad Administration (FRA) recently called for input for obstructive sleep apnea screening and treatment for transportation workers.

The DOT (https://www.transportation.gov) encouraged input from the public regarding this important transportation safety issue. This concept of engaging the public (which includes patients) with sleep disorders is gaining momentum as patients are increasingly partnering with researchers, clinicians, and policy makers to improve the delivery of care and research efforts in sleep medicine.


DR. SHAH

A remarkable example of such an effort is the Sleep Apnea Patient-Centered Outcomes Network (SAPCON; MyApnea.Org) (Redline et al. *JCSM*. 2016;12[7]:1053). This patient-powered research network was initiated in 2013 to improve the diagnosis and treatment of sleep apnea through the active engagement of patients, families, researchers, and health-care providers in a virtual community that facilitates patient-centered research. The need for such an initiative reflects the paucity of patient-centric evidence from large populations to inform insurers, public policy makers, medical schools, and clinicians on the best ways to screen, diagnose, and treat patients with sleep apnea.

As of August 2016, over 8,000 individuals across the globe have joined SAPCON. There are approximately 500 unique visitors to the site per day, with over 2,500 posts on over 250 topics, including driving and general transportation safety concerns. Further engagement of patients and key stakeholders through forums and patient-centered networks can promote the "patient voice" in public policy, while linking patient needs for better information with responsive research and policy development.

Neomi Shah, MD, MPH
Steering Committee Member

NetWorks Challenge 2016

Donate to the CHEST Foundation from now until the CHEST Annual Meeting 2016. Mark your NetWork when making your donation to receive credit. Donate here:

- Online: at chestmeeting.chestnet.org
- By phone: 224/521-9527
- By mail: download our donation form and mail to CHEST Foundation, 2595 Patriot Boulevard, Glenview, IL 60026

Three Ways to Win

Round 1

Highest percentage of participation by NetWork Steering Committee

Winning NetWork Steering Committees will receive:

- Additional time at the meeting – 90 minutes total
- Travel grants to CHEST 2016

First Half Winners are: Women's Health NetWork and Occupational and Environmental Health NetWork

Second Half Winners (announced during CHEST)

Round 2

Total amount contributed by NetWork Steering Committee

Winning NetWork Steering Committees will receive:

- One seat (public member) on the CHEST Foundation Awards Committee for the following year

Bonus: The CHEST Foundation will match funds raised by the two winning NetWork Steering Committees that meet a minimum of $15,000 and up to $25,000 for a clinical research grant.

Round 3

Highest percentage of participation by a NetWork's membership

Number of winners: two for travel grants, four for membership waivers

Need more info?

Visit: http://chestmeeting.chestnet.org/Blogs/2016/04/CHEST-2016-NetWorks-Challenge

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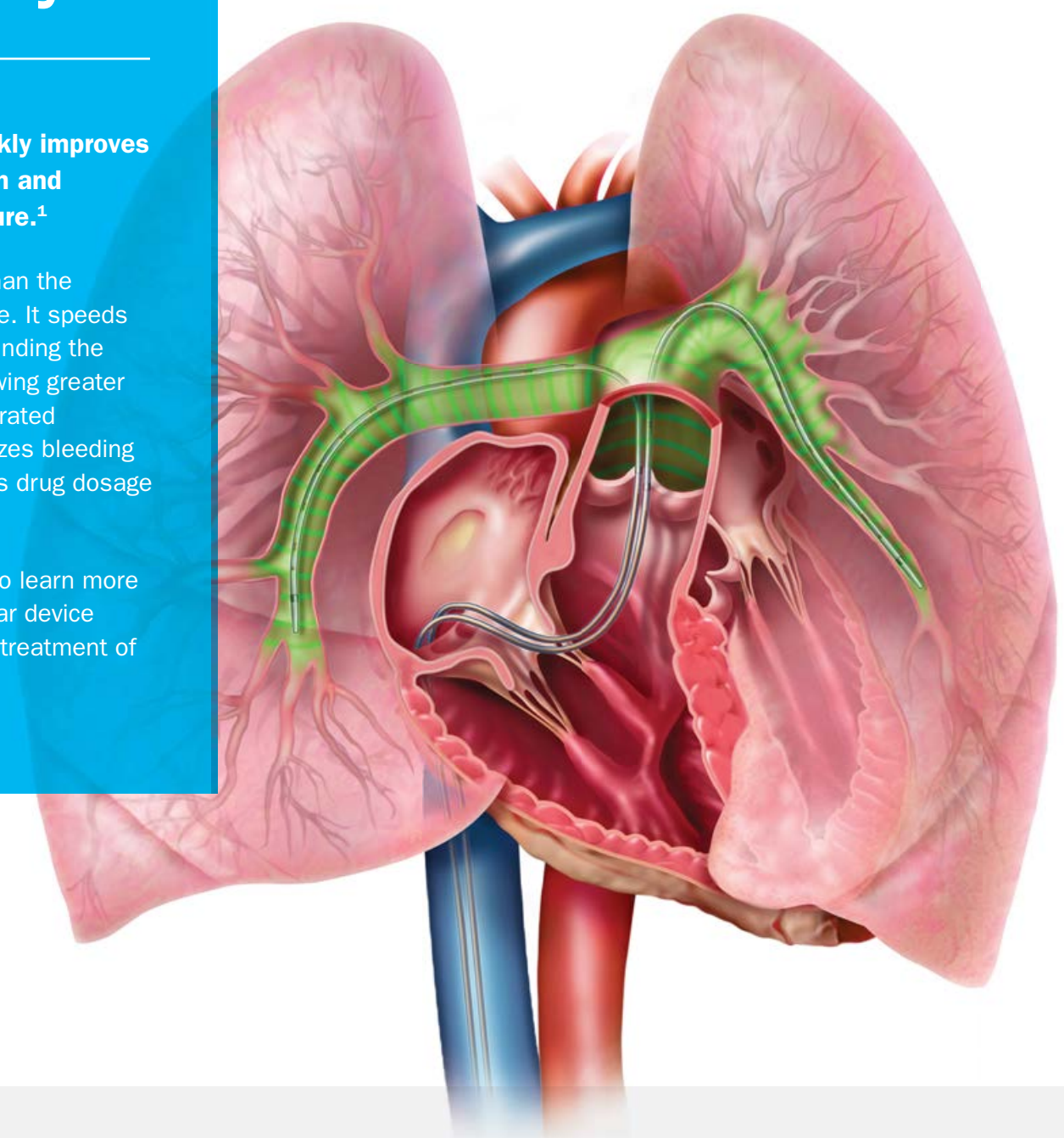
Dear Clot,

You really don't take my breath away.

The EKOS® System quickly improves right ventricular function and pulmonary artery pressure.[1]

EKOS® does much more than the current standard of PE care. It speeds time to dissolution by unwinding the clot's fibrin structure, allowing greater lytic dispersion and accelerated absorption.[2] It also minimizes bleeding risk, requiring up to 4x less drug dosage than systemic delivery.[3,4]

Visit **www.ekoscorp.com** to learn more about the only endovascular device cleared by the FDA for the treatment of pulmonary embolism.



1 *In the Seattle II study of 150 patients with massive or submassive PE using an EKOS® and lytic combination, the mean RV/LV ratio decreased from 1.55 pre-procedure to 1.13 at 48 hours post-procedure (P<0.0001) while PA systolic pressure decreased from 51.4mmHg to 36.9mmHg (P<0.0001).*

2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

3 *Kucher, N., et al., Circulation, Vol. 129, No. 4, 2014, 479–486.*

4 *Piazza, G., et al., American College of Cardiology 63rd Annual Scientific Session, Wash D.C., March 30, 2014.*

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

EKOS CORPORATION | 11911 N. Creek Pkwy S. | Bothell, WA 98011 | 888.400.3567 | **EKOSCORP.COM**