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MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Emphysema in the right-middle lobe regressed 0.7% with losartan and progressed 3.3% with placebo, Dr. Allison Lambert reported.

Losartan may slow emphysema's progress

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2015

MONTREAL – Daily treatment with the antihypertensive drug losartan for a year appeared to slow progression of emphysema, compared with placebo, in a controlled pilot study involving 46 patients at one U.S. center, Dr. Allison Lambert reported at the annual meeting of the American College of Chest Physicians.

One year of daily, 100-mg oral treatment with the angiotensin receptor–blocking drug losartan in patients with emphysema produced a statistically significant regression of the disease in their right-middle lung lobes, compared with progression of right-middle lung lobe disease among control patients, as assessed by CT lung scans. In this lung segment, emphysema regressed by 0.7% in patients on losartan (Cozaar), compared with an average 3.3% rate of progression in patients on placebo.

The losartan-treated patients also showed a consistent pattern of either substantially slowed or reversed emphysema throughout multiple lung segments, although the between-group differences did not reach statistical significance in any

See **Losartan** • *page 10*

Pediatric pulmonary hypertension guideline is issued

Includes section on pharmacotherapy.

BY MARY ANN MOON
Frontline Medical News

The first-ever clinical practice guideline for assessing and managing pulmonary hypertension (PH) in the pediatric population was released by the American Heart Association and the American Thoracic Society and has been published online in Circulation.

The two organizations developed this guideline because the causes and treatments of PH in neonates, infants, and children are often different from those in adults.

The literature for adult PH is "robust," and there are several treatment guidelines available, whereas pediatric PH has not been well studied, "and little is understood about the natural history, fundamental mechanisms, and treatment of childhood PH," said Dr. Steven H. Abman, cochair of the guideline committee and a pediatric pulmonologist at the University of Colorado and Children's Hospital, both in Denver.

"It's important to note that, although these guidelines provide a foundation for taking care of children with pulmonary hyperten-

See **Pediatric PH** • *page 6*

INSIDE

MMF as effective as cyclophosphamide for sclerodermal lung disease

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2015

MONTREAL – The immunosuppressant mycophenolate mofetil worked as effectively as cyclophosphamide for treating scleroderma-related interstitial lung disease while being better tolerated and causing fewer adverse effects in a multicenter, head-to-head comparison with 142 randomized patients.

"The findings support the increasingly common clinical practice of prescribing MMF [mycophenolate mofetil] for this disease," Dr. Donald P. Tashkin, FCCP, said at the annual meeting of the American College of Chest Physicians.

Another limitation of

See **MMF** • *page 4*

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How could we improve utilization of this important pathway for patients with PAH?

In the REVEAL Registry, more than 50% of patients with PAH were not receiving a parenteral prostanoid at time of death[1]*

*Data from REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management); US-based, observational registry involving 55 academic and community-based treatment centers. 3515 patients enrolled between March 2006 and December 2009.[2] REVEAL was funded and sponsored by Actelion Pharmaceuticals US, Inc.

References: 1. Farber HW, Miller DP, Meltzer LA, McGoon MD. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: insights from the REVEAL Registry. *J Heart Lung Transplant*. 2013;32(11):1114-1122. **2.** McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. *Eur Respir Rev*. 2012;21(123):8-18.

ACTELION

Yoga performs like pulmonary rehab for COPD patients

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2015

MONTREAL – A structured regimen of regular yoga exercises was as effective as a standard pulmonary rehabilitation program in patients with chronic obstructive pulmonary disease for improving lung function, exercise tolerance, dyspnea severity, and quality of life in a single-center, randomized comparison of the two strategies with 60 patients.

Also, chronic obstructive pulmonary disease (COPD) patients had a higher level of acceptance of yoga and were more comfortable doing it, compared with standard pulmonary rehabilitation, and yoga is cost effective given the minimal equipment required, Dr. Randeep Guleria said at the annual meeting of the American College of Chest Physicians.

"Patients with difficulty walking, osteoarthritis, knee problems, or unable to do exercises like cycling or treadmill found yoga to be much more acceptable," Dr. Guleria said in an interview. Acceptance of yoga was also higher than standard rehabilitation among patients with more severe COPD, said Dr. Guleria, professor and head of the department of pulmonary medicine and sleep disorders at the All India Institute of Medical Sciences in New Delhi.

"I think that yoga could be a very valuable adjunct" to pulmonary rehabilitation in COPD patients, commented Dr. Roger S. Goldstein, FCCP, director of the divisional program in respiratory rehabilitation at the University of Toronto. Dr. Goldstein speculated that even better than comparing yoga against conventional pulmonary rehabilitation would be a study that compared a combined yoga plus rehabilitation program against standard rehabilitation alone.

The 12-week study enrolled 60 patients who averaged 56 years old and who had been diagnosed with COPD for an average of 8 years. Just under a third of the patients had moderate COPD, 42% had severe COPD, and 28% had very severe COPD.

Thirty patients were randomized into a yoga program that included 4 weeks of biweekly 1-hour sessions that instructed patients in a series of physical postures, breathing technique, and meditation and relaxation. That was followed by 8 weeks during which patients were mostly left to perform their learned exercises on their own, but with a supervised session once every 2 weeks. The other 30 patients participated for 12 weeks in a pulmonary rehabilitation program that included patient education, upper and lower limb exercises, and breathing exercises.

At baseline and 12 weeks, researchers performed two measures of dyspnea severity, 6-minute walk distance, a quality of life assessment, and two serum markers of inflammation, C-reactive protein and interleukin 6.

Both interventions resulted in modest but statistically significant improvements, such as increases in 6-minute walk distance and a reduced modified Borg scale assessment. The average Borg scale score fell from 1.5 at baseline to 1.0 after 12 weeks in the yoga patients, and from 3.0 at baseline to 0.5 after 12 weeks in the rehabilitation patients. A score that measured total quality of life improved by an average of 32% in the yoga patients and by 21% in the rehabilitation patients. At 12 weeks, there were no statistically significant between-group differences.

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VIEW ON THE NEWS

Dr. Eric Gartman, FCCP comments: As our patients with progressive COPD have increasing amounts of functional decline, we are often left with little to offer. This study using yoga mirrors similar successes using alternative low impact exercise strategies in COPD patients in efforts ranging from smoking cessation to symptom reduction. It is clear that patients are very accepting of these modalities, and they should find their way into formal rehab programs. Furthermore, given the nature of the exercises, they hold promise to create a longlasting effect on functional improvements, and may prove more successful if patients can continue their regimen independently long after formal rehab has been completed.

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

CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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Reduced-nicotine cigarettes cut smoking

BY MARY ANN MOON
Frontline Medical News

Reduced-nicotine cigarettes decreased tobacco dependence and the number of cigarettes smoked, with very little evidence of withdrawal or compensatory smoking, in a preliminary study reported online Oct. 1 in the New England Journal of Medicine.

Moreover, study participants who smoked very-low-nicotine cigarettes for the 6-week study were twice as likely to report that they attempted to quit 1 month later, compared with participants who smoked their usual brand or control cigarettes that had the usual nicotine content.

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Reduced-nicotine cigarettes differ from "light" cigarettes in that the latter don't actually reduce the nicotine content of the tobacco but instead increase ventilation of the cigarette – a strategy that is often circumvented by smokers who cover the ventilation holes or increase the number of cigarettes they smoke, said Eric C. Donny, Ph.D., of the department of psychology, University of Pittsburgh, and his associates.

The U.S. Food and Drug Administration recently was granted the authority to reduce, but not eliminate, nicotine in cigarettes if such action were deemed likely to benefit public health. However, no large-scale clinical trials have yet been performed to assess the potential benefit to public health.

Dr. Donny and his associates, supported by the National Institute on Drug Abuse and the FDA Center for Tobacco Products, conducted a double-blind, randomized trial at 10 sites comparing cigarettes with five levels of nicotine content among 839 adult smokers who were not planning to quit in the near future.

The study participants were assigned to smoke their usual brand of cigarettes (118 study subjects); control cigarettes containing the usual 15.8 mg of nicotine/g of tobacco (119 subjects); or experimental reduced-nicotine cigarettes containing 5.2 mg/g of nicotine (122 subjects), 2.4 mg/g (119 subjects), 1.3 mg/g (119 subjects), or 0.4 mg/g (242 subjects).

All the cigarettes were provided free of charge, and the smokers were paid for participating in the study. The dropout rate was only 8% at week 6 and did not differ significantly among the study groups.

The primary outcome – the average number of cigarettes smoked per day during week 6 – was markedly higher with the usual-brand group (22.2) and the control-cigarette group (21.3) than it was with the three lowest-nicotine groups (16.5, 16.3, and 14.9, respectively). That represents a reduction of 23%-30% in the number of cigarettes smoked in the latter three groups.

Tobacco dependence, as measured by the Wisconsin Inventory of Smoking Dependence Motives and the Fagerstrom Test for Nicotine Dependence, also was markedly lower with reduced-nicotine cigarettes.

Withdrawal symptoms did not increase; and during a brief voluntary abstinence period, smokers in the three lowest-nicotine groups actually reported fewer cravings than did those in the higher-nicotine groups, the investigators said (N Engl J Med. 2015 Oct 1;373[14]:1340-9).

At follow-up 30 days after completing the study, 34.7% of the participants who had smoked cigarettes with 0.4 mg/g of nicotine reported attempting to quit smoking, compared with 17% of those who had smoked cigarettes with 15.8 mg/g. In addition, participants who had smoked cigarettes with 1.3 mg/g or 0.4 mg/g of nicotine were still smoking significantly fewer cigarettes per day, even though the study had ended.

"In summary, these data suggest that if nicotine content is adequately reduced, smokers may benefit by smoking fewer cigarettes and experiencing less nicotine dependence, with few negative consequences," Dr. Donny and his associates wrote. "If confirmed in longer-term studies, these findings suggest that, when combined with other tobacco-control policies (e.g., taxation and expanded access to treatment), limiting the nicotine content of cigarettes ... could improve public health."

The study authors added that a longer clinical trial is now underway to further assess reduced-nicotine cigarettes.

NIDA and the FDA Center for Tobacco Products supported the study. Dr. Donny reported having no relevant financial disclosures. Two of his associates reported ties to Pfizer, and two reported serving as expert witnesses regarding addiction litigation against tobacco companies.

VIEW ON THE NEWS

Time for a nicotine-reduction policy?

The findings of Dr. Donny and his colleagues justify exploration of a national nicotine-reduction policy and should encourage clinicians in practice to consider reduced-nicotine cigarettes as a potential resource for patients who want to quit smoking.

Given the number of current smokers in the United States, we can expect at least 20 million Americans to die prematurely if they continue to smoke. Reducing the nicotine content of cigarettes so that they are less addictive appears to be the most-promising regulatory policy option for preventing those 20 million premature deaths.

Dr. Michael Fiore and Timothy Baker, Ph.D., are at the Center for Tobacco Research and Intervention and the department of medicine at the University of Wisconsin, Madison. They reported having no relevant financial disclosures. Dr. Fiore and Dr. Baker made these remarks in an editorial accompanying Dr. Donny's report (N Engl J Med. 2015 Oct 1; 373[14]:1289-91).

Fewer side effects

MMF *from page 1*

cyclophosphamide is that it is usually not used for more than 1 year because of concerns that longer use substantially increases a patient's risk for developing malignancy. That's another reason why there is a "strong need for longer and safer immunosuppressive treatment with a drug like MMF," said Dr. Tashkin, a pulmonologist at the University of California, Los Angeles.

When used in this trial on patients with scleroderma, as defined by the American College of Rheumatology and with a baseline forced vital capacity of no more than 80% of predicted, "MMF was effective at reducing the rate of decline in vital capacity, improving symptoms such as dyspnea – the cardinal symptom of interstitial lung disease, and reducing lung fibrosis seen on CT scans, and MMF was better tolerated" than cyclophosphamide, Dr. Tashkin said in an interview. Cyclophosphamide treatment in this new trial "was associated with more toxicity, especially hematologic toxicity, an was not nearly as well tolerated, with more patients withdrawing because of side effects or a perceived lack of benefit."

"Cyclophosphamide has a lot of side effects. MMF is just now coming into increased use. I think we'll see it being used more for first-line treatment because the side effects with cyclophosphamide are so bad," commented Dr. Thomas Fuhrman, chief of anesthesiology at the Bay Pines (Fla.) VA Healthcare System.

Dr. Tashkin and his associates conceived the Scleroderma Lung Study II (SLSII) as a follow-up to the first SLC run about a decade ago that compared cyclosphosphamide against placebo for controlling progression of interstitial lung disease in scleroderma patients. The results from the first SLC trial established cyclosphosphamide as a treatment that could preserve forced vital capacity percent predicted in patients with scleroderma-induced interstitial

Continued on following page

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

I think we'll see MMF being used more for first-line treatment because the side effects with cyclophosphamide are so bad, Dr. Donald P. Tashkin said.

Continued from previous page

lung disease (N Engl J Med. 2006 Jun 22;354[25]:2655-666).

For the new study they enrolled patients who averaged 52 years old, with an average scleroderma duration of almost 3 years. Their average percent predicted forced vital capacity was 67%, and their baseline dyspnea index was 7.1.

Patients received either a target oral MMF dosage of 1.5 g b.i.d. for 2 years, or a target cyclophosphamide dosage of 2 mg/kg/day for up to 1 year, followed by a year of placebo. Cyclophosphamide treatment was capped at 1 year to protect against causing malignancy. Among the 73 patients randomized to the cyclophosphamide arm, 58 had data available after 12 months with 48 patients continuing on cyclophosphamide, and 53 had data available out to 2 years, with 37 patients remaining on their assigned regimen. Among 69 patients randomized to MMF 58 had data available after 12 months with 53 continuing on MMF, and 53 patients had data available through 24 months with 49 remaining on their MMF regimen.

After 24 months, the average percent predicted forced vital capacity, the study's primary endpoint, had increased by 3.3% among patients on MMF and 3.0% among those in the cyclophosphamide arm in an intention-to-treat analysis, a nonsignificant difference. After 24 months 72% of patients in the MMF arm and 65% in the cyclophosphamide arm had a positive change, compared with baseline, in their percent predicted forced vital capacity, Dr. Tashkin reported.

MMF also showed a superior overall safety profile. Patients on cyclophosphamide had a significantly increased rate of withdrawal from the study medication. Drug discontinuations occurred in 36 of the cyclophosphamide patients and in 20 of those on MMF. Serious adverse events attributable to study medication occurred in eight patients on cyclophosphamide and three patients on MMF. The most frequent protocol-defined adverse event was leukopenia, which occurred in 30 patients on cyclophosphamide and four patients on MMF.

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VIEW ON THE NEWS

More experience needed to confirm results

Dr. Daniel R. Ouellette, FCCP, comments: Unlike idiopathic pulmonary fibrosis (UIP pattern) unrelated to collagen vascular disease, interstitial lung diseases related to autoimmune conditions are sometimes amenable to treatment. However, the potent immunosuppressive agents used to treat these conditions are frequently associated with adverse side-effect profiles. Increasingly, safer agents such as mycophenolate have been successfully used. The recent report that treatment of scleroderma-related interstitial lung disease with mycophenolate may be just as effective as cyclophosphamide treatment is therefore welcome news. Some caution must be urged, as more experience must be gained with this treatment to confirm the results.

First-ever guideline issued

Pediatric PAH *from page 1*

sion, we still have a huge need for more specific data and research to further improve outcomes," he said in a statement accompanying the guideline.

The guideline was developed by a working group of 27 clinicians and researchers with expertise in pediatric pulmonology, pediatric and adult cardiology, pediatric intensivism, neonatology, and translational science.

The guideline authors reviewed more than 600 articles in the literature, but given the paucity of high-quality data regarding pediatric PH, the guideline relies heavily on expert opinion and primarily describes "generally acceptable approaches" to diagnosis and management; more specific and detailed recommendations await the findings of future research, said Dr. Abman and his associates (Circulation. 2015 Oct 26. doi:10.1161/CIR.0000000000000329).

In the pediatric population, PH is defined as a resting mean pulmo-

We still have a huge need for more specific data and research to further improve outcomes.

DR. ABMAN

nary artery pressure greater than 25 mm Hg after the first few months of life and is usually related to cardiac, lung, or systemic diseases.

Idiopathic PH, a pulmonary vasculopathy, is a diagnosis of exclusion after diseases of the left side of the heart, lung parenchyma, heart valves, thromboembolism, and other miscellaneous causes have been ruled out.

The guideline emphasizes that children thought to have PH should be evaluated and receive treatment at comprehensive, multidisciplinary clinics at specialized pediatric centers.

"When children are diagnosed, parents often feel helpless. However, it's important that parents seek doctors and centers that see these children on a regular basis and can offer them access to new molecular diagnostics, new drug therapies, and new devices, as well as surgeries that have recently been

Continued on following page

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developed," Dr. Stephen L. Archer, cochair of the guideline committee and head of medicine at Queen's University, Kingston, Ont., said in the statement.

"These children suffer with health issues throughout their lives or die prematurely, particularly if they're not properly diagnosed and managed. But with the proper diagnosis and treatment at a specialized center for PH, the prognosis for many of these children is excellent," he noted.

Properly classifying the type of PH is a key first step in determining treatment.

Properly classifying the type of PH is a key first step in determining treatment.

The guideline addresses numerous methods for diagnosing and monitoring PH, including imaging studies, echocardiograms, cardiac catheterization, brain natriuretic peptide and other laboratory testing, 6-minute walk distance (at appropriate ages), sleep studies, and genetic testing.

The guideline specifically deals with persistent PH of the newborn and PH arising from congenital diaphragmatic hernia; bronchopulmonary dysplasia or other lung diseases; heart disease such as atrial-septal defect or patent ductus arteriosus; and systemic diseases such as hemolytic hemoglobinopathies and hepatic, renal, or metabolic illness; as well as idiopathic PH and PH that is related to high-altitude pulmonary edema.

Regarding ongoing outpatient care, the guideline recommends that children with PH receive influenza and pneumococcal vaccinations and prophylaxis for respiratory syncytial virus (if they are eligible), as well as antibiotic prophylaxis to prevent subacute bacterial endocarditis in those who are cyanotic or have indwelling central lines.

Growth must be monitored rigorously, and infections and respiratory illnesses must be recognized and treated promptly.

Any surgeries require careful preoperative planning and should be performed at hospitals with expertise in PH.

The guideline includes an extensive section on pharmacotherapy for childhood PH.

Topics addressed include the use of digitalis, diuretics, long-term anticoagulation, oxygen therapy, calcium channel blockers, phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, intravenous and subcutaneous prostacyclin therapy, and the transition from parenteral to oral or inhaled treatment.

In addition, the guideline addresses exercise and sports participation, travel restrictions, and contraceptive counseling for adolescent PH patients.

Finally, "given the impact of childhood PH on the entire family, [patients], siblings, and caregivers should be assessed for psychosocial stress and be readily provided support and referral as needed," the guideline recommends.

The pediatric PH guidelines are available at http://my.americanheart.org/statements.

VIEW ON THE NEWS

A new roadmap to pediatric PH diagnosis, care

Dr. Susan L. Millard, FCCP, comments: The pediatric pulmonary, pediatric cardiology, and neonatal and pediatric intensivists all have greatly anticipated directions for the care of pediatric pulmonary hypertension.

The guidelines have excellent care maps for the diagnosis and evaluation of the various etiologies of pulmonary hypertension.

The new pediatric PH guidelines also should help with insurance authorizations for the expensive medications for pulmonary hypertension.

Dr. Robyn J. Barst, who was a renowned leader in pediatric pulmonary hypertension and passed away in 2013, would have been so proud of this new pediatric PH guideline.

Decline in extent of emphysema

Losartan *from page 1*

other segment, said Dr. Lambert, of Johns Hopkins Hospital in Baltimore.

Throughout the entire lung, 12 months of losartan treatment was linked to an average 0.32% reduction in emphysema extent from baseline when measured by CT, compared with a 2.18% rate of emphysema progression in control patients on usual care, which just missed statistical significance ($P = .064$).

Data from other researchers "suggest the right-middle lobe most commonly progresses in emphysema," which may explain why that lung segment showed the most dramatic effect from treatment, Dr. Lambert said. Also striking was the consistent trend toward slowed emphysema progression in multiple lung segments.

Dr. Lambert called this a "proof of concept" trial. She and her associates have begun a larger, phase III version that will study the effect of 100-mg daily losartan during 1 year of treatment in 220 patients with emphysema, she said. This trial received funding from the Pulmonary Trials Cooperative of the National Heart Lung and Blood Institute.

"These are some of the most interesting and exciting data I've seen," commented Dr. David P.L. Sachs, who practices in Stanford, Calif., and cochaired the session in which Dr. Lambert gave her report.

"Having an agent that could slow progression of emphysema would be unique," he said in an interview. One aspect that makes this treatment especially attractive is losartan's extensive safety record as an antihypertensive drug that is also often used to treat patients with heart failure.

To put the 100-mg/day dosage used in the current study in perspective, results from a multicenter randomized trial of more than 3,800 heart failure patients published in 2009 showed that a losartan dosage of 150 mg once daily was safe and effective and produced outcomes superior to those seen with a 50 mg once-daily dosage (Lancet. 2009;374[9704]:1840-8).

Previously reported results from other groups showed favorable effects of losartan on animal models of emphysema. Nonprospective clinical studies also have suggested angiotensin-receptor blockers might benefit lung function and COPD.

The current study enrolled patients with mild to severe COPD who were current or former cigarette smokers with at least a 10 pack-year history and were on stable treatment for their COPD. The researchers excluded patients already taking an angiotensin-receptor blocker or angiotensin-converting enzyme inhibitor.

The study included 106 patients with COPD, including the 46 with emphysema at baseline. Their average age was about 58 years old, the enrolled patients included roughly equal numbers of men and women, and about two-thirds were current smokers. All patients had CT lung scans at baseline and after 6 and 12 months, as well as other lung function assessments. The primary endpoint was the amount of additional emphysema in patients' lungs beyond that seen at baseline using CT imaging.

The entire group of 106 COPD patients showed no significant differences in emphysema progression at either 6 or 12 months between the 54 patients treated with losartan and the 52 controls on placebo, but a second, prespecified analysis that focused only on the 46 enrolled patients who had visible emphysema at baseline showed a significant slowing of progression at the 1-year follow-up.

The study received partial funding from Merck, which markets losartan (Cozaar). Dr. Lambert and Dr. Sachs had no disclosures.

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VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP comments: These provocative results may have significant implication for future treatment of COPD patients. Until now, the mainstay of COPD treatment has been inhaled medications to optimize respiratory functional status. As needed, treatment of inflammation, supplemental oxygen use, antibiotics, and pulmonary rehab have been added. The reported study outlines a slowed progression, and some regression of emphysema changes. The addition, to the armamentarium for COPD treatment, of a medication that could slow progression and potentially lead to regression of disease would truly be life-changing for our COPD patients. Continued studies are needed to understand the potential promise for patients.

Inhaled budesonide cut bronchopulmonary dysplasia

BY MARY ANN MOON
Frontline Medical News

Inhaled budesonide delivered within 24 hours of birth decreases the incidence of bronchopulmonary dysplasia in extremely preterm neonates, but this benefit may be offset by a possible increase in mortality, according to a report published in the New England Journal of Medicine.

Systemic glucocorticoids reduce the rate of bronchopulmonary dysplasia, but appear to cause severe short- and long-term adverse effects including intestinal perforation and cerebral palsy. Administering the drugs by inhalation may avert these adverse systemic effects, but until now most studies of this mode of delivery have been small, haven't initiated the treatment immediately after birth, and have produced inconclusive results. So researchers performed a large double-blind placebo-controlled randomized trial in which inhaled budesonide or a matching placebo was administered within 24 hours of birth to 863 extremely preterm neonates.

The infants were treated at 40 medical centers in nine countries during a 3-year period, until they no longer needed supplemental oxygen and positive-pressure support or reached a postmenstrual age of 32 weeks, said Dr. Dirk Bassler of the University Hospital Zurich, and his associates.

The primary outcome measure – a composite of death or bronchopulmonary dysplasia at 36 weeks postmenstrual age – occurred in 40% of the budesonide group and 46% of the placebo group (relative risk, 0.86), indicating that the active drug produced a benefit of borderline significance, Dr. Bassler and his associates noted (N Engl J Med. 2015 Oct 14; doi: 10.1056/NEJMoa1501917).

However, when the two components of the composite outcome were examined separately, inhaled budesonide was significantly better than was placebo at reducing the rate of bronchopulmonary dysplasia but was associated with a nonsignificant excess in mortality. The lung disorder developed in 28% of neonates assigned to active treatment and in 38% of those assigned to placebo (RR, 0.74), while mortality was 17% for budesonide and 14% for placebo (RR, 1.24). Notably, the nonsignificant difference in mortality may have been due to chance, the investigators said.

Budesonide also significantly reduced the incidence of two important secondary outcomes: patent ductus arteriosus requiring surgical ligation (RR, 0.55) and the need for reintubation after completion of the study drug (RR, 0.58). The therapy did not offer any benefit over placebo in the frequency of all other secondary outcomes, including retinopathy of prematurity, brain injury, necrotizing enterocolitis, patent ductus arteriosus requiring medical treatment, infections, oral candidiasis requiring treatment, hypertension requiring treatment, hyperglycemia requiring treatment, length of hospital stay, increase in weight or head circumference, and age at the last use of respiratory pressure support.

The rates of adverse events did not differ significantly between the groups.

The overall efficacy of early inhaled budesonide, as well as its associated risks, cannot be ascertained from these short-term outcomes alone. "Follow-up of our study cohort, including assessment of neurodevelopmental outcomes at 18-22 months of corrected age, is currently under way," the researchers wrote.

This study was supported by the European Union and Chiesi Farmaceutici. Chiesi supplied the study drugs and Trudell Medical International supplied spacers for the inhalers. Dr. Bassler and three of his associates reported receiving grant support and personal fees from Chiesi Farmaceutici. The other authors reported no financial disclosures.

HERJUA/THINKSTOCK

VIEW ON THE NEWS

Budesonide's risks remain uncertain

The risk/benefit profile of inhaled budesonide to prevent bronchopulmonary dysplasia remains uncertain, given that the treatment effects on the composite outcome in this study moved in opposite directions.

Inhaled budesonide's ability to reduce rates of bronchopulmonary dysplasia, severe patent ductus arteriosus, and reintubation are probably real. But according to the available data, it is still uncertain whether the differential in mortality in favor of placebo represents truth or artifact.

Dr. Barbara Schmidt is in the division of neonatology at Children's Hospital of Philadelphia. She reported receiving nonfinancial support from Chiesi Farmaceutici outside of this work. Dr. Schmidt made these remarks in an editorial accompanying Dr. Bassler's report (N Engl J Med. 2015 Oct 14. doi: 10.1056/NEJMe1509243).

CMS 2016 schedule will pay for advance care planning

BY ALICIA GALLEGOS
Frontline Medical News

Officials at the Centers for Medicare & Medicaid Services have issued the final 2016 fee schedule for physicians, making modifications to the Physician Quality Reporting System (PQRS) and loosening requirements for its controversial two-midnight rule.

The fee schedule – the first since repeal of the Sustainable Growth Rate (SGR) formula and enactment of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) – includes changes to payment policies, modifications to misvalued codes, and updates to quality performance metrics under the PQRS, the Medicare Shared Savings Program, and Physician Compare, among others.

As part of the final fee schedule rule, CMS is relaxing its two-midnight rule to allow doctors greater flexibility when determining whether hospital stays are subject to the regulation.

For hospital stays for which physicians expect the patient will need less than two midnights of hospital care, an inpatient admission may still be payable under Medicare Part A on a case-by-case basis based on the admitting physician's judgment. CMS plans to use Beneficiary and Family Centered Care Quality Improvement Organizations to conduct initial medical reviews of claims for short-stay inpatient admissions. The claim reviews will focus on educating physicians and hospitals about the policy for inpatient admissions. Only physicians with questionable practice patterns, such as high rates of claims denial after medical review, will be referred to auditors, according to CMS.

"These changes continue CMS' long-standing emphasis on the importance of a physician's medical judgment in meeting the needs of Medicare beneficiaries," CMS officials stated in a fact sheet.

CMS also finalized two new advance care planning codes that will pay physicians for time spent discussing patient options for advance directives. The first code will cover an initial 30 minutes of the physicians' time, and the second code will cover additional 30-minute blocks as necessary.

The AMA Current Procedural Terminology (CPT) Editorial Panel and the AMA Relative Value Update Committee (RUC) created the new CPT codes and recommended the associated payments for calendar year 2015, but CMS delayed the codes' enactment until collecting public comment.

The fee schedule also includes modifications to the Medicare Shared Savings Program including a new measure on statin therapy for cardiovascular disease in the "preventive health domain" of the Shared Savings Program quality measure set. The final rule also clarifies how PQRS-eligible professionals participating within an Accountable Care Organization can meet reporting requirements.

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SELECTED IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

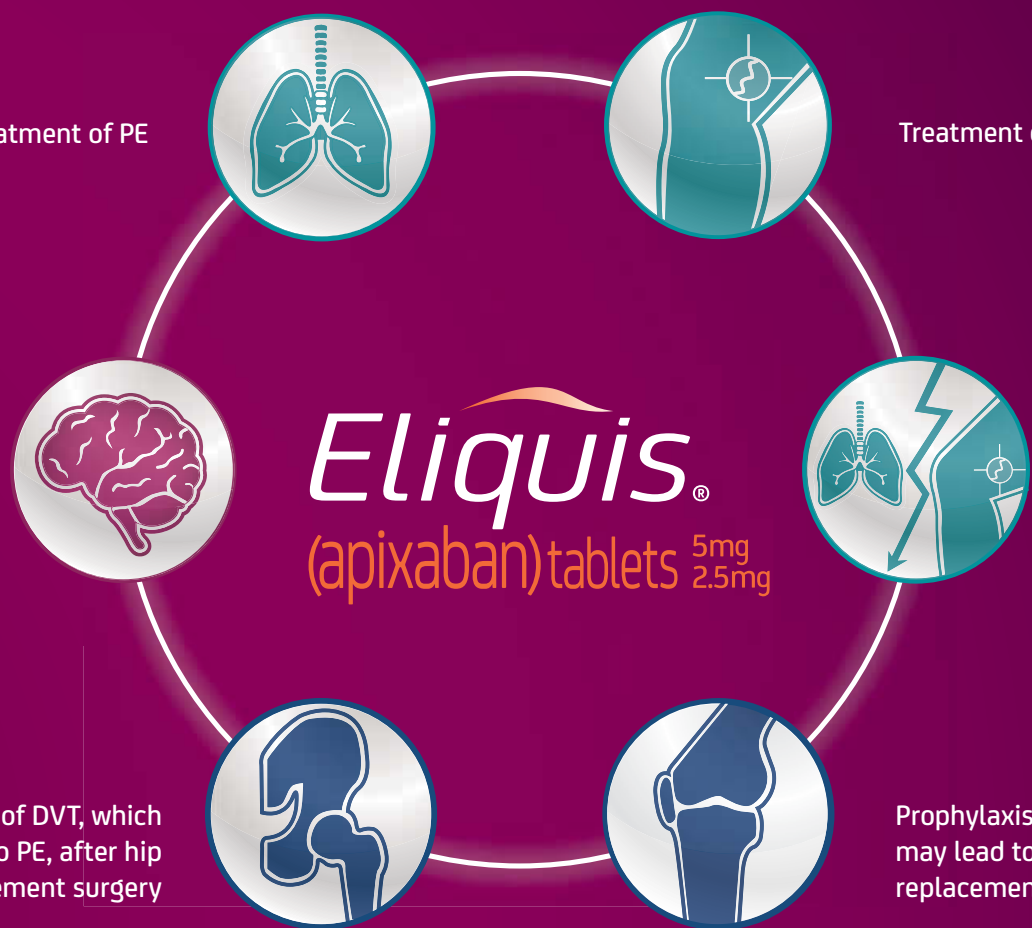
DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

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

Bristol-Myers Squibb Pfizer

Approved for 6 indications



Learn more about ELIQUIS for the treatment of DVT/PE and access reprints of our clinical studies.

hcp.eliquis.com

NVAF=nonvalvular atrial fibrillation; DVT=deep vein thrombosis; PE=pulmonary embolism.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

DRUG INTERACTIONS (CONT'D)

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

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

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

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

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

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

¶ GI bleed includes upper GI, lower GI, and rectal bleeding.

** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

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

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except nonvalvular atrial fibrillation patients who meet the criteria for dosage adjustment *[see Dosage and Administration (2.1) in full Prescribing Information]*. Patients with ESRD (CrCl <15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction *[see Warnings and Precautions]*. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

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COMMENTARY: Flu vaccine safety in patients with egg allergy

BY DOUGLAS S. PAAUW, M.D.
Frontline Medical News

A 35-year-old woman with asthma presents for a follow-up visit in October. You recommend that she receive the influenza vaccine. She tells you that she cannot take the influenza vaccine because she is allergic to eggs.

What do you recommend?

A. Give her the influenza vaccine.
B. Give her an oseltamivir prescription, and have her start it if any flu-like symptoms appear.
C. Give her the nasal influenza vaccine.
D. Give her the cell-based influenza vaccine.

The clinic I work in asks all patients if they have allergy to eggs before giving the influenza vaccine. If the patient replies yes, then the vaccine is not given and the physician is consulted.


DR. PAAUW

For many years, allergy to egg was considered a contraindication to receiving the influenza vaccine. This contraindication was based on the fear that administering a vaccine that was grown in eggs and could contain egg protein might cause anaphylaxis in patients with immunoglobulin E antibodies against egg proteins.

Fortunately, there is a good evidence base that shows that administering influenza vaccine to patients with egg allergy is safe.

This is extremely important information, because it is estimated that there are about 200,000-300,000 hospitalizations annually because of influenza. For the 2012-2013 influenza season, the CDC estimated that the flu vaccine prevented 6.6 million cases of influenza, 3.2 million doctor visits, and 79,000 hospitalizations. There were 170 pediatric deaths from the flu during the 2012-2013 influenza season (MMWR Morb Mortal Wkly Rep. 2013 Dec 13;62[49]:997-1000). The need for widespread vaccination is great, and decreasing the number of people unable to receive the vaccine is an important goal.

There are many studies in children and adults that show that those with egg allergy can be safely vaccinated with influenza vaccine. Dr. John M. James and colleagues reported a study of mostly children (average age, 3 years) with egg allergy confirmed with skin testing receiving influenza vaccine (J Pediatr. 1998 Nov;133[5]:624-8). A total of 83 patients with egg allergy received the vaccine (including 27 with a history of anaphylaxis or severe reactions after egg ingestion). No patients suffered severe reactions with the vaccine, with only four patients having mild, self-limited symptoms.

In another study, Dr. Anne Des Roches and colleagues performed a prospective, cohort study recruiting and vaccinating egg-allergic

RAQUEL CAMACHO GÃ³MEZ/THINKSTOCK

patients with trivalent inactivated influenza vaccine between 2010 and 2012 (J Allergy Clin Immunol. 2012 Nov;130[5]:1213-1216.e1). In the second year of the study, the focus was on recruiting patients with a history of anaphylaxis or severe cardiopulmonary symptoms upon egg ingestion. In addition, a retrospective study of all egg-allergic patients who had received an influenza vaccine between 2007 and 2010 was included.

A total of 457 doses of vaccine were administered to 367 patients with egg allergy, of whom 132 had a history of severe allergy. No patients developed anaphylaxis, and 13 patients developed mild allergiclike symptoms in the 24 hours after vaccination.

In an authoritative review on the subject of influenza vaccination in egg-allergic patients, Dr. John Kelso reported on 28 studies with a total of 4,315 patients with egg allergy, including 656 with history of anaphylaxis with egg ingestion (Expert Rev Vaccines. 2014 Aug;13[8]:1049-57). None of these patients developed a serious reaction when they received influenza vaccine.

Dr. De Roches and colleagues reported on a prospective, cohort study in which 68 children with previous egg allergy received intranasal live attenuated influenza vaccine (J Allergy Clin Immunol Pract. 2015 Jan-Feb;3[1]:138-9). No patients had anaphylaxis or a severe allergic reaction. There were more adverse reactions in the patients with egg (7 patients) than in the control group (1 patient), but these were mild and nonspecific (abdominal pain, nasal congestion, headache, and cough).

The 2012 adverse reactions to vaccines practice parameter update recommended that patients with egg allergy should receive influenza vaccinations (trivalent influenza vaccine), because the risks of vaccinating are outweighed by the risks of not vaccinating (J Allergy Clin Immunol. 2012 Jul;130[1]:25-43).

A subsequent recommendation takes this a step further, recommending that all patients with egg allergy of any severity should receive inactivated influenza vaccine annually, using any age-approved brand (Ann Allergy Asthma Immunol. 2013 Oct;111[4]:301-2). In addition, there are no special waiting periods after vaccination of egg allergic patients beyond what is standard practice for any vaccine.

I think that we have plenty of evidence now to immunize all patients who report egg allergy, and to do so in the primary care setting.

Dr. Paauw is professor of medicine in the division of general internal medicine at the University of Washington, Seattle, and he serves as third-year medical student clerkship director at the University of Washington. Contact Dr. Paauw at dpaauw@uw.edu.

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AstraZeneca

Rifapentine boosts adherence for workers with LTBI

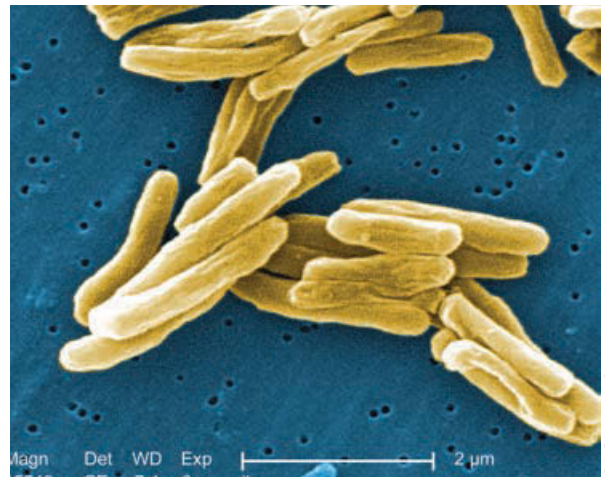
BY AMY KARON
Frontline Medical News

SAN DIEGO – Health care workers with latent tuberculosis infection (LTBI) were significantly more likely to continue a shorter course of weekly rifapentine plus isoniazid (INH) than daily INH monotherapy, researchers reported at an annual scientific meeting on infectious diseases.

"Consideration should be given to no longer routinely recommending INH for the treatment of LTBI among health care workers," said Dr. Esther Arguello Perez of Memorial Sloan Kettering Cancer Center, New York.

Health care workers face a greater risk of TB infection than the general population, regardless of the income level in the country where they live; patients with undiagnosed laryngeal or pulmonary TB usually pose the greatest risk, especially during procedures that cause coughing, such as sputum induction and bronchoscopy (Int J Tuberc Lung Dis. 2007;11[6]:593-605).

Although occupational TB testing is routine in U.S. health care organizations, more than half of health care workers who start treatment for LTBI historically have failed to finish (Chest. 2010;137[2]:401-9. doi: 10.1378/chest.09-0394). The standard LTBI regimen – 300 mg INH daily for 9 months – has been linked to potentially intolerable adverse effects such as hepatotoxicity, persistent gastrointestinal symptoms, rash, and neuropsychiatric problems (Drug Healthc Patient Saf. 2014;6:145-9. doi: 10.2147/DHPS.S68837).



CDC/JANICE CARR

In a 2011 multicenter trial, investigators reported a significantly higher completion rate for weekly rifapentine plus INH (900 mg each; 82% vs. 69% for daily INH; $P < .001$).

Rates of adverse effects were significantly lower with weekly rifapentine plus INH, although grade 3-4 events and risk of death did not differ between the groups (N Engl J Med. 2011;365:2155-66. doi: 10.1056/NEJMoa1104875). The results of that trial quickly transformed recommendations for LTBI treatment (MMWR. 2011:60[48];1650-53).

Memorial Sloan Kettering implemented weekly rifapentine plus INH for its LTBI personnel in 2011. By 2014, about three-quarters of personnel with LTBI received rifapentine plus INH, while the rest were evenly split between rifampin and INH monotherapy, Dr. Arguello Perez reported at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

To understand how health care workers' attitudes and treatment acceptance shifted along with practice, the investigators reviewed records from all health care workers at Memorial Sloan Kettering who were diagnosed with LTBI for 2005-2014. Among 930 patients, only 357 (38%) accepted treatment, although 76% of these individuals finished the regimen they started, she noted.

Rifapentine plus INH had the highest completion rate (88%), significantly exceeding rates for a 4-month course of daily rifampin (84%) and for 9 months of INH monotherapy (70%; $P < .01$ for both differences).

In contrast, completion rates for rifampin and INH did not differ significantly, Dr. Arguello Perez said.

Notably, LTBI treatment completion rates among health care workers rose by 26% between 2013, when most prescriptions were for rifampin or INH monotherapy, and 2014, when most were for rifapentine plus INH. "Health care workers might be more likely to accept treatment for LTBI if they know about alternatives to INH," she concluded.

Dr. Arguello Perez and her associates reported no funding sources and had no financial disclosures.

Simple breath test effectively detected tuberculosis

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Researchers in England used a novel gas analysis technique to detect tuberculosis in the breath, with a sensitivity of 93% and a specificity of 94%.

"Clearly these are promising results," Dr. Amandip Sahota said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. "What interested me the most is that we were able to detect a significant difference in chemicals in both pulmonary and extra-pulmonary TB, which did indicate to us that the disease does not need to be limited to the lungs to be detectable in the breath."

According to the latest data from the World Health Organization, there were 9 million active TB cases and 1.5 million deaths from the disease in 2013. Of these deaths, 80,000 were in children.

"TB remains a diagnostic challenge well into the 21st Century," said Dr. Sahota, a consultant physician in infectious diseases at University Hospitals of Leicester, England. "We are still heavily reliant on the standard culture, which is both slow and resource-intensive throughout the world. Despite the advent of TB-PCR, we are still far away from a diagnostic test which is both available at point of care, at low cost, and is available throughout the world."

What is exciting 'is the advent of newer gas sensor technologies ... being developed in line with a clinical need.'

DR. SAHOTA

In a study he conducted during his time as a research fellow at the University Hospitals of Coventry, in association with colleagues at the University of Warwick, Dr. Sahota and his associates used a field asymmetric ion mobility spectrometry device to collect samples of exhaled breath from 25 patients with suspected pulmonary or extra-pulmonary TB over a period of 6 months, before or within 1 week of treatment. For comparison, exhaled breath from 19 healthy controls was also obtained.

While ion mobility spectrometry has been used for years by the military and the security industry to detect explosives, for example, the technology has more recently been used to help diagnose medical conditions ranging from cancers to infections.

"Breath testing for TB is not new, but what is very exciting is the advent of newer gas sensor technologies which are being developed in line with a clinical need," Dr. Sahota explained. "The point of interest here is volatile organic compounds: chemicals which are gaseous at ambient temperatures often produce odors, and are endogenous products of metabolism in both health and disease states. So testing for breath can be quick, easy, and noninvasive. Clearly there's plenty of sample. It's rapid, and it allows access to chemicals in the blood, which are visible in the breath through ventilator processes."

Patients in the study, which is believed to be the first of its kind, breathed into a 3L Tedlar air sample bag and the samples were tested within 2 hours with a portable field asymmetric ion mobility spectrometry device made by Oxford Immunotec, Inc.

After measuring the ionic mobility of volatile organic compounds in the headspace, the researchers determined that the test was highly effective in detecting TB in the breath, with a sensitivity of 93% and a specificity of 94%.

"Clearly this is a small study and we do need to repeat this in a larger cohort to validate it further," Dr. Sahota said. "We also need to investigate potential confounders such as other comorbidities and medications. Ideally, we'd like to use a smaller, more portable instrument which is ideally hand-held, so we're exploring commercial partnerships."

The study was funded by the Medical Research Council. The researchers reported having no financial disclosures.

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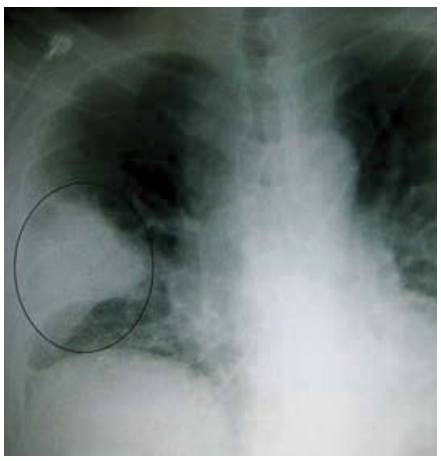
Biofilm pathogens dominate waterborne illnesses

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Emerging biofilm-associated pathogens are overtaking those transmitted by the fecal-oral route as the most-common cause of death from waterborne illness in the United States, according to findings from a review of administrative and disease-specific surveillance data.

Between 2003 and 2009, a mean of 2,516 deaths occurred per year as a result of exposure to 1 of more of 14 different waterborne germs or diseases, including campylobacteriosis, cryptosporidiosis, *Escherichia coli* infections, free-living amoeba, giardiasis, hemolytic uremic syndrome, hepatitis A, Legionnaires' disease, nontuberculous *Mycobacterium*, otitis externa, *Pseudomonas*, salmonellosis, shigellosis, and vibriosis, Julia Gargano, Ph.D., reported in a poster at the International Conference on Emerging Infectious Diseases.



James Heilman, M.D./CC BY-SA-3.0/Wikimedia Commons

The most commonly documented causes of death, accounting for 88% of deaths, were *Pseudomonas* pneumonia or *P.* septicemia, nontuberculosis *Mycobacterium*, and Legionnaires' disease – all biofilm pathogens. For those illnesses potentially linked to ingestion of contaminated water – as opposed to those associated with inhalation and contact – the most-commonly documented causes of death were hepatitis A, hemolytic uremic syndrome, and vibriosis, noted Dr. Gargano of the Center for Disease Control and Prevention's National Center for Emerging and Zoonotic Infectious Diseases, Atlanta.

The findings were obtained from U.S. death certificates, the Nationwide Inpatient Sample, and disease-specific surveillance.

Although surveillance data consistently show that transmission of waterborne diarrheal diseases continue, such diseases are rarely fatal in the United States. Further, advances in water treatment and sanitation have reduced the burden of such diseases.

The findings of this study demonstrate that the burden of mortality has shifted.

"This is the first time the annual number of deaths due to potentially waterborne disease has been calculated, and [the findings] highlight the emerging trend in biofilm-related illness," she wrote.

Dr. Gargano reported having no financial disclosures.

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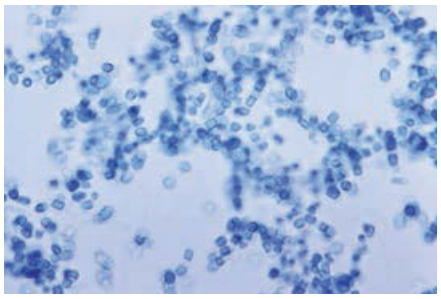
Coccidioidomycosis threatens Southwestern workers

BY BIANCA NOGRADY
Frontline Medical News

The expansion of the solar energy industry in *Coccidioides*-endemic areas of the Southwestern United States is exposing more workers to the infection, say the authors of a study that found an attack rate of 1.2 cases per 100 workers.

A study among 3,572 workers at two solar power–generating facilities in California identified 44 individuals with the infection between October 2011 and April 2014, 9 of whom were hospitalized.

The disease is acquired through inhalation of the soil-dwelling *Coccidioides* fungus spores and while the majority of the patients said they had received safety training about the risk of coccidioidomycosis, only six of those who regularly performed soil-disruptive work re-



COURTESY CDC/ LUCILLE GEORG

ported regularly using respiratory protection (Emerg Infect Dis. 2015 Nov;21[11]:1997-2005).

"Large-scale construction, including solar farm construction, might involve substantial soil disturbance for months, and many employees, particularly from non–*Coccidioides*-endemic areas, probably lack immunity to *Coccidioides*," wrote Jason A. Wilken, Ph.D., of the Centers for Disease Control and Prevention, and his coauthors.

"Medical providers should consider work-related coccidioidomycosis when evaluating construction workers with prolonged febrile respiratory illness, particularly after work in Central or Southern California or in Arizona, and medical providers should follow all statutory requirements for documenting and reporting occupational illness," Dr. Wilken concluded.

The study was supported by the Centers for Disease Control and Prevention. No conflicts of interest were declared.

Big declines seen in aspergillosis mortality

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – In-hospital mortality in patients with aspergillosis plummeted nationally, according to data from 2001-2011, with the biggest improvement seen in immunocompromised patients traditionally considered at high mortality risk, Dr. Masako Mizusawa reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The decline in in-hospital mortality wasn't linear. Rather, it followed a stepwise pattern, and those steps occurred in association with three major advances during the study years: Food and Drug Administration approval of voriconazole in 2002, the FDA's 2003 approval of the galactomannan serologic assay allowing for speedier diagnosis of aspergillosis, and the 2008 Infectious Diseases

Society of America clinical practice guidelines on the treatment of aspergillosis (Clin Infect Dis. 2008 Feb 1;46[3]:327-60).

"This was an observational study and we can't actually say that these events are causative. But just looking at the time relationship, it certainly looks plausible," Dr. Mizusawa said.

The stepwise mortality decline mirrored FDA approvals of voriconazole and an assay for galactomannan.

DR. MIZUSAWA

In addition, the median hospital length of stay decreased from 9 to 7 days in patients with this potentially life-threatening infection, noted Dr. Mizusawa of Tufts Medical Center, Boston.

She presented what she believes is the largest U.S. longitudinal study of hospital care for aspergillosis. The retrospective study used nationally representative data from the Agency for Healthcare Research and Quality's Healthcare Utilization and Cost Project–Nationwide Inpatient Sample.

Dr. Mizusawa and coinvestigators defined aspergillosis patients as being at high mortality risk if they had

Continued on following page

Continued from previous page

they had established risk factors indicative of immunocompromise, including hematologic malignancy, neutropenia, recent stem cell or solid organ transplantation, HIV, or rheumatologic disease. Patients at lower mortality risk included those with asthma, COPD, diabetes, malnutrition, pulmonary tuberculosis, or non-TB mycobacterial infection.

The proportion of patients who were high risk climbed over the years, from 41% among the 892 patients with aspergillosis-related hospitalization in the 2001 sample to 50% among 1,420 patients in 2011. Yet in-hospital mortality in high-risk patients fell from 26.4% in 2001 to 9.1% in 2011. Meanwhile, the mortality rate in lower-risk patients improved from 14.6% to 6.6%. The overall in-hospital mortality rate went from 18.8% to 7.7%.

Of note, the proportion of aspergillosis patients with renal failure jumped from 9.8% in 2001 to 21.5% in 2011, even though the treatments for aspergillosis are relatively non-nephrotoxic, with the exception of amphotericin B. The outlook for these patients has improved greatly: In-hospital mortality for aspergillosis patients in renal failure went from 40.2% in 2001 to 16.1% in 2011.

While in-hospital mortality and length of stay were decreasing during the study years, total hospital charges for patients with aspergillosis were going up: from a median of $29,998 in 2001 to $44,888 in 2001 dollars a decade later. This cost-of-care increase was confined to patients at lower baseline risk or with no risk factors. Somewhat surprisingly, the high-risk group didn't have a significant increase in hospital charges over the 10-year period.

"Maybe we're just doing a better job of treating them, so they may not necessarily have to use a lot of resources," Dr. Mizusawa offered as explanation.

VITALS

Key clinical point: In-hospital mortality has more than halved for patients with aspergillosis-related hospitalization during a recent 10-year period.

Major finding: In-hospital mortality among patients with an aspergillosis-related hospitalization fell nationally from 18.8% in 2001 to 7.7% in 2011, with the biggest drop occurring in those at high risk.

Data source: A retrospective study of nationally representative data from the Healthcare Utilization and Cost Project–Nationwide Inpatient Sample for 2001-2011.

Disclosures: The presenter reported having no financial conflicts regarding this unfunded study.

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True pertussis incidence 93-fold higher than reported

BY BRUCE JANCIN
Frontline Medical News

SAN DIEGO – The true incidence of pertussis in recent years in Americans less than 50 years old is estimated to be 58- to 93-fold greater than the laboratory-confirmed reported case count, Philip O. Buck, Ph.D., reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

It's widely accepted that national surveillance systems vastly underestimate the incidence of pertussis because most cases don't get reported.

Bruce Jancin/Frontline Medical News

In order to obtain a more complete picture of the situation, Dr. Buck utilized a regression equation to estimate the proportion of cough illnesses attributable to laboratory-confirmed pertussis.

A closely similar regression model has previously been utilized by other investigators in published studies that provided estimates of the true burdens of influenza (Epidemiol Infect. 2002 Aug;129:99-106) and respiratory syncytial virus (Eur J Pediatr. 2010 Aug;169:997-1008), noted Dr. Buck, director of U.S. Health Outcomes at GlaxoSmithKline in Philadelphia.

He applied the regression model to medical claims for ICD-9-CM–diagnosed pertussis in individuals under age 50 in the IMS PharmMetric Plus claims database for the years 2008-2013. The database includes more than 150 million enrollees. The average reported incidence of pertussis in individuals less than 50 years old during the study years was 9 cases per 100,000 per year; however, the average regression-estimated incidence was 649 per 100,000, a 72-fold greater figure.

During 2011-2013, the 3 most recent years covered by the study, the regression-estimated incidence of pertussis was 93-fold, 62-fold, and 87-fold greater than the reported rates.

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VITALS

Key clinical point: The annual rate of pertussis in Americans less than 50 years old is up to 93-fold greater than the reported incidence.

Major finding: The true incidence of pertussis in Americans less than 50 years old is estimated to be 58-93 times greater per year than the reported annual rates during recent years.

Data source: This was a retrospective cohort study which utilized a regression model to estimate the true fraction of cough illness attributable to laboratory-confirmed pertussis through analysis of 6 years worth of medical claims data from a large national database.

Disclosures: The study was funded by GlaxoSmithKline. The presenter is a company employee.

Oxygen alone best for immunocompromised patients

BY JENNIFER SHEPPHIRD
Frontline Medical News

Early noninvasive ventilation, compared with oxygen therapy alone, did not reduce 28-day all-cause mortality in critically ill immunocompromised patients with acute respiratory failure, based on a randomized, parallel-group study of 374 patients conducted in 28 ICUs in France and Belgium.

Overall, 46 of 191 patients (24%) in the noninvasive ventilation group died, compared with 50 of 183 (27%) in the oxygen-alone group. A similar number of patients from each group required intubation – 38% in the noninvasive ventilation group and 45% in the oxygen group – with similar time to intubation. Nearly 85% of the patients were receiving treatment for hematologic malignancies or solid tumors, researchers reported.

No significant differences between groups were observed in requirement for intubation, ICU or hospital length of stay, or duration of invasive mechanical ventilation. The study found no evidence that noninvasive ventilation influenced mortality estimates or was beneficial to any subgroup based on hypoxemia severity or underlying condition.

The study was limited, however, by a lower than expected mortality rate with oxygen alone, and as a result was not powered to detect significant between-group differences. Based on earlier studies, the researchers assumed a 35% mortality rate in the oxygen-alone group, but the actual rate was 27% (JAMA. 2015 Oct 7. doi: 10.1001/jama.2015.12402).

"Therefore, there remains uncertainty regarding our null finding, which may nonetheless fail to exclude a clinically important effect," wrote Dr. Virginie Lemiale of Saint-Louis University Hospital, Paris, and colleagues.

Furthermore, high-flow nasal oxygen was used in about 40% of all patients, which may have decreased requirements for intubation as well as mortality rates. High-flow nasal oxygen was used more often in the oxygen group (44%) than in the noninvasive ventilation group (31%) ($P = .01$).

VITALS

Key clinical point: Noninvasive ventilation, compared with oxygen therapy alone, did not reduce 28-day mortality among immunocompromised patients with acute respiratory failure.

Major finding: After 28 days, 46 of 191 patients (24%) in the noninvasive ventilation group had died, compared with 50 of 183 (27%) in the oxygen-alone group.

Data source: The randomized, parallel-group study was conducted in 28 ICUs in France and Belgium and included 374 immunocompromised patients with acute respiratory failure.

Disclosures: Dr. Lemiale and coauthors reported having no disclosures.

VIEW ON THE NEWS

Noninvasive ventilation in flux

In contrast to reports from 10 years ago, the current study by Lemiale et al. failed to demonstrate a mortality benefit for noninvasive ventilation, compared with oxygen alone. However, the results should be interpreted in the context of recent advances in ICU care. Targeted chemotherapy, prophylactic use of antibiotics, and improved supportive care have contributed to overall mortality declines in the immunocompromised critically ill population. Dr. Lemiale and colleagues anticipated a higher baseline mortality rate (35% vs. 27% observed). The lower mortality rate limited the study's power to detect a mortality difference between groups.

Second, patients in this trial may have had a lower acuity of illness, evidenced by less tachypnea, compared with that seen in earlier studies.

Third, the oxygen-alone group received more high-flow oxygen via nasal cannula than the noninvasive ventilation group, which may have diluted the benefits of noninvasive ventilation.

As efforts continue to reduce requirements for invasive mechanical ventilation, further examination of strategies for noninvasive ventilation, such as high-flow oxygen, compared with noninvasive ventilation, are warranted.

Dr. Bhakti Patel is a clinical instructor of medicine in the section of pulmonary and critical care, department of medicine, University of Chicago. Dr. John Kress is professor of medicine and director of the Medical Intensive Care Unit at University of Chicago Medicine. These remarks were part of an editorial accompanying the report (JAMA. 2015 Oct 7. doi: 10.1001/jama.2015.12401). Dr. Patel and Dr. Kress reported having no disclosures.

Venovenous ECMO effective for trauma lung failure

BY M. ALEXANDER OTTO
Frontline Medical News

CHICAGO – Venovenous extracorporeal membrane oxygenation will save perhaps a third of patients who – despite maximum ventilator support – go into end-stage respiratory failure after trauma, according to investigators from the University of Maryland, Baltimore.

Venovenous ECMO life support 'should not be overlooked due to fear of complications.'

DR. AHMAD

"Institutions without the available expertise and ICU capabilities should promptly refer patients with end-stage respiratory failure secondary to trauma to a tertiary care center. Venovenous ECMO [extracorporeal membrane oxygenation] life support may be their only chance for survival and should not be overlooked due to fear of complications," they concluded.

ECMO usually requires heparin anticoagulation to prevent clots; the fear of subsequent bleeding is one of the things that prevents ECMO's widespread use in trauma. As a result, "a lot of patients who need ECMO lung support don't get it," said Dr. Sarwat Ahmad, of the university.

Dr. Ahmad and her colleagues, however, found that ECMO did not lead to worse outcomes in their lung failure patients.

Their conclusions come from a review of 39 adult blunt and penetrating trauma patients who received ECMO at the university's Level I trauma center over the past 9 years.

Thirty-two patients had venovenous ECMO mostly for acute respiratory distress; maximal ventilator support, adjunctive medications, and chest therapy did not help. ECMO outflow was from the femoral vein, and blood was returned to the internal jugular vein. Twelve patients (38%) survived, which "is good in this scenario because they otherwise would have died," Dr. Ahmad said.

The mean pre-ECMO P/F ratio – arterial oxygen partial pressure to fractional inspired oxygen – among the survivors was 98 mm Hg. Values below 100 mm Hg indicate severe lung injury, but some patients had values approaching 200 mm Hg, meaning that ECMO was a good idea even in patients with less severe lung injury.

Seven patients received venoarterial ECMO mostly for cardiac arrest, with outflow from the femoral vein and blood returned via the femoral artery. The patients were pulseless on arrival, so bypassing the heart seemed the only option, but none of them survived. Because of that, the investigators concluded that venoarterial ECMO is "not going to help" in trauma patients, Dr. Ahmad said.

One of the 12 survivors and over half of those who died had injury severity scores above 40 points. Also, Glasgow coma scores below 8 points were far more common among patients who died.

All 12 of the survivors and 14 of the 27 who died were anticoagulated with heparin. "There was no increased incidence of complications between those who got heparin and those who did not," and there wasn't a higher incidence of complications in ECMO patients than in other trauma patients.

VITALS

Key clinical point: Venovenous ECMO can be life saving when trauma patients go into respiratory failure.

Major finding: Thirty-two patients had venovenous ECMO, mostly for acute respiratory distress; twelve (38%) survived.

Data source: Review of ECMO in 39 trauma patients.

Disclosures: The lead investigator has no disclosures, and there was no external funding for the work.

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Considering treatment options for your pulmonary arterial hypertension (PAH) patients?

REVATIO® (sildenafil)— is now available as an oral suspension treatment for PAH

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.

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.

Consider REVATIO oral suspension for your appropriate PAH patients.
To learn more about REVATIO, please visit REVATIOHCP.com.

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

Revatio® sildenafil
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June 2015

Revatio®
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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

Undiagnosed OSA often underlies insomnia

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – The prevalence of insomnia in obstructive sleep apnea (OSA) patients "is not that surprising," and adds to the complexity of managing these patients, Dr. David N. Neubauer said at the annual U.S. Psychiatric and Mental Health Congress.

In a study of 810 primary care outpatients with no sleep disorder history, 11% were found to have potential complex insomnia: a mix of symptoms meeting criteria for moderate/severe insomnia disorder and specific sleep-disordered breathing (Sleep Med. 2013;14[9]:814-23). Further, at least three sleep studies conducted in older patients with insomnia found a high prevalence of OSA. The largest study, of 394 postmenopausal women aged 55-70 years, found that 67% had an apnea-hypopnea index (AHI) of greater than 5, said Dr. Neubauer, associate director of the Johns Hopkins Sleep Disorders Center, Baltimore.

Sleep-onset insomnia is common and is associated with functional somatic syndromes.

DR. NEUBAUER

In another trial, 435 community-dwelling veterans in the Los Angeles area who were at least 60 years old and had seen a Veterans Affairs outpatient provider in the past 2 years were recruited for an insomnia behavioral intervention trial (J Clin Sleep Med. 2013; 9[11]:1173-8). To be eligible for the trial, participants must have had a sleep disturbance with daytime consequences for at least 3 months; those with a history of sleep apnea diagnosis or treatment were excluded.

Researchers found that the prevalence of OSA – defined as an AHI threshold of 15 or greater – was 47%.

In another study from Stanford (Calif.) University, researchers set out to evaluate the impact of a cognitive-behavioral intervention in people with insomnia and major depression (J Psychosom Res. 2009;67[2]:135-41).

The screening consisted of a phone interview, in-person screening, and an overnight polysomnography test. Again, sleep apnea proved to be part of the underlying problem, as 24% had an AHI between 15 and 25, and 16% had an AHI of greater than 25.

Patients with a combination of OSA and insomnia symptoms "tend to be some of the people with milder sleep apnea, or those who are under the radar, who wouldn't even get diagnosed with OSA, but they have that same physiologic process of some inspiratory flow limitation," Dr. Neubauer said. This subset of patients might meet criteria for upper airway resistance syndrome, which was first described in 1993 and is characterized by repetitive increases in resistance to airflow, increased respiratory effort, absence of oxygen desaturation, brief sleep state changes or arousals, and daytime somnolence.

"The diagnosis of upper airway resistance syndrome is somewhat debatable, because some people think that if you don't have absolute apnea events, they don't count [as a sleep disorder]," Dr. Neubauer said. "But these 'under the radar' events may still have a significant effect on sleep."

Compared with OSA patients, those with upper airway resistance syndrome tend to be younger, female, and have a lower body mass index (Respiration 2012;83[6]:559-66). In addition, he said, sleep-onset insomnia is common, and the condition is associated with functional somatic syndromes, such as headache, irritable bowel syndrome, gastroesophageal reflux, rhinitis, and orthostatic intolerance.

A recent analysis of 14 second-generation antidepressants based on Food and Drug Administration data and pharmaceutical company records found that the Top 5 most likely to cause insomnia, compared with placebo, are bupropion, desvenlafaxine, sertraline, fluvoxamine, and fluoxetine (J Clin Psychopharmacol. 2015;35[3]:296-303). The Top 5 most likely to cause somnolence, compared with placebo, are fluvoxamine, mirtazapine, reboxetine, paroxetine, and desvenlafaxine.

Dr. Neubauer reported having no financial disclosures.

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SLEEP STRATEGIES: Pain and Sleep

BY DR. TIMOTHY ROEHRS

Sleep and pain interact in complex ways to compromise the biological and behavioral capacity of individuals. Disturbed sleep is frequently reported by people with acute and chronic pain conditions, and it is now becoming clear the sleep-pain relation is bidirectional; that is, pain disrupts sleep and sleep disturbance in turn enhances pain. Serious limitations to the currently available pharmacotherapies for pain exist and as a consequence, inadequate pain control and management remain serious problems for clinicians.

Sleep Laboratory Studies

Epidemiologic studies show 60% to 80% of people experiencing acute and/or chronic pain report disturbed sleep and sleep laboratory studies using polysomnography (PSG) [the terminology used to describe the continuous 8-h recording of multiple physiologic measures during sleep (ie, EEG, EMG, EOG, and ECG)] have well documented the nature of the sleep disturbance.

Most typically, the PSGs show sleep maintenance is disturbed, often with brief arousals and awakenings (often referred to as sleep fragmentation) of which the individual is unaware. Persons with such pain-related sleep disturbance report in the morning having experienced light and unrefreshing sleep.

We also know that sleep disturbance enhances daytime sleepiness/fatigue and that sleepiness/fatigue is associated with increased pain. For example, when people are asked to rate their nightly sleep, daily pain, and fatigue over several weeks, nights with poorer sleep are associated with greater daytime fatigue and pain and the greater the fatigue, the greater the pain.

Some studies have suggested that the sleep-pain side of the relation accounts for a greater amount of the variance among these variables than the pain-sleep side of the relation. What accounts for the sleepiness/fatigue and pain relation is not well known.

Sleep laboratory studies in pain-free individuals have totally deprived sleep, reduced sleep time by 2 to 4 h, disrupted the continuity of sleep with brief awakenings, and selectively deprived specific sleep stages thought to be critical in pain processing (ie, slow wave NREM or REM sleep). These experimental studies have found next-day pain thresholds to mechanical pressure and hot or cold stimuli are reduced, pain sensitivity to radiant heat is increased, and normal pain processing is compromised. While total sleep loss and shortened and disrupted sleep clearly enhance pain, it is not as certain that specific sleep stages are critical.

Given the early 1970s clinical description of the alpha-delta sleep anomaly in fibromyalgia, the majority of the specific sleep stages studies have focused on the deprivation or disruption of slow wave sleep. But, the studies have been equivocal regarding the impact of slow wave sleep loss on pain. However, it is difficult to reduce slow wave sleep without also reducing sleep time and, as we noted above, even 2-hour reductions of sleep time can enhance pain sensitivity.


DR. ROEHRS

The other important sleep stage is REM sleep, which has been little studied in humans. One study showed a modest correlation of REM sleep time with pain reports and a second study selectively deprived REM sleep while controlling for sleep time and sleep fragmentation. That REM deprivation study found pain sensitivity to a radiant heat stimulus was enhanced.

Mechanism(s)

Thus, it is fairly well established that the sleep-pain relation is bidirectional and what remains to be determined is the mechanism(s) that underlie this relation. One strong explanatory candidate is proinflammatory activation. First, there are emerging data that show sleep loss, either total sleep deprivation or sleep restriction, produces elevations in proinflammatory cytokines. A number of controlled laboratory studies has shown elevations of IL-1, IL-6, and TNF-alpha associated with sleep loss. In healthy volunteers, 1 week of restricted bedtime to 6 h nightly produced, relative to the 8-h baseline, increased sleepiness/fatigue and elevated 24-h secretion of IL-6. Another recent study in healthy normal subjects restricted bedtime to 4 h nightly for 12 consecutive nights and found elevated levels of IL-6 relative to an 8-h bedtime control group. The IL-6 levels were correlated with self-rated bodily discomfort and tiredness-fatigue. Finally, in healthy normal subjects, after one night of total sleep deprivation, sleepiness was increased as were IL-6 levels. A midday nap the following day reduced the sleepiness and importantly, the IL-6 levels relative to a no-nap condition.

Second, the proinflammatory cytokines in both the peripheral and central nervous system are known to play a key role in both acute and chronic pain conditions. In the periphery, the cytokines are released by macrophages in response to tissue injury. In human chronic pain conditions, both IL-6 and TNF-alpha levels are elevated locally, and their levels are correlated with experienced pain.

The proinflammatory cytokines that are released peripherally are also recognized as having a signaling function in the central nervous system that then produces de novo central synthesis and release of the cytokines from brain glia cells. Thus, pain transmission is facilitated downward from central to spinal pathways by the central cytokine release.

Proinflammatory activation has been shown to enhance dorsal root ganglion cell excitability, as well as A-delta and C nerve fiber excitability in the periphery. Thus, one likely mechanism by which sleep loss enhances pain is through proinflammatory cytokine activation.

Treatments

Numerous studies of antidepressants, including sedating tricyclics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, have been done in patients with fibromyalgia and other chronic pain populations. While some of these studies have shown improved pain outcomes, not all patients seem to benefit. More importantly, this literature is limited as to understanding the role of sleep in chronic pain in that sleep is either inadequately or not assessed.

Pharmacologic treatment studies directed toward sleep in chronic pain conditions have been done in patients with rheumatoid arthritis (RA) and fibromyalgia. The non-benzodiazepine hypnotic zopiclone, 7.5 mg, improved sleep in patients with rheumatoid arthritis and fibromyalgia but did not improve self-rated pain. Similarly, zolpidem, 10 mg, improved sleep but not pain in patients with fibromyalgia. In contrast, triazolam, 0.25 mg, improved sleep, reduced daytime sleepiness, and morning stiffness; and eszopiclone, 2 mg, improved both sleep and daytime pain and disability in patients with RA. The precursor of GABA in sodium salt form, sodium oxybate, 4.5 and 6 g/night, reduced daytime pain and fatigue and improved sleep in patients with fibromyalgia. Sodium oxybate is known to increase slow wave sleep. The alpha 2-delta ligand, pregabalin, 450 mg/day, which in healthy normal subjects also increases slow wave sleep, improved self-reported pain, sleep, fatigue, and quality of life in a large trial in patients with fibromyalgia.

The few behavioral treatment trials for sleep in chronic pain have produced equivocal results.

Cognitive behavioral treatment directed to sleep (CBT-I) in chronic pain patients relative to wait-list controls improved measures of sleep but not pain.

In older adults with a range of medical or psychiatric illnesses, CBT-I relative to no treatment reduced wake time during sleep, but, again, did not improve daytime outcomes. CBT-I in older adults, 36% with osteoarthritis, reported improved sleep, but pain assessments were not improved. In a follow-up study that included 55% patients with osteoarthritis, CBT-I improved 8 of 10 sleep measures and a global rating of daytime function but not specifically pain. CBT-I involving sleep restriction improved sleep efficiency and wake time relative to the control group, but it did not improve pain measures. In post-hoc analyses, a sleep hygiene sub-group which regularized their sleep schedule showed improved pain scores.

The major problem with the behavioral treatment studies is that although sleep continuity was improved, sleep time was not increased. A major component of CBT-I is sleep restriction and in healthy normal subjects and pain patients, reducing sleep time enhances pain sensitivity. This would suggest consolidating sleep alone is not sufficient to improve pain. Increasing sleep time after having consolidated it is probably also necessary. Those pharmacologic studies that improved pain outcomes increased sleep time by 30 min or more.

Summary

While a more complete understanding of the role of sleep disturbance in the normal physiology and pathophysiology of acute and chronic

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pain continues to emerge, barriers to managing pain clinically continue. There are serious limitations to the currently available pharmacotherapies. The modulating role of sleep in acute and chronic pain and the extent to which pharmacologic and behavioral treatment of sleep may have an impact on the medical, social, and economic burdens of acute and chronic pain need further exploration.

Dr. Roehrs is with the Sleep Disorders & Research Center, Henry Ford Hospital and Department of Psychiatry and Behavioral Neuroscience, Wayne State University, School of Medicine, Detroit, Michigan.

Further Reading

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What's the hottest recent advance in cardiology?

BY BRUCE JANCIN
Frontline Medical News

LONDON – What was the top development in all of cardiology during the past year, the advance that holds the most far-reaching implications for clinical practice?

At the annual congress of the European Society of Cardiology, six experts each made a case for the biggest game changer in their discipline – risk prevention, electrophysiology, imaging, heart failure, percutaneous coronary intervention, and acute cardiac care. And when the audience of perhaps 400-strong had cast their votes, the winner was … the novel angiotensin receptor neprilysin inhibitor (ARNI) known as LCZ696 or sacubitril/valsartan. In the landmark PARADIGM-HF trial, the drug reduced the risk of cardiovascular death by 20% and heart failure hospitalization by 21% over and above what's achieved with enalapril plus the other current guideline-recommended heart failure medications. "I'm a device person, but I've decided a device is not the most important recent innovation in heart failure," Dr. Cecilia Linde said in her winning argument.

"This ARNI is the first new drug in years with a very clear impact on morbidity and mortality. This is why I believe PARADIGM-HF is the most

Sacubitril/valsartan 'is the first new drug in years with a very clear impact on morbidity and mortality.'

DR. LINDE

important study result of the last year in heart failure. It will directly impact treatment and will change the ESC guidelines for heart failure therapy. The PARADIGM-HF results suggest that the ARNI should be given as first-line therapy instead of an ACE inhibitor or angiotensin receptor blocker," said Dr. Linde, professor and head of cardiology at the Karolinska Institute, Stockholm.

In the double-blind, randomized 8,399-patient PARADIGM-HF trial (N Engl J Med. 2014 Sep 11;371[11]:993-1004), the number needed to treat with LCZ696 instead of enalapril for 27 months in order to avoid one cardiovascular death or heart failure hospitalization was 21. The number needed to treat to avoid one cardiovascular death was 32.

Electrophysiology

The big news here is the concept of the autonomic nervous system as the master controller of atrial fibrillation (AF), governing both the firing of arrhythmic triggers and the change in the arrhythmogenic substrate over time, according to Dr. Sabine Ernst of the National Heart and Lung Institute at Imperial College, London.

"There is a new recognition of how the sympathetic and parasympathetic nervous systems interact to initiate and maintain arrhythmias. This

The future of antiarrhythmic therapy lies in neuromodulation of the autonomic nervous system.

DR. ERNST

will change the electrophysiology world forever," she predicted.

Indeed, the future of antiarrhythmic therapy lies in neuromodulation of the autonomic nervous system, and it's a lot closer than most cardiologists realize, she said.

She pointed to a study in which investigators at the University of Oklahoma Heart Rhythm Institute randomized 40 patients with paroxysmal AF to noninvasive low-level electrical stimulation of the vagus nerve or to sham treatment. The stimulation at 20 Hz suppressed AF and reduced levels of inflammatory cytokines (J Am Coll Cardiol. 2015 Mar 10;65[9]:867-75).

Vagus nerve stimulation was accomplished using a pair of clips attached to the external ear in order to access the tragus nerve. At just 20 Hz, participants felt no discomfort.

"This is just the very first step. It's probably not the right frequency or intensity yet. But maybe – and I just want you to start to dream about this – just maybe this could be easily implanted in something we put in our ears. How nice it would be if we could add it to a hearing aid for a patient with atrial fibrillation; we would not need to bother with rate control anymore," Dr. Ernst said.

Cardiovascular prevention

Dr. Joep Perk nominated as the most important development of the past year in this field a new set of refined ECG screening criteria for asymptomatic hypertrophic cardiomyopathy (HCM) in athletes. Previous criteria have unacceptably high false-positive rates, which lead to further testing, particularly in black athletes," said Dr. Perk, head of internal medicine at Oskarshamn (Sweden) Hospital.

The so-called refined criteria (Circulation. 2014 Apr 22;129[16]:1637-49) were designed to improve upon the specificity of the ESC and Seattle criteria by excluding several isolated ECG patterns that have been shown not relevant in black athletes.

When the developers of the refined criteria applied all three sets of criteria to a large population of black and white athletes, including 103 young athletes with HCM, all three showed 98% sensitivity for the detection of HCM. However, the false-positive ECG rate in black athletes improved from 40.4% using the ESC criteria, to 18.4% with the Seattle criteria, to 11.5% using the refined criteria. Among white athletes, the false-positive rates using the three sets of criteria were 16.2%, 7.1%, and 5.3%.

"These new refined criteria should be incorporated into guidelines for the screening of athletes. They provide a 71% reduction in positive ECGs in black athletes, compared with ESC recommendations," Dr. Perk said.

Cardiac imaging

"I really think 3-D printing is going to revolutionize every aspect of medicine," asserted Dr. Luigi Badano of the University of Padua (Italy).

His research group presented a study in which they used custom software to create an exact model of a real patient's tricuspid valve out of liquid resin based on transthoracic echo images. It took 90 minutes.

"This technology allows us to hold the physical structure of the heart in our hands," he noted. "We can use it to teach anatomy to medical students without a corpse, plan surgical interventions, and communicate with patients, showing them exact structures and revolutionizing the concept of informed consent."

And that's just scratching the surface. He noted that investigators at Wake Forest Baptist Medical Center Institute for Regenerative Medicine in North Carolina recently utilized 3-D printing with bio-ink and bio-paper to print 3-D beating cardiac cells clustered into "organoids." It's the first step toward creating a prototype beating heart.

"Can you dream about that? The donor heart shortage could in the future be solved by printing a beating heart for insertion into the patient. The investigators predict they'll have a functional beating heart within 20 years," Dr. Badano said.

Acute cardiac care

Dr. Maddalena Lettino said that the breakthrough of the year in their field was validation of a novel 1-hour rule-in/rule-out algorithm using high-sensitivity cardiac troponin T to accelerate management of patients who present to the emergency department with chest pain. According to studies totaling more than 3,000

Using this assay and algorithm, roughly 75% of patients can have acute MI ruled out or ruled in within 1 hour.

DR. LETTINO

patients with more than 600 MIs in which the assay and algorithm were tested, roughly 75% of patients can safely and accurately have acute MI ruled out or ruled in within 1 hour.

Given that close to 10% of all ED visits are for chest pain, adoption of this algorithm will reduce ED overcrowding, speed physician workflow, save health care systems money, and spare patients and families the anxiety that comes with a delayed diagnosis, said Dr. Lettino of Humanitas Research Hospital in Milan.

Coronary intervention

The 15%-20% of coronary stent recipients who are at high bleeding risk constitute "the forgotten patient population," said Dr. Philippe Garot of the Paris South Cardiovascular Institute.

He noted that the key question of whether such patients can be managed safely with a mere 1-month course of dual antiplatelet therapy

'This [3-D printing] technology allows us to hold the physical structure of the heart in our hands.'

DR. BADANO

will finally be answered this fall with the release of the LEADERS FREE trial results. This large, randomized double-blind trial compares safety and efficacy outcomes in patients assigned to a bare metal stent or the novel drug-eluting BioFreedom stent.

The six presenters indicated they had no relevant financial conflicts.

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Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Once-daily ANORO ELLIPTA significantly improved lung function by 167 mL (*P*<0.001) vs placebo at Day 169[1]*

*As measured by the primary endpoint, trough (predose) FEV_1 at Day 169 (mean of the FEV_1 values at 23 and 24 hours after dosing on Day 168), in a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Least squares mean change from baseline of 171 mL for ANORO ELLIPTA (n=413) and 4 mL for placebo (n=280).

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol.**
- **The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA following this advertisement.

Theravance

ANORO® ELLIPTA®
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

Lung function comparison studies with tiotropium

Indications

- ANORO ELLIPTA is a combination anticholinergic/LABA indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD.
- SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.[2]

Description of Studies[3-5]

Design: Three 24-week, multicenter, randomized, blinded, active-controlled, double-dummy, parallel-group studies that evaluated the efficacy and safety of ANORO ELLIPTA (administered once daily by the ELLIPTA inhaler) and other treatment arms, including tiotropium 18 mcg (administered once daily by the HandiHaler).

Treatment arms: In the 1st study, patients were randomized to treatment with ANORO ELLIPTA, tiotropium 18 mcg, UMEC/VI 125 mcg/25 mcg,* or VI 25 mcg.† In the 2nd study, patients were randomized to treatment with ANORO ELLIPTA, tiotropium 18 mcg, UMEC/VI 125 mcg/25 mcg,* or UMEC 125 mcg.* In the 3rd study, patients were randomized to treatment with ANORO ELLIPTA or tiotropium 18 mcg.

Patients: Studied in patients (mean age range: 62 to 65 years) with COPD. At screening, patients had a mean postbronchodilator FEV_1 range of 46.4% to 47.7% predicted, a mean reversibility range of 11.7% to 15.6%, and a mean postbronchodilator FEV_1/FVC ratio range of 0.46 to 0.48.

Primary endpoint: Trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; UMEC=umeclidinium; VI=vilanterol.

*UMEC/VI 125 mcg/25 mcg and UMEC 125 mcg are not approved strengths.

†Vilanterol is not approved as monotherapy.

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

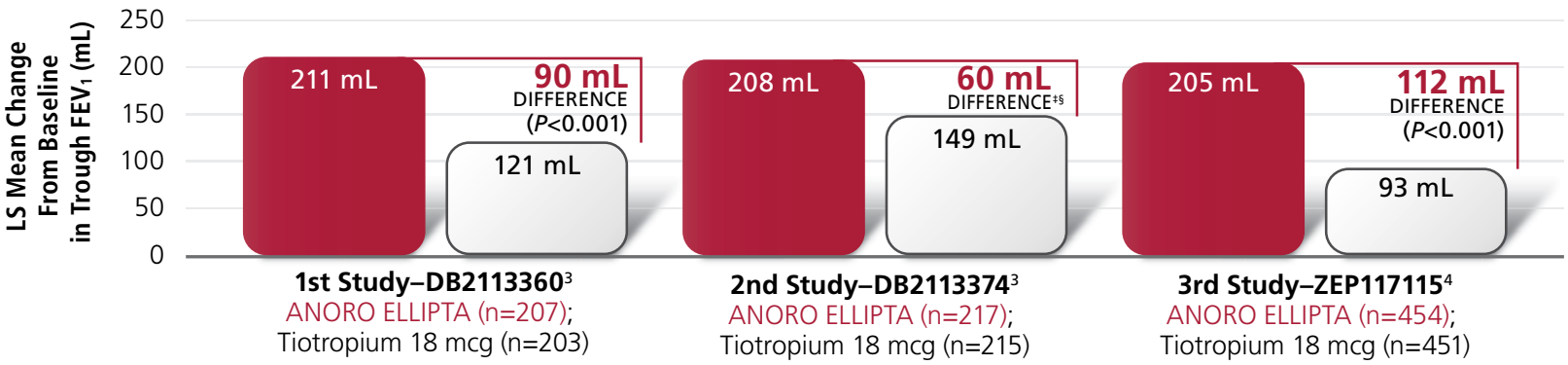
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO ELLIPTA (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO ELLIPTA, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

Once-daily ANORO ELLIPTA demonstrated superior lung function improvement compared with tiotropium in 2 studies

PRIMARY ENDPOINT: TROUGH (PREDOSE) FEV_1 AT DAY 169[3,4]



‡The comparison of UMEC/VI 125 mcg/25 mcg with UMEC 125 mcg preceded that of ANORO ELLIPTA with tiotropium as part of a predefined hierarchy of treatment comparisons and did not achieve statistical significance. Therefore, results of the comparison of ANORO ELLIPTA with tiotropium were descriptive only and statistical significance could not be inferred.[3]

§Reflects rounding.

LS=least squares.

Adverse events (AEs) occurring in ≥3% of subjects in any of the 3 studies[3-5]

Safety data were descriptive only. The studies were not powered to compare the safety profile of ANORO ELLIPTA with that of tiotropium. The range of AEs across the 3 studies for ANORO ELLIPTA (n=883) and tiotropium 18 mcg (n=874), respectively, were: headache (9-10%, 4-7%), nasopharyngitis (6-10%, 7-8%), back pain (2-5%, 2-5%), lower respiratory tract infection (0-4%, <1-1%), upper respiratory tract infection (<1-4%, <1-7%), COPD (<1-3%, <1-2%), cough (2-3%, 2-3%), gastritis (0-3%, <1%), pain in extremity (<1-3%, <1-2%), hypertension (<1-2%, <1-3%), and urinary tract infection (0-<1%, <1-3%).

Important Safety Information for ANORO ELLIPTA (cont'd)

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO ELLIPTA 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 produce severe bronchospasm in patients with COPD.
- 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.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

References: 1. Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546, Appendix A. **2.** SPIRIVA HandiHaler [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. **3.** Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med.* 2014;2(6):472-486. **4.** Maleki-Yazdi MR, Kaelin T, Richard N, et al. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med.* 2014;108(12):1752-1760. **5.** Data on file, GSK.

Please see additional Important Safety Information for ANORO ELLIPTA on preceding pages.

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

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ANORO ELLIPTA was developed in collaboration with Theravance

ANORO® ELLIPTA®
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

ANORO® ELLIPTA®
(umeclidinium and vilanterol inhalation powder)
FOR ORAL INHALATION USE
The following is a brief summary only; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting $beta_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting $beta_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full Prescribing Information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; 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 ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA 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 ANORO ELLIPTA, 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 ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting $Beta_2$-Agonists
ANORO ELLIPTA 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 ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 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, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, 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.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.11 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 medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions With ANORO ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Reaction	Placebo (n = 555) %	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %
Infections and infestations				
Pharyngitis	<1	2	1	2
Sinusitis	<1	1	<1	1
Lower respiratory tract infection	<1	1	<1	<1
Gastrointestinal disorders				
Constipation	<1	1	<1	<1
Diarrhea	1	2	<1	2
Musculoskeletal and connective tissue disorders				
Pain in extremity	1	2	<1	2
Muscle spasms	<1	1	<1	<1
Neck pain	<1	1	<1	<1
General disorders and administration site conditions				
Chest pain	<1	1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

7 DRUG INTERACTIONS
7.1 Inhibitors of Cytochrome P450 3A4
Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when

considering the coadministration of ANORO ELLIPTA with 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 (5.4), 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 ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. Therefore, patients with COPD 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, such as vilanterol, a component of ANORO ELLIPTA, 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 ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA 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 ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 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 450 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.

Nonteratogenic Effects: *Umeclidinium:* There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments 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).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA: It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium: It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol: It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

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

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl<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 case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA 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 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

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., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umeclidinium and vilanterol, as described below.

Umeclidinium: Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vivo* rat bone marrow micronucleus assay, *in vivo* rat unscheduled DNA synthesis (UDS) assay, and *in vitro* Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the *in vitro* mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

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 that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

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. Instruct patients to consult a physician immediately should any of these signs or symptoms develops.

Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

ANORO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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Stilled leaflets on bioprosthetic valves trigger concern

BY MITCHEL L. ZOLER
Frontline Medical News

SAN FRANCISCO – The newly discovered issue of reduced leaflet motion and possible thrombus on bioprosthetic aortic heart valves, called by one expert "an imaging observation of uncertain clinical significance," nonetheless drew lots of attention at the Transcatheter Cardiovascular Therapeutics annual meeting. Reduced leaflet motion was the focus of the meeting's opening session as well as a specially scheduled press conference.

Much of the attention dealt with clarifying the situation and calling for calm after patient concerns were aroused by a report that examination of detailed CT scans from small series of patients who had recently undergone aortic valve replacement showed reduced-motion or immobilized valve leaflets on some of the bioprosthetic valves. The pattern of the finding, made using four-dimensional CT imaging, indicated that reduced-motion leaflets did not occur, and possibly even resolved, when patients were on anticoagulant therapy, suggesting that leaflet immobilization involved thrombus. Also, reduced-motion leaflets appeared following both transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR), said Dr. Raj R. Makkar.

Dr. Makkar summarized his CT findings in several talks during the meeting and also in a report published a few days before the meeting (N Engl J Med. 2015 Oct 5. doi:

What we thought was an imaging artifact is in fact real, and it is almost certainly related to thrombus.

DR. MAKKAR

10.1056/NEJMoa1509233).

"We started with what we thought was an imaging artifact and established that is it real. We also established with reasonable certainty that it is related to thrombus," said Dr. Makkar, professor at the University of California, Los Angeles, and director of the Cardiovascular Interventional Center at Cedars-Sinai Medical Center in Los Angeles. The evidence also indicates that this is a class effect that occurs with all types of TAVR systems as well as surgically placed valves.

What the evidence so far does not indicate is that patients with reduced-motion leaflets face any clinical consequence nor need for routine CT imaging of a newly-placed TAVR or SAVR valve. Also no need for routine anticoagulant therapy instead of standard treatment with dual antiplatelet therapy for several months following placement of a bioprosthetic aortic valve. "We should not make the leap that following TAVR, everyone should be on an anticoagulant" because anticoagulant treatment carries it own risks, said Dr. Makkar, who noted that roughly a quarter of TAVR patients receive anticoagulant treatment because of another indication, such as atrial fibrillation.

"The study did not show a temporal or causal relationship between the imaging findings and stroke. That needs emphasis," commented Dr. Susheel Kodali, codirector of the Heart Valve Center at the Center for Interventional Vascular Therapy at

'The study did not show a temporal or causal relationship between the imaging findings and stroke.'

DR. KODALI

Columbia University in New York. The possible link between leaflet immobility and strokes or other neurologic events "warrants further study," as the data that Dr. Makkar reported involved a total of only six strokes or transient ischemic attacks. Data from all the TAVR trials and registries reported so far showed "no late signal of stroke," said Dr. Kodali, who added that SAVR had a 30-year record of net benefit for appropriate patients.

"Is valve-leaflet thickening an important controversy or much ado about nothing?" wondered Dr. Martin B. Leon, director of the Center for Interventional Vascular Therapy of Columbia University.

'Is valve-leaflet thickening an important controversy or much ado about nothing?'

DR. LEON

"Patients should not feel at risk, and there is no need to do anything differently" for the time being in routine practice, commented Dr. Jeffrey J. Popma, professor at Harvard Medical School and director of interventional cardiology at Beth Israel

'Patients should not feel at risk, and there is no need to do anything differently' in routine practice.

DR. POPMA

Deaconess Medical Center, both in Boston.

Dr. Makkar said that in the days following the publication of his report, he had "a lot of phone calls and time spent allaying anxiety in patients and reassuring them."

One reason why these leaflet-motion abnormalities may have shown up on CT examinations recently is that "the cameras have gotten better," said Dr. Jonathon A. Leipsic, codirector of advanced cardiac imaging at the Providence Health Care Heart Center at St. Paul's Hospital in Vancouver. Dr. Leipsic also highlighted that with state-of-the-art CT images, immobilized leaflets are easy to identify.

Despite that, Dr. Popma stressed that standardized imaging protocols are needed going forward to produce reliable incidence data.

The data that Dr. Makkar reported came from a review of four-dimensional CT imaging done on 187 replacement aortic valves, usually within 3 months of placement. Images for 55 aortic valves came from the device-approval trial for a new TAVR system, taken 30 days after patients underwent TAVR with any of three types of systems. The images showed reduced leaflet motion in 22 valves (40%).

CT images for another 132 valves came from a Cedar's-Sinai registry and a second, independent registry maintained in Denmark. CT images showed that 17 (13%) of the replaced aortic valves showed a leaflet-motion abnormality, including two valves placed using SAVR. Half the registry patients had undergone CT imaging within 88 days of valve replacement. The only signal of a clinical outcome linked with reduced-motion leaflets was a small increase in the incidence of transient ischemic attacks, but Dr. Makkar cautioned that transient ischemic attacks "are hard to adjudicate."

Dr. Makkar's report was "a small but important study, one of the first reports of this phenomenon. You don't want to lose sight of all the evidence of patient benefit" from aortic valve replacement, stressed Dr. Kodali at the meeting, sponsored by

One reason these leaflet-motion abnormalities may have shown up on CT scans is that 'the cameras have gotten better.'

DR. LEIPSIC

the Cardiovascular Research Foundation. "This needs to be investigated further, probably by a Food and Drug Administration–mandated trial with CT imaging."

"Aortic valves are lifesaving devices. The last thing that should happen is patients not getting their aortic valves replaced" when their condition demands it, Dr. Makkar said.

Dr. Kodali has been a consultant to Edwards Lifesciences and Claret Medical and has an equity interest in Thubrikar Aortic Valve. Dr. Leon has been a consultant to Edwards. Dr. Popma has been a consultant to Abbott Laboratories, Boston Scientific, and St. Jude, and he has been a speaker for and received grants from Medtronic, Dr. Leipsic has been a consultant to Edwards and Heartflow and received grants from Edwards, Neovasc, and Tendyne.

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VITALS

Key clinical point: CT imaging of recently placed bioprosthetic aortic valves showed several cases of leaflets with reduced motion, suggesting possible clinical consequences.

Major finding: CT imaging showed reduced leaflet motion in 22 of 55 (40%) trial patients and 17 of 132 (13%) registry patients.

Data source: An observational study of CT images collected on 187 patients who had undergone aortic valve replacement from the PORTICO IDE study (55 patients), and the RESOLVE and SAVORY registries (132 total patients).

Disclosures: The PORTICO IDE study and RESOLVE registry were funded by St. Jude. Dr. Makkar has received honoraria and research support from St. Jude, lecture fees from Edwards Lifesciences, research grants from Edwards and Medtronic, and has an equity interest in Entourage.

What if your PAH patient may not have PAH?

A ventilation-perfusion (V/Q) scan can rule out chronic thromboembolic pulmonary hypertension (CTEPH) in patients diagnosed with PAH, which is the only form of pulmonary hypertension that can be potentially cured by surgery.[1]

If you know what to look for, a V/Q scan makes it relatively easy to spot.[1]

1 in 25*

As many as **1 out of every 25** of your previously treated PE patients (>3 months of anticoagulation[2]) may develop CTEPH.[3,4*]

*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5). CTEPH did not develop after two years in any of the 132 remaining patients with more than 2 years of follow up.

VISIT **scan4CTEPH.COM** FOR MORE INFORMATION

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Screening for CTEPH in Patients With Suspected Pulmonary Hypertension

presented by

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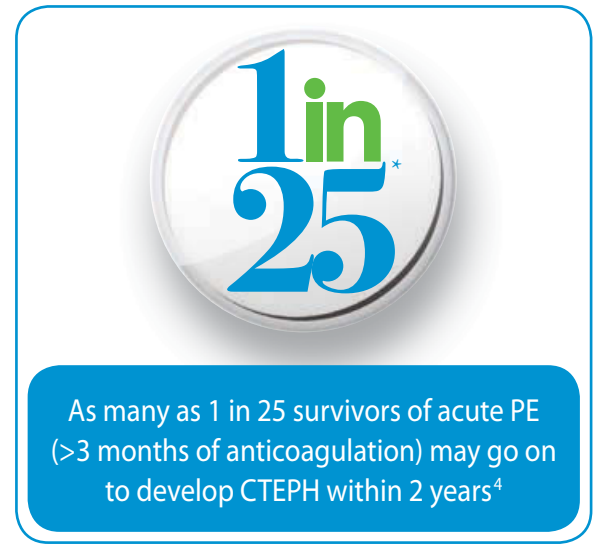

CTEPH IS A FORM OF PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension is a form of pulmonary hypertension (PH), designated by the World Health Organization as Group 4 PH. There are 5 WHO Groups of PH[1]:

1: Pulmonary arterial hypertension

2: PH due to left heart disease

3: PH due to lung diseases and/or hypoxia

4: CTEPH

5: PH with unclear multifactorial mechanisms

Recently, Klok et al have coined the term "post-pulmonary embolism syndrome" to describe chronic complications of pulmonary embolism (PE), involving permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function which are associated with symptoms of dyspnea and decreased exercise capacity.[2] The most serious manifestation of this syndrome—and the most serious complication of acute PE—is chronic thromboembolic pulmonary hypertension, or CTEPH.[2,3] As many as 1 in 25 survivors of acute PE may go on to develop CTEPH within 2 years.[4]

Hemodynamically, CTEPH is most often defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. These levels must be obtained via right heart catheterization, and they must be observed in the presence of multiple chronic/organized, occlusive thrombi/emboli in the pulmonary arteries after at least 3 months of effective anticoagulation.[5]

Symptoms of CTEPH are nonspecific[6] and include dyspnea on exertion, fatigue, weakness, chest pain, syncope, hemoptysis, and lower-extremity edema.[7] Among the risk factors for CTEPH are unprovoked or recurrent PE, young age at the time of first PE, and splenectomy.[7]

CTEPH is unique among the five groups of PH insofar as it is the only form that is potentially curable—via pulmonary thromboendarterectomy (PTE, also known as pulmonary endarterectomy [PEA]), the treatment of choice for surgical candidates with CTEPH.[8-10] It is this potential to effect a curative treatment that makes it imperative to suspect and screen for CTEPH—and to differentiate CTEPH from other forms of PH—when patients present with symptoms consistent with PH.

HOW DOES CTEPH DEVELOP?

CTEPH results after a single PE or recurrent PEs that create endothelialized residua that obstruct or substantially narrow pulmonary arteries.[11] The absence or depletion of endogenous nitric oxide may contribute to endothelial dysfunction in CTEPH.[12] Obstruction and narrowing of the pulmonary arteries drives pulmonary arterial pressures to abnormal levels and increases pulmonary vascular resistance (PVR).[11] Over time, developing small vessel vasculopathy can lead to right ventricular afterload, progression of PH, and CTEPH.[13] If CTEPH is unrecognized or left untreated, right ventricular dysfunction can progress, ultimately resulting in right heart failure.[13]

HOW COMMON IS CTEPH?

Based on data from small observational studies that followed survivors of acute PE, incidence of CTEPH has been estimated to be 0.57% (N=866 survivors of acute PE observed) to 3.8% (N=314 survivors of acute PE observed)—or almost 1 in 25—within 2 years of the first acute event.[3,13] A more recent, but smaller (N=146 acute PE survivors followed for 26 months) study found that 8 survivors of acute PE were suspected to have CTEPH, and 7 of these—or 4.8% of the study population—were confirmed to have CTEPH.[14] Yet another study of survivors of acute PE (N=104) saw 5.8% of patients develop CTEPH within 2 years. Further follow-up saw an additional 4 cases develop beyond 2 years (time period not specified) for a total of 9.1% of the original study population.[15]

> The absence of prior acute PE does not exclude a diagnosis of CTEPH[9,16,17]

Applying even the lower end of this range of estimates to the annual population of survivors of acute PE suggests there could be thousands of incident cases of CTEPH each year in the US. Further, though CTEPH is a complication of acute PE, as many as 25% to 30% of patients who have CTEPH may never have had an overt PE or a history suggestive of PE.[9,16,17] The true incidence of CTEPH may, therefore, be underestimated, because postembolism observational studies do not include patients who have no history of venous thromboembolism.[13]

HOW DO WE SCREEN FOR CTEPH?

As noted, symptoms of CTEPH are nonspecific, and as a result, CTEPH is often misdiagnosed and is under recognized in practice.[6] If after at least 3 months of anticoagulation following an episode of acute PE a patient still has or develops symptoms of dyspnea, fatigue, decreased exercise capacity, or another of the symptoms of PH, one should suspect and either screen for CTEPH or refer the patient to a PH specialist who can perform CTEPH screening.[18,19]

As noted above, as many as 30% of patients who are ultimately diagnosed with CTEPH may have no history of overt acute PE, so any patient who has unexplained dyspnea should also be screened for CTEPH.[9, 16,17]

> If after 3 months of anticoagulation following an episode of acute PE a patient still has or develops such symptoms, CTEPH should be suspected and the patient referred to a PH specialist who can perform CTEPH screening[17]

Computed tomographic pulmonary angiography (CTPA) has become the standard diagnostic test for acute PE, and a good-quality CTPA that is negative for acute PE effectively rules the diagnosis out.[19] Unlike for acute PE, though, CTPA is not a preferred diagnostic test for CTEPH.[8] Instead, the ventilation/perfusion, or V/Q, scan is the preferred and recommended screening test for CTEPH.[8] Tunariu et al demonstrated that as a screening test for CTEPH, the V/Q scan had >96% sensitivity, meaning that a negative (ie, normal) V/Q scan essentially rules out the presence of CTEPH.[20] Conversely, Tunariu et al also showed that CTPA had a sensitivity of only 51% as a screening test for CTEPH, with a falsely negative finding in 38 of 78 cases studied.[20] Multiple national and international guidelines recommend the use of the V/Q scan as the CTEPH screening tool of choice.[5,8,21-23] Though it can detect chronic thromboembolic disease in segmental, lobar, or main pulmonary arteries, CTPA may miss disease that is

confined to very distal segmental or subsegmental pulmonary arteries.[8,24]

The V/Q scan has many attributes that contribute to its utility as a screening tool for CTEPH.[8] It is easy to read—suspected perfusion defects, regardless of origin, are readily recognizable. V/Q scanning also requires less radiation exposure than CTPA, and it avoids complications from administration of IV contrast. Finally, it offers a lower likelihood of incidental findings.

> PTE surgery is the first-line treatment of choice for surgical candidates who have CTEPH[15]

Many patients who have been diagnosed with pulmonary arterial hypertension (PAH) have never had a V/Q scan to rule out potentially curable CTEPH. Findings from the Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QuERI, N=786) demonstrated that 43% of patients who had been diagnosed with PAH had been so diagnosed despite never having received a V/Q scan to screen for, and potentially rule out, CTEPH.[25] This finding suggests that patients who have been previously diagnosed with PAH without having had a V/Q scan and who are not meeting their PAH treatment goals should receive a V/Q scan to screen for CTEPH.

To stress the importance of the V/Q scan as a screening tool for CTEPH, the World Symposium on Pulmonary Hypertension observed that "underutilization of V/Q scans in screening PH invites potential misdiagnosis of PAH."[8] Such misdiagnosis can result in delay of assessment for potentially curative surgery for CTEPH.[6,26] If V/Q scanning is not readily available, the patient should be referred to a center that can perform a V/Q scan.

CONFIRMATION OF CTEPH DIAGNOSIS

An abnormal V/Q scan showing perfusion defects is not enough on its own to diagnose CTEPH. To confirm CTEPH, right heart catheterization (RHC) must be performed to confirm mean PAP ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. Selective pulmonary angiography is typically used to confirm presence of CTEPH lesions.[8] CTPA and magnetic resonance angiography can contribute complementary information on the lesions, their surroundings, and their accessibility.[5,8]

Once the diagnosis of CTEPH is confirmed, all CTEPH patients must be assessed for operability by an experienced CTEPH team that would plan, perform, and follow-up the patient's surgery. Operability assessment must consider the patient's risk, including quality of and accessibility of lesions, hemodynamic assessment, and consideration of comorbidities and patient characteristics.[8] If one experienced CTEPH team determines that a patient has inoperable disease, a corroborating opinion from a second experienced CTEPH team should be secured, if possible.[8] This is because operability assessment is subjective, and what may be deemed by one CTEPH team as inoperable disease may well be deemed operable by another experienced CTEPH team.

CTEPH TREATMENT IN SURGICAL CANDIDATES: PULMONARY THROMBOENDARTERECTOMY

Referral of CTEPH patients to PH centers for confirmation of diagnosis, operability assessment, and comprehensive care is essential.[5] Because it is potentially curative, PTE surgery is considered the first-line treatment of choice for patients diagnosed with CTEPH who are appropriate surgical candidates.[8-10] Rather than reserving PTE surgery as a "last-ditch" treatment option, patients who have operable CTEPH should be referred for surgery without delay.[8] Though all CTEPH patients require lifelong anticoagulation to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism,[8] anticoagulation is not sufficient to treat the progressive right ventricular dysfunction that results from CTEPH. PTE surgery allows for the removal of central obstructing lesions, resulting in improvement and often normalization of pulmonary hemodynamics.[7] About two-thirds of patients have normal hemodynamics following PTE.[27]

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*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5).[4]

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Risk score predicts need for early postop nutrition

BY M. ALEXANDER OTTO
Frontline Medical News

CHICAGO – A few simple baseline variables predict if heart surgery patients will need early nutritional support after their operations, based on a review of more than 1,000 cardiac surgery patients from Johns Hopkins Hospital in Baltimore.

Nonelective surgery and a cardiopulmonary bypass time of 100 minutes or more, plus five preop variables – previous cardiac interventions; total albumin below 4 g/dL; total bilirubin at or above 1.2 mg/dL; white blood cell counts at or above 11,000/mcL; and hematocrit below 27% – predict the need for nutrition in the first few days after cardiac surgery, they found (J Am Coll Surg. 2015 Oct: 221[4];e70).

The Hopkins team has combined those factors into a risk score, with 4 points assigned for low albumin, 6 points for nonelective surgery, 6 points for low hematocrit, and 5 points for the other four variables, yielding a maximum score of 36 points.

The researchers developed the system after discovering that it sometimes took more than a week for cardiac patients who needed postop nutrition to get it. About 40% of patients with scores of 20 or higher will need early nutritional support, and those heart patients are now the ones at Hopkins who get a nutrition consult as soon as they return from the operating room, said Dr. Rika Ohkuma, a general surgery research fellow at Johns Hopkins. "The score can be used for risk stratification and has potential quality improvement implications related to early initiation of nutritional support in high-risk patients."

Just 2% of patients who score 10 points or below need early nutrition, so consults are less pressing. About 9% of patients who score from 10-20 points will require nutrition, so consults are at the discretion of the physician, the investigators concluded.

Those insights came from a review of 1,056 adult heart cases in 2012. Just 87 patients (8%) had a postop consult for nutritional support. Most wound up with enteral feedings, but they started an average of 5 days after surgery. The handful that needed both parenteral and enteric feedings started them an average of 7 days after surgery.

Meanwhile, those 87 patients had significantly higher hospital mortality (29% vs. 3%), ventilator time (278 vs. 20 hours), and gastrointestinal complications (32% vs. 5%), and fewer discharges to home (49% vs. 84%) than did other patients.

Thinking that the delay in feeding might be related to poor outcomes, "we tried to improve our behavior. We know that nutrition is beneficial for critically ill patients and that we need to start early, but there was no gold standard for when to start," Dr. Ohkuma said.

If patients are likely to need support, 'we immediately call the nutritional support service for a consult.'

DR. OHKUMA

The investigators came up with the risk score after figuring out how patients who needed nutrition differed from those who did not. They found, for example, that patients who have emergent surgery were more than three times as likely to have a nutrition consult than were those who had elective procedures.

Now when patients are admitted to the ICU after cardiac surgery, "we all know their [nutrition] score; if they are likely to need support, we immediately call the nutritional support service for a consult," Dr. Ohkuma said.

The researchers launched a prospective study in January 2015. Nutritional needs were addressed sooner, at about postop day 4, for the 70 patients who have needed, and mortality seems to be dropping.

The investigators had no relevant disclosures.

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Drug-coated balloons offer option for in-stent restenosis

BY MITCHEL L. ZOLER
Frontline Medical News

SAN FRANCISCO – Drug-coated balloons have become a widely used option in Europe for treating coronary in-stent restenosis, and the scoring-balloon pretreatment tested in ISAR-DESIRE 4 boosted the efficacy of a drug-coated balloon in a clinically meaningful way, Dr. Marco Valgimigli said in an interview at the Transcatheter Cardiovascular Therapeutics annual meeting.

When patients develop restenosis within a stent, many times it's because the stent was not properly expanded during initial placement. An advantage to a drug-coated balloon is that it pairs well with therapeutic reexpansion of the existing stent to its proper, fully open position.

In addition, this approach spares the patient from receiving a second stent inside the first stent, said Dr. Valgimigli, an interventional cardiologist at Inselspital in Bern, Switzerland.

Often when patients develop in-stent restenosis, it tends to keep recurring. And when that happens, eventually the only remaining option for effective revascularization of the patient's coronary arteries is coronary bypass surgery.

Pretreating in-stent restenosis with a scoring balloon prior to treatment with a drug-coated balloon improved efficacy in the ISAR-DESIRE 4 trial by a modest amount. But if this treatment strategy can successfully defer or obviate just a few cases that might otherwise require coronary bypass surgery, then using the scoring balloon is a reasonable approach, Dr. Valgimigli said at the meeting, sponsored by the Cardiovascular Research Foundation.

FRONTLINE MEDICAL NEWS

Watch the video interview at chestphysician.org.

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Novel device aids severe tricuspid regurgitation

BY MICHELE G. SULLIVAN
Frontline Medical News

The investigational FORMA system seems safe and may be effective in patients with NYHA Class III/IV heart failure and severe tricuspid valve regurgitation, based on 13 first-in-human cases.

A Canadian surgical team employed the FORMA system (Edwards Lifesciences) as compassionate use therapy for a set of patients with inoperable tricuspid regurgitation. The device was successfully deployed in 12 of the 13 patients, according to data presented at the Transcatheter Cardiovascular Therapeutics annual meeting. There were no deaths or major clinical complications in any of the patients.

A report on seven of these patients was simultaneously published in the Journal of the American College of Cardiology. All of the patients had severe tricuspid regurgitation and heart failure; before surgery, six had a New York Heart Association (NYHA) Functional Classification of III/IV. By 30 days after the procedure, all had improved to NYHA II, wrote Dr. Francisco Campelo-Parada of the Quebec Heart and Lung Institute, the paper's primary author. Peripheral edema declined and all patients experienced functional improvement, as well.

According to Edwards Lifesciences, the FORMA device uses a foam-filled polymer balloon spacer to reduce tricuspid regurgitation by occupying the regurgitant orifice area and providing a surface for the coaptation of the valve's native leaflets. Implantation is performed via the left axillary vein.

Patients in the series were a mean of 76 years old. All had severe tricuspid regurgitation. The mean maximal vena contracta was 15.5 mm.

Six had coronary artery disease and five had previously undergone open heart surgery. Additionally, two had previously undergone mitral valve surgery and two had undergone aortic valve surgery. Pulmonary hypertension was present in five. Five

Continued on following page

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patients also had persistent atrial fibrillation. Six had renal insufficiency, with one patient on dialysis. The baseline furosemide dose was 80 mg/day.

All procedures were performed under general sedation and fluoroscopic guidance, with postprocedural positioning checked by cardiac-CT and/or a chest x-ray. The mean postop stay was 4 days.

Tricuspid regurgitation was reduced by at least 1 degree in all patients during the operation; four patients had an immediate 2-degree reduction, reclassifying their regurgitation as mild. Two experienced new-onset atrial fibrillation, and one had several episodes of nonsustained ventricular tachycardia that was managed with beta-blockers.

At the first clinical follow-up 30 days after surgery, all but one patient had an improvement to Class II NYHA status.

Two patients were able to reduce their diuretic dosage; there were no other medication changes. Peripheral edema declined in the entire cohort. Tricuspid regurgitation was graded as moderate in all patients.

There were also associated improvements in quality of life, based on scores on the Kansas City Cardiomyopathy Questionnaire, which increased from 59 before surgery to 86 after surgery. Exercise capacity as measured by the 6-Minute Walk Test improved from 297 meters to 326 meters.

The authors suggested that the 15-mm spacer used in the FORMA device was not well-matched with the mean 15.5-mm vena contracta size in the cohort. Better outcomes might be possible if a larger spacer were available.

"Despite good device positioning, complete coaptation was not achieved, resulting in significant residual degree of postprocedural tricuspid regurgitation," they said. "Also, the very advanced stage of the disease in most patients may have played a role in the mild reduction at 30 days."

Despite the rather mild, 1-degree improvement, patients did make considerable improvements in heart failure and functional status. Therefore, the team recommended further study for FORMA, with an eye toward optimizing patient selection.

"Specific criteria for quantifying right ventricular dysfunction and pulmonary hypertension, along with novel quantitative echocardiographic imaging criteria may be required," the investigators said. "It is conceivable that larger than the currently available spacer sizes may be required to improve echocardiographic results in patients with large noncoaptation defects and vena contracta."

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VITALS

Key clinical point: The investigational FORMA system seems safe and may be effective in patients with NYHA Class III/IV heart failure and severe tricuspid valve regurgitation.

Major finding: The improved heart failure from NYHA Class III/IV to Class II in six of seven patients with severe tricuspid valve regurgitation.

Data source: The device has been used in 13 patients thus far, under compassionate use allowance.

Disclosures: Edwards Lifesciences manufactures and is investigating the device. Dr. Campelo-Parada had no disclosures.

Early intervention cut mortality in severe AS

BY MICHELE G. SULLIVAN
Frontline Medical News

Early valve replacement may be in the best interest of asymptomatic patients with severe aortic stenosis, possibly halving their 5-year risk of death, based on data from the CURRENT AS registry study.

Compared to watchful waiting, early surgical intervention also reduced by 81% the risk of hospitalization for heart failure, Dr. Tomohiko Taniguchi said at the Transcatheter Cardiovascular Therapeutics annual meeting. The study was simultaneously published (J Am Coll Cardiol. 2015. doi: 10.1016/j.jacc.2015.10.001).

Observation has been the byword for asymptomatic patients with severe aortic stenosis (AS). The American College of Cardiology recommends a conservative approach

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VIEW ON THE NEWS

Should we intervene earlier?

The findings make a good case for carefully considering which patients might benefit more from early intervention than from close observation. They also suggest a place for less invasive valve replacement rather than watchful waiting in some asymptomatic patients.

I think this finding is fabulous, and raises the question of whether the ventricle cares even if the patient doesn't care. Should we be intervening earlier with transcatheter aortic valve replacement? A less-invasive therapy early on may have benefits.

Dr. Jeffrey J. Popma is professor of medicine at Harvard Medical School and director of interventional cardiology at the Beth Israel Deaconess Medical Center, Boston.

Continued from page 46

to the asymptomatic AS patient, but acknowledges the disorder inevitably progresses in nearly all patients.

But the CURRENT AS registry results suggest that "the long-term outcome of asymptomatic patients with severe aortic stenosis was dismal when they were managed conservatively in real clinical practice," Dr. Taniguchi said at the meeting, sponsored by the Cardiovascular Research Foundation.

"If you're watching and waiting, and you wait for sudden death, then that is a problem," commented Dr. Ajay J. Kirtane. Early intervention "potentially changes the game because we do have a less-invasive procedure we can offer – transcatheter aortic valve replacement (TAVR)," said Dr. Kirtane of New York-Presbyterian Hospital.

In the CURRENT AS study, severe AS was considered a peak aortic jet velocity over 4.0 m/s, or a mean aortic pressure gradient greater than 40 mm Hg, or an aortic valve area less than 1.0 cm^2. The registry includes 3,815 patients; Dr. Taniguchi of Kyoto University reported outcomes for a propensity-score matched cohort of 582 patients, 291 in the initial TAVR group and 291 in the conservatively managed group. There was no treat-

ment randomization; treatment decisions were made at the clinical level.

Patients in the matched cohort were in their early 70s; in 80%, the AS etiology was degenerative. The mean aortic pressure gradient was 54 mm Hg in the early intervention group and 45 mm Hg in the watchful waiting group. In 79% of the early intervention group and in 54% of the watchful waiting group, the mean aortic pressure gradient was below 40 mm Hg.

Among the patients who underwent TAVR despite being asymptomatic, most (63%) had at least one surgical indication, including severe AS (41%), left ventricular dysfunction (7%), rapid hemodynamic progression (11%), or active infective endocarditis (0.3%). Other cardiac surgery indications we, Dr. Taniguchi noted.

By the end of the 5-year follow-up period, 26% of the conservative therapy group and 15% of the early AVR group had died – a significant difference (hazard ratio, 0.64; $P = .02$).

The coprimary endpoint of heart failure hospitalization was also significantly more common among the conservatively treated group (19.9% vs. 3.8%; HR, 0.19; P less than .001).

The study was sponsored by Kyoto University,

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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** and **CLINICAL PHARMACOLOGY** in full Prescribing Information (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**]. 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** and **USE IN SPECIFIC POPULATIONS**].

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** in full Prescribing Information (12.2)]. 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**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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*	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
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

* All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	160/4.5 mcg N = 771 %	160 mcg N = 275 %	4.5 mcg N = 779 %	N = 781 %
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. 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. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

FDA expands nivolumab use to nonsquamous NSCLC

BY LAURA NIKOLAIDES
Frontline Medical News

The Food and Drug Administration approved nivolumab for the treatment of patients with metastatic nonsquamous non–small cell lung cancer (NSCLC) that has progressed during or after platinum-based chemotherapy, along with a companion diagnostic to detect PD-L1 protein expression levels.

The FDA approved nivolumab for patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy in March of this year. The October approval expands the use of nivolumab to include patients with nonsquamous NSCLC.

The approval was based on improvement in overall survival (OS) in an international, multicenter, open-label, randomized trial comparing nivolumab to docetaxel in 582 patients with metastatic nonsquamous NSCLC with progression on or after platinum-based chemotherapy, according to an Oct. 9 statement issued by the FDA.

Median OS was 12.2 months in patients treated with 3 mg/kg nivolumab every 2 weeks (n = 292) compared with 9.4 months in patients treated with 75 mg/m^2 docetaxel every 3 weeks (n = 290). There was also a significant improvement in overall response rate in the nivolumab arm (19% vs 12%); the median response duration was 17 months in the nivolumab arm and 6 months in the docetaxel arm. There was no significant difference in progression-free survival. Patients with PD-L1 positive NSCLC had a greater survival benefit than did those with PD-L1 negative NSCLC, and therefore, the FDA also approved the PD-L1 IHC 28-8 pharmDx test to detect PD-L1 protein expression levels.

Serious adverse events were reported in 47 of the 292 patients in the nivolumab arm. The most common serious adverse events were pneumonia, pulmonary embolism, dyspnea, and pleural effusion. Immune-mediated adverse events included hypothyroidism/thyroiditis, rash, pneumonitis, diarrhea/colitis, hyperthyroidism, hepatitis, nephritis, limbic encephalitis, and polymyalgia rheumatica.

The most common grade 3-4 adverse reactions in the nivolumab arm were dyspnea, fatigue, pneumonia, pulmonary embolism, pleural effusion, hyperglycemia, respiratory failure, and pain. The most common grade 3-4 laboratory abnormalities included lymphopenia, hyponatremia, anemia, increased AST, and increased ALT, the FDA said.

This approval follows closely behind the accelerated approval of pembrolizumab to treat patients with metastatic NSCLC who have disease that has progressed after other treatments and tumors that express PD-L1. This anti–PD-L1 drug was also approved with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test.

Nivolumab is marketed as Opdivo by Bristol-Myers Squibb and the PD-L1 IHC 28-8 pharmDx test is marketed by Dako North America Inc.

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Workshop focuses on CT screening for lung cancer

BY SUSAN LONDON
Frontline Medical News

DENVER – In its third CT Screening Workshop, the Strategic Screening Advisory Committee of the International Association for the Study of Lung Cancer discussed the finer points of using this imaging technology to screen for lung cancer, including issues such as metrics, quality control, and cost-effectiveness.

"Lung cancer is the major problem of all cancers," committee chair Dr. John K. Field maintained in press conference at the annual World Conference on Lung Cancer, which was held in conjunction with the workshop. This cancer still causes more deaths than all of those from breast, colon, and prostate cancer combined.

"However, the good news is that the future does lie in early detection," he said. The National Lung Screening Trial established that low-dose CT screening reduces the risk of lung cancer death by 20% compared with plain chest radiographic screening (N Engl J Med. 2011;365:395-409).

"That was the first time anybody had actually demonstrated such a mortality advantage with anything in lung cancer, so it led to an enormous stage shift in our thinking," noted Dr. Field, who is also Personal Clinical Chair in Molecular Oncology at the University of Liverpool, England.

In the workshop, committee members reviewed new guidelines

Cost-effectiveness [of CT screening] is going to be a major issue, especially in Europe.

DR. FIELD

on managing screen-detected nodules from the ongoing NELSON (Dutch Belgian Randomised Lung Cancer Screening Trial) (Lancet Oncol. 2014;15:1332-41) and from the British Thoracic Society (Thorax. 2015;70:794-8). Main results from NELSON, as well as from the similar U.K. Lung Cancer Screening Trial, are expected shortly.

"We also looked at quality control for future screening programs. It's extremely important that if we do have screening in place, that we have the necessary quality control behind it," Dr. Field asserted.

Another topic discussed was whether CT screening is cost-effective. "Cost-effectiveness is going to be a major issue, especially in Europe," where policy makers are awaiting results from the two trials before implementing screening, he said. "At this moment in time, it looks as though we will be cost-effective."

The committee also assessed the potential of lung cancer biomarkers. "If we can actually improve the CT screening by using a particular biomarker, that would help us identify individuals easier. But also, once we undertake the CT, we are sometimes left with a gray situation of nodules that may become malignant but are not large enough to actually undertake any surgical intervention. And if we had a biomarker that would tell us if it was an aggressive tumor, that would be an enormous advantage," Dr. Field elaborated.

Finally, the committee reviewed the status of national plans for implementing lung cancer CT screening around the world. Implementation is a multistep process requiring clinical experts and policy makers to hammer out a variety of issues, he noted (Lancet. 2013;382:732-41).

These issues include how best to identify individuals at high risk, typically accomplished with the LLP (Liverpool Lung Project) risk model in the United Kingdom and the PLCO (Prostate, Lung, Colorectal, and Ovarian) risk model in the United States. Screening age must also be considered. "In the U.K., our recommendation would probably be 60-75, but in the U.S. it would be 55-80, which came from the U.S. Preventive Services Task Force," Dr. Field noted.

Another issue is whether nodules identified on CT are better measured by their maximal diameter (used in the National Lung Screening Trial) or their volume (used in the ongoing NELSON and U.K. trials).

"There are advantages and disadvantages of both. We feel that volume is the way forward," he said.

The nature of any subsequent work-up, including whether a biopsy is performed and additional tests, is also a consideration, as is the management of small nodules, including whether patients should undergo video-assisted thoracoscopic surgery.

Dr. Field disclosed no relevant conflicts of interest.

Carboplatin-vinorelbine supported in early NSCLC

BY SUSAN LONDON
Frontline Medical News

DENVER – An adjuvant regimen of carboplatin plus vinorelbine is well tolerated and efficacious in patients who have undergone complete resection of early non–small cell lung cancer (NSCLC), results from a multicenter phase II trial suggested.

The 74 patients in SWITCH 1 received carboplatin plus intravenous vinorelbine on day 1, with a switch to oral vinorelbine on day 8. A total of four cycles of a 21-day regimen were planned.

Main results reported at a world lung cancer conference sponsored by the International Association for the Study of Lung Cancer showed that the regimen was well tolerated, with higher-grade neutropenia seen in only about a quarter of patients and no deaths because of toxicity. More than four-fifths of patients completed all of the planned treatment, and median survival was nearly 6 years.

"Adjuvant chemotherapy with carboplatin and vinorelbine given [intravenously] and switched to oral formula is feasible, tolerable, and effective in early-stage NSCLC," commented first author Dr. Vitezslav Kolek, a pulmonary oncologist at University Hospital in Olomouc, Czech Republic.

Although comparison with large phase III adjuvant trials is problematic, he acknowledged, "this regimen gives better comfort to the patients, and provides high dose intensity and more completed treatments, compared with cisplatin-based trials. And the present regimen achieved comparable survival to cisplatin-based therapy."

"The take-home message could be that we don't have reliable, routinely used predictors in the adjuvant setting. Under these conditions, probably the most intensive [therapy] doesn't mean the best," he concluded.

Dr. Giorgio V. Scagliotti of the University of Torino (Italy) took issue with the lack of presentation of a statistical hypothesis and with the cross-trial comparison.

"The most proven regimen is cisplatin-vinorelbine. … Cisplatin doublets with proven efficacy in advanced disease remain the standard of care for adjuvant chemotherapy," he said. "For elderly or unfit patients, carboplatin may be considered in individual cases."

Dr. Kolek noted that carboplatin and cisplatin have not been directly compared in the adjuvant setting. The combination of cisplatin and vinorelbine, however, is known to result in some deaths due to toxicity, and a large share of patients are unable to complete the therapy. In addition, oral vinorelbine seems to perform as well as the intravenous formulation, and patients generally prefer oral therapy, he said.

The patients enrolled in SWITCH 1 had undergone complete resection of stage IB, II, or IIIA NSCLC. The median age was 64 years, and 72% were male; 62% had squamous histology.

The regimen 'gives better comfort to the patients, and provides high dose intensity and more completed treatments.'

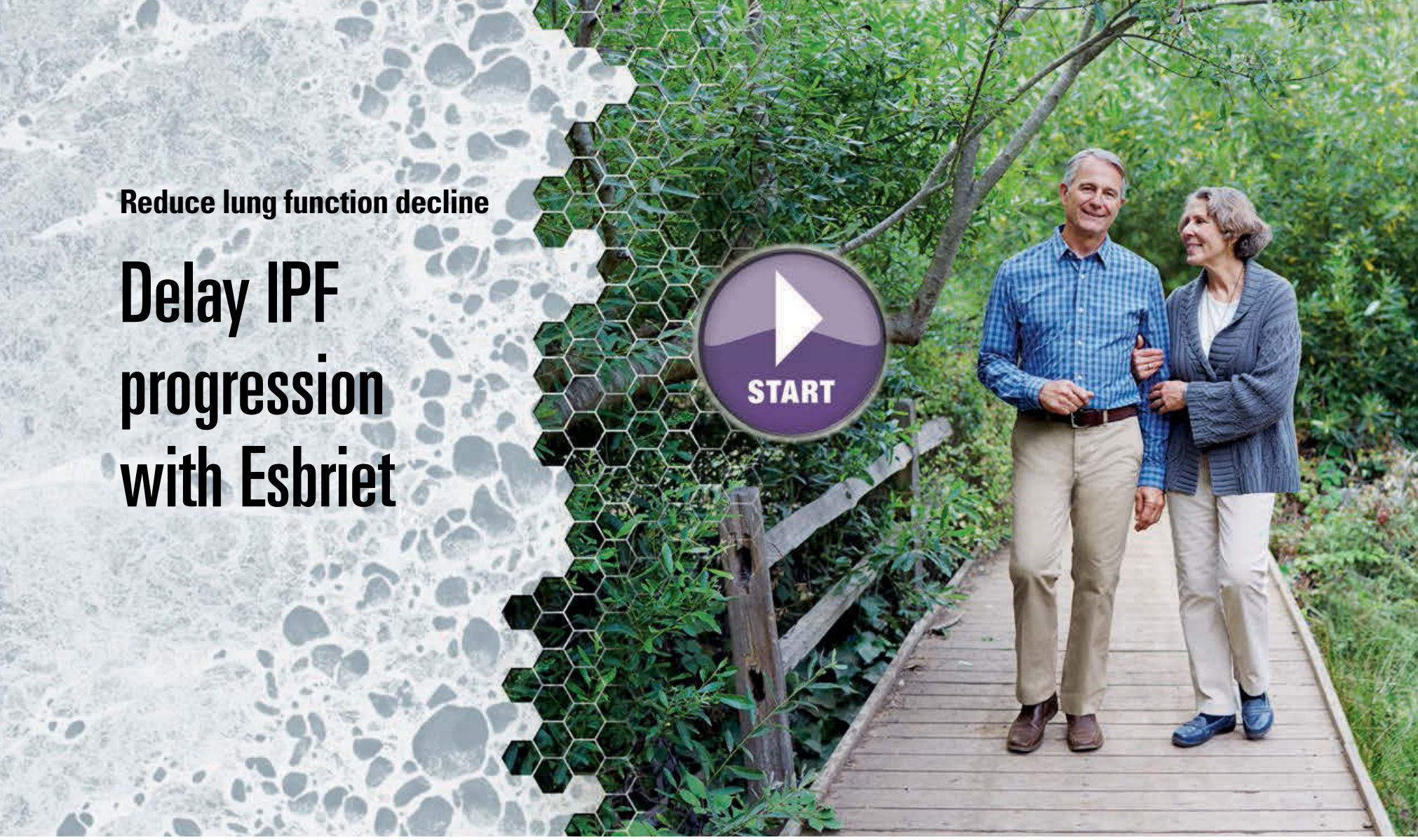
DR. KOLEK

The mean relative dose intensity was 83% for oral vinorelbine, 93% for intravenous vinorelbine, and 89% for carboplatin, Dr. Kolek reported. The mean number of cycles of chemotherapy received was 3.8 per patient and, overall, 82% of patients completed the planned therapy.

With a median follow-up of 4.7 years, median disease-free and overall survival were 4.4 years and 5.9 years, respectively. Corresponding 5-year rates were 48% and 56%.

The most common grade 3 or 4 toxicities per cycle were neutropenia (seen in 26% of patients), leukopenia (16%), alopecia (12%), and anemia (8%). None of the patients died from treatment toxicity.

Dr. Kolek reported that he receives honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, Pierre Fabre, and Roche.



Reduce lung function decline

Delay IPF progression with Esbriet

Indication

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

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

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 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.

Esbriet®
(pirfenidone) capsules 267 mg

Proven to delay progression in IPF[1]

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had ≥10% decline in %FVC, $P<0.001$). Treatment effect was evident at 13 weeks ($P<0.001$) and increased through trial duration[1,2,*,†]
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)[2,*,‡]
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet[2]
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide[3]

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

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled 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 $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the ≥10% decline category.
‡Stable was defined as no decline in lung function.

References: 1. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. **2.** Esbriet full Prescribing Information. InterMune, Inc. October 2014. **3.** InterMune, Inc. Data on file.

Genentech
A Member of the Roche Group

Esbriet®
(pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.

INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations *[see Warnings and Precautions]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions]*
- Gastrointestinal Disorders *[see Warnings and Precautions]*

Clinical Trials Experience

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

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

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

Table 1. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

Postmarketing Experience

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

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

DRUG INTERACTIONS

CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration section 2.4 in full Prescribing Information]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

ESBRIET® (pirfenidone)

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.2 in full Prescribing Information]*.

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 *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Renal 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 *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information],* which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005 USA

INTERMUNE®

ABIM 2020 Goals Align With CHEST Educational Principles

BY ROBB RABITO, CHCP
Director, CHEST Education Operations

The American Board of Internal Medicine (ABIM) recently released *Assessment 2020, A Vision for Certification in Internal Medicine in 2020*, developed by a commissioned task force to "develop a vision for the future of assessment for certification (initial and maintenance) in internal medicine and associated subspecialties."

Assessment 2020 highlights three key recommendations that aim to reduce the burden of recertification, deliver more relevant assessments focused on practice-based skills, and recognize the value of specialization.

The Assessment 2020 recommendations include the following:

1. Replace the 10-Year Maintenance of Certification examination with more frequent, less burdensome assessments

2. Focus assessments on cognitive and technical skills

3. Recognize specialization

CHEST supports this effort to better align certification and recertification with the relevant practice of physicians and has long promoted the principles behind these recommendations. CHEST is the first medical society to receive accreditation from the Society for Simulation in Healthcare, and The CHEST Certificate of Completion (COC) program provides ongoing opportunity for learning and formative evaluation of knowledge and performance alongside rigorous assessment.

We are interested in your feedback on this report and each of these recommendations. Please provide us with your comments at https://www.surveymonkey.com/r/FWHCCS5.

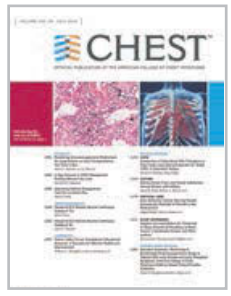
CHEST will incorporate your feedback into our future work with ABIM and will continue to inform you of any important changes to certification and recertification.

This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

The Association Between Heroin Inhalation and Early Onset Emphysema. *By Dr. P. P. Walker et al.*

A Randomized Controlled Study to Examine the Effect of a Lifestyle Modification Program in OSA. *By Dr. S. S. Ng et al.*



Prognosis for Spontaneous Resolution of OSA in Children. *By Dr. R D. Chervin et al.*

Giants in Chest Medicine: Dr. John F. Murray. *By Dr. Philip C. Hopewell.* (Video included)

ERS International Congress 2015

Enjoying the ERS International Congress 2015 in Amsterdam (L-R): Canadian Thoracic Society President, Dr. Diane Lougheed; European Respiratory Society Immediate Past President, Dr. Elisabeth Bel; and new CHEST President, Dr. Barbara A. Phillips, FCCP.

CHEST World Congress 2016 in Shanghai, China

Get Your Fill of the Latest Clinical Science, Authentic Cuisine

As you plan your trip to Shanghai for CHEST World Congress 2016, you are probably eagerly anticipating authentic Chinese cuisine. You may be imagining Chinese food as you know it in North America – buffets; fortune cookies; and small, white takeout boxes. Buffets actually are commonplace in Shanghai, but you likely won't find a fortune cookie anywhere. We're here to give you a rundown of what to expect from Chinese cuisine, but read this at your own risk. Your stomach may growl, and we can't promise that your local Chinese restaurant will serve many of the authentic dishes featured below.

Let's get started with the basics. Shanghai cooking is known for a heavy, highly flavorful sauce. Dishes favor sugar, soy sauce, and oil, and seafood is featured prominently. You may find it to be rather oily and sweet. Generally expect to find meals served as family-style, and soup is oftentimes served as the last course. Finally, tips aren't needed, though there may be a service charge added to your bill at hotel restaurants.

Shanghai is most famous for its Shengjian Bao, fried soup dumplings. These dumplings are a thin dough wrapped around ground pork and a gelatinous soup. Yang's Dumpling franchise is the most popular place to get this tasty snack or breakfast treat, but you can also find them at many other restaurants in Shanghai. Follow Chinese tradition, and save yourself from getting burned, by eating dumplings in this order:

EURNGKWAN/THINKSTOCK

- Place your dumpling on a spoon with help from your chopsticks.
- Bite off a small piece on top to make a hole.
- Blow and wait for the soup to cool.
- Slurp the soup inside.
- Dip into vinegar, if you wish.
- Eat the remainder of the dumpling.

Shanghai is also known for these popular street foods:

- Jianbing - These egg pancakes are served for breakfast by street vendors. The batter is made from mung bean flour, and crepes are topped with an egg or two, chopped pickled greens, scallions, and cilantro. Then spice is added with red bean, hoisin, and chili sauces.
- Hot Pot - Basic stock or spicy stock is offered with sides of thinly sliced raw meats, vegetables, and noodles.
- Chuanr - These skewers are made with lamb, chicken, beef, seafood like shellfish, and vegetarian options like eggplant and tofu. They are topped with cumin seeds, salt, sesame seeds or sesame oil, dried pepper flakes, and a spicy sauce.

If you're looking for a more upscale dining experience, the travel site, Frommers, has recommendations. Here are a few recommended restaurants located at the luxurious development, Three on the Bund:

- Jean Georges - contemporary and light French fare.
- Whampoa Club - Classic Shanghai foods with a contemporary spin.
- Laris - A seafood restaurant with an Australian chef.
- New Heights - casual, more affordable bistro fare.

Whether you decide to fill up with eats from the street, or you sit down at a cafe or restaurant, we know you'll find the cuisine you're craving with one of Shanghai's many dining options.

Similarly, you'll get your fill of science at CHEST World Congress with assorted clinical education opportunities. When CHEST travels to Shanghai, April 15 - 17, 2016, you'll have your choice of simulation-based education, case and problem-based sessions, and evidence-based medicine for clinical respirologists, intensive care physicians, and specialists in sleep medicine. Learn more at chestworldcongress2016.org.

CHEST Foundation Grants Seed Future Research

As CHEST 2015 wraps up, and the CHEST Foundation begins to award new grants to fund research in chest medicine, it's important to check in with previous grant winners to see how their innovative projects have progressed.

One notable and inspiring CHEST Foundation grant recipient, Dr. Ghada Bourjeily, FCCP, turned her two $10,000 CHEST Foundation grants into a $2.8 million federally funded, interdisciplinary, team-based research program for women's health.

"These grants were instrumental in helping my team," Dr. Bourjelly stated when asked about the effects winning the grants had on her research. "Without the results from the CHEST Foundation grant-funded research, my team and I would have been unable to apply for federal funding. We were recently awarded about $2.8 million in federal funding." Her projects, Differences in Respiratory Sleep Parameters of Pregnant and Nonpregnant Women, and Sleep-Disordered Breathing in Pregnant Women With Gestational Diabetes Mellitus: Prevalence and Mechanisms, both aimed at gaining a better understanding of sleep-disordered breathing during pregnancy. "I am extremely grateful to the CHEST Foundation for its generous support in helping launch our project and to the CHEST NetWorks and steering committees, which are helpful for guiding young physicians toward opportunities like CHEST Foundation grants, which help them succeed in their careers."

Dr. Bourjelly's research coordinators, nurses, and administrators. People collaborating on the projects but not pictured: Dr. Jennifer Fung; Dr. Mary Kao, (MD'16); and Palak Walia.

The CHEST Foundation believes that a team-based approach to chest medicine research is a cornerstone for advancing lung health. Our grants support such team-based, interdisciplinary efforts, and we are excited to continue partnering with CHEST members on new clinical research and community-based projects in the upcoming grant cycle for 2016.

It is critical to acknowledge that the success of these projects is made possible by the support of members and friends in the chest medicine community who donate each year to the foundation's Annual Fund. Become part of our Annual Fund Giving Club today by visiting chestnet.org/donate, and learn more about grant opportunities for 2016 by stopping by chestnet.org/grants. Thank you for your contributions and for your support of the CHEST Foundation's mission to champion lung health.

Dr. Bourjelly is with the Women's Medicine Collaborative through Miriam Hospital/Lifespan.

EV-D68 less dangerous than flu in children

BY AMY KARON
Frontline Medical News

SAN DIEGO – *Enterovirus* D68 appeared more virulent – but not more lethal – than rhinovirus and other strains of enterovirus among children, said the authors of a single-center study.

EV-D68 was linked to higher rates of respiratory distress, hospital admission, and magnesium sulfate therapy, but patients were no more likely to die or require critical care unit admission than were those infected with other EV genotypes or rhinovirus, said Dr. Dominik Mertz of the division of infectious diseases at McMaster University, in Hamilton, Ont.

The study also uncovered no evidence of EV-68 transmission at the hospital, Dr. Mertz and his associates said at an annual scientific meeting on infectious diseases.

In 2014, an outbreak of EV-D68 in the United States included more than 1,000 confirmed cases, almost all among children, and many of whom had comorbid asthma or a history of wheezing. Fourteen patients died, and the Centers for Disease Control and Prevention noted that millions more individuals probably had milder EV-D68 infections for which they were never tested.

Amy Karon/Frontline Medical News

Although EV-D68 appears more virulent than other enteroviruses and rhinoviruses, it is no deadlier, said Dr. Jeffrey Pernica (left) and Dr. Dominik Mertz.

Dr. Mertz and his associates studied children who presented consecutively to the hospital during the 3 months between Aug. 1 and Oct. 31, 2014. During that time, nasopharyngeal swabs that were positive for EV or rhinovirus were automatically tested for EV-D68. The researchers matched EV-D68–positive patients with children who were positive for rhinovirus or other EVs on the basis of sex, age, and date of presentation to the hospital.

Almost a third (93 of 297; 31%) of rhinovirus or EV samples were positive for EV-D68. Among 87 matched pairs, EV-D68 infection was associated with a threefold greater odds of respiratory distress (95% confidence interval, 1.47-6.14), and a more than twofold rise in the odds of needing magnesium sulfate therapy (odds ratio, 2.62; 95% CI, 1.06-6.47). There was a trend toward greater risk of hospital admission with EV-D68, although it was not statistically significant (OR, 2.29; 95% CI, 0.96-5.46; $P = .06$).

Notably, EV-68 did not increase the likelihood of death or CCU admission, while, influenza causes dozens of deaths among children in the United States every year, Dr. Mertz and his coinvestigator Dr. Jeffrey Pernica noted in an interview (MMWR. 2014 Jun 6:63[22];483-90). "There was a lot of fuss made about EV-D68," said Dr. Mertz. "But we have flu every year, and many more kids get the flu and die of flu than EV-D68."

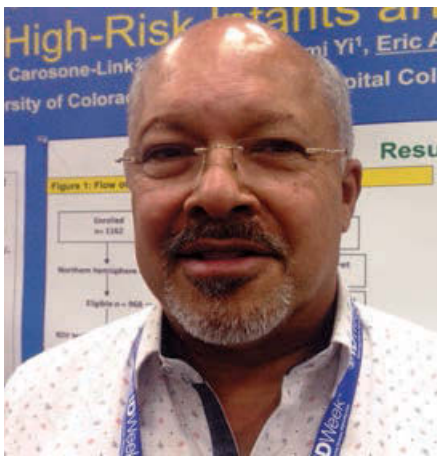
Patients with EV-D68 infection were more likely than others to have a family history of atopy (OR, 2.25) and a personal history of asthma or wheezing (OR, 1.77), hay fever (1.22), and eosinophilia (4.5), although none of these associations reached statistical significance, the investigators reported. "It seems reasonable to hypothesize that EV-D68 is a more virulent pulmonary pathogen to those with preexisting atopic disease than other rhinoviruses and enteroviruses," Dr. Mertz and his associates wrote in an associated article (CMAJ. 2015 Oct. 13. doi: 10.1503/cmaj.150619). The investigators received no funding for the study and reported no conflicts of interest.

Palivizumab reduced RSV hospitalization risk

BY AMY KARON
Frontline Medical News

SAN DIEGO – Prophylactic palivizumab cut the odds of hospitalization for severe respiratory syncytial virus (RSV) infection by about 75% in preterm infants born at more than 29 weeks' gestational age – even those without congenital heart disease or chronic lung disease.

The finding belies the American Academy of Pediatrics' recommendation to limit use of the humanized monoclonal antibody to infants born before 29 weeks' gestation and to children who have other risk factors for severe RSV infection, Dr. Ram Yogev of Ann and Robert H. Lurie Children's Hospital, Chicago, said in an interview.



FRONTLINE MEDICAL NEWS

'Our results validate the older studies, except this was done in real life,' said Dr. Eric Simões.

"Our results validate the older studies, except this was done in real life," added lead investigator Dr. Eric Simões of Children's Hospital Colorado, Aurora, who presented the findings at an annual scientific meeting on infectious diseases.

RSV usually causes mild upper respiratory tract infections, but premature infants and children who have comorbid cardiac or pulmonary disease can develop severe infections of the lower respiratory tract. Weekly palivizumab dosing was 45%-80% effective in preventing RSV-related hospitalizations in clinical trials of these high-risk patients, noted Dr. Simões and his associates.

But in 2014, the American Academy of Pediatrics reviewed the literature and revised its guidance to limit palivizumab to preterm infants born before 29 weeks' gestation and to infants with comorbid risk conditions. The biologic "has been shown to have a limited effect on reducing RSV hospitalization," the academy concluded.

The update drew criticism from some pediatric infectious disease experts, who contended that AAP cited observational studies that actually contradicted its conclusions.

To further examine the issue, Dr. Simões and associates analyzed data from a multicenter study of high-risk infants and children under the age of 2 years who had been hospitalized with lower respiratory tract infections. During 2002-2006, 849 of these patients had a nasopharyngeal wash or endotracheal aspirate tested for RSV, and 403 were positive. The investigators determined that the odds of a positive RSV test were 58% lower for patients who had received prophylactic palivizumab, compared

Continued on following page

Continued from previous page

with patients who had not (95% confidence interval for efficacy, 43%-69%; *P* less than .0001).

Furthermore, palivizumab was 75% effective against severe RSV disease in preterm patients born at 29-35 weeks' gestation who were chronologically younger than 6 months and had no congenital heart disease or chronic lung disease, said the investigators. Based on that finding, AAP should reconsider its recommendations on palivizumab, said Dr. Yogev.

"This study should answer some of the issues raised in the AAP recommendations," added Dr. Simões.

Palivizumab did not prevent hospitalizations for human metapneumovirus (hMPV) infection, which further validated the results on RSV, said Dr. Simões.

IDWeek marked the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

MedImmune sponsored the original study of hMPV tract infections, from which these data were obtained. Dr. Simões reported having received funding support and consulting fees from MedImmune.

Antibiotic prescribing varies widely for pediatric CAP

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Antibiotic prescribing patterns for pediatric community-acquired pneumonia vary substantially across both children's hospitals and facilities that are not children's hospitals, a large analysis found.

Specifically, children's hospitals are far more likely to prescribe in accordance with national guidelines than are other hospitals.

"Moving forward, there's a need for further study to understand these differences, so we can begin to narrow this gap between children's and non–children's hospitals," lead study author Dr. Alison Tribble said at an annual scientific meeting on infectious diseases. "Across the board, we need to continue efforts to improve guideline adherence for all children hospitalized with community-acquired pneumonia."

In 2012, community-acquired pneumonia (CAP) accounted for 120,000 known pneumonia admissions among children in the United States and about 7% of all pediatric hospitalizations, said Dr. Tribble, a pediatric infectious disease specialist at C.S. Mott Children's Hospital and the University of Michigan Medical Center, both in Ann Arbor. "We also know that pneumonia accounts for more days of antibiotic therapy than any other indication for admission to U.S. children's hospitals," she said.

In 2011, the Infectious Diseases Society of America and Pediatric Infectious Diseases Society released guidelines for pediatric CAP, which recommend a first-line therapy with penicillin, ampicillin, or amoxicillin for most children who are immunized and healthy. "Only in situations where there's a significant concern for an atypical organism should we be adding coverage for that – even in older children," Dr. Tribble said. Following the release of the guidelines, she continued, multiple studies have shown that the use of first-line therapy is increasing in children's hospitals. "However, a substantial proportion of children with pneumonia are admitted to non–children's hospitals," she said. "Prior to release of the guidelines, one study showed that use of first-line therapy for pediatric CAP was low in non–children's hospitals (J Pediatr. 2014 165[3]:585-91), but postguideline CAP therapy in non–children's hospitals has not yet been evaluated."

Children's hospitals are far more likely to prescribe in accordance with national guidelines.

DR. TRIBBLE

For the current study, Dr. Tribble and her associates set out to evaluate antibiotic prescribing patterns for pediatric CAP in non–children's hospitals and to compare prescribing patterns between children's and non–children's hospitals. They conducted a retrospective cross-sectional study of children aged 1-17 years admitted for CAP in 2013 to 323 hospitals, captured via the Pediatric Health Information System (PHIS) and Premier Perspective databases. PHIS is an administrative database that includes billing data, diagnosis codes, and procedure codes for about 44 freestanding children's hospitals nationwide, while Premier Perspective encompasses data from 522 hospitals nationwide. The researchers used a validated ICD-9 code-based algorithm to identify patients with CAP and excluded those with complicated pneumonia or complex chronic conditions, those who received intensive care, and those with methicillin-resistant *Staphylococcus aureus* infection or colonization.

Children's hospitals were defined as those with pediatric admissions accounting for more than 75% of all admissions. "This was after excluding newborns and admission for childbirth, because many community hospitals will have a birthing center or a NICU, but otherwise would not be considered a children's hospital," Dr. Tribble explained. Any other hospital was considered a non–children's hospital.

Three different outcomes for antibiotic use were examined: those who ever received penicillin, amoxicillin, or ampicillin (guideline therapy); those who ever received a macrolide, fluoroquinolone, or tetracycline (atypical therapy); and those who received anything other than penicillin, amoxicillin, or ampicillin (nonguideline therapy). The standardized probability of exposure to select antibiotics was compared between children's and non–children's hospitals, adjusted for age, sex, and insurance provider.

In all, 323 hospitals contributed 15,495 CAP cases. Of the 323 hospitals, 49 were identified as children's hospitals (44 from the PHIS database and 5 from the Premier database). Dr. Tribble reported results from 9,224 subjects admitted to children's hospitals and 6,271 subjects admitted to non–children's hospitals. The demographics between the two groups were similar: The patients' mean age was 3 years, and 66% were younger than age 5 years.

After adjustment of data, patients admitted to children's hospitals were found to be more likely to receive guideline therapy, compared with those admitted to non–children's hospitals (46% vs. 15%, respectively), were less likely to received atypical therapy (36% vs. 51%), and were less likely to receive nonguideline therapy (78% vs. 94%; *P* less than .001 for all comparisons).

Dr. Tribble acknowledged certain limitations of the study, including the potential for misclassification of children's hospitals in the Premier database. Another limitation is that the study design did not account for the potential of combination therapy, "and you can't account for change in therapy during hospitalization. Lastly, we compared data across different databases and across different hospital types."

IDWeek marks the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society. The study was supported by a training grant from the National Institute of Child Health and Human Development. The researchers reported having no relevant financial disclosures.

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Carbapenem resistance on the rise in children

BY BIANCA NOGRADY
Frontline Medical News

The prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) in children is low but has increased significantly since 1999, particularly among isolates from intensive care units and from blood and lower respiratory tract cultures, new data suggest.

Analysis of 316,253 *Enterobacteriaceae* isolates reported to 300 U.S. laboratories participating in the Surveillance Network-USA database between 1999 and 2012 showed 0.08% of isolates were carbapenem resistant, with the most common resistant isolates being *Enterobacter* species isolated from urinary sources and from the inpatient non-ICU setting.

"Unlike for adults, where increases were greater than for children, we did not find that the increase in CRE in children appeared to be related to residence in long-term care facilities, because only 0.1% of CRE isolates came from this setting," wrote Dr. Latania K. Logan, director of pediatric infectious diseases at Rush University Medical Center, Chicago, and her coauthors.

The study, published Oct. 14 in Emerging Infectious Diseases, showed a significant overall increase from 0% to 0.47% in carbapenem-resistant *Enterobacteriaceae* over the 12-year study period; among ICU isolates, the prevalence increased from 0% to 4.5% over the same period.

©CDC/James Archer

Many of the carbapenem-resistant isolates also were resistant to other antimicrobial drugs, such as trimethoprim/sulfamethoxazole and ciprofloxacin, and nearly half (48.3%) were resistant to more than three antimicrobial drug classes (Emerg Infect Dis. 2015 Oct 14. doi: 10.3201/eid2111.150548).

The study was supported by the National Institutes of Health, the Children's Foundation, the Global Antibiotic Resistance Partnership, the Bill and Melinda Gates Foundation, and the Health Grand Challenges Program at Princeton University. No conflicts of interest were declared.

For the long-term, once-daily, maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)

Prescribe INCRUSE ELLIPTA one inhalation, once daily

& help patients add more breath to their day

Indication

- INCRUSE ELLIPTA is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Safety Information for INCRUSE ELLIPTA

CONTRAINDICATIONS

- The use of INCRUSE ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have hypersensitivity to umeclidinium or any of the excipients.

WARNINGS AND PRECAUTIONS

- INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- INCRUSE ELLIPTA 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.
- If paradoxical bronchospasm occurs, discontinue INCRUSE ELLIPTA and institute alternative therapy.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.

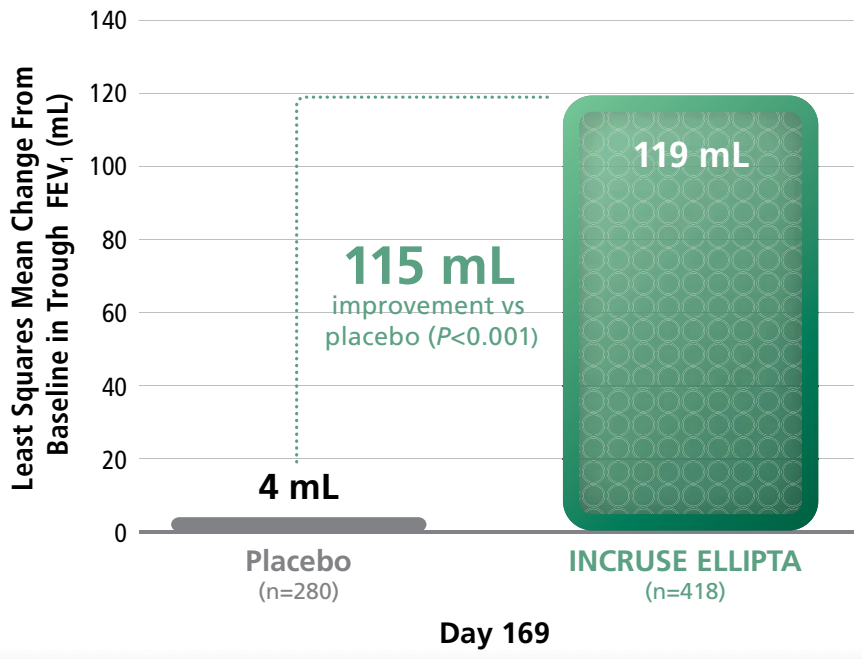
ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in one 12-week and one 24-week clinical trial with INCRUSE ELLIPTA (and placebo) were: nasopharyngitis, 8% (7%); upper respiratory tract infection, 5% (4%); pharyngitis, 1% (<1%); viral upper respiratory tract infection, 1% (<1%); cough, 3% (2%); arthralgia, 2% (1%); myalgia, 1% (<1%); upper abdominal pain, 1% (<1%); toothache, 1% (<1%); contusion, 1% (<1%); tachycardia, 1% (<1%). Other adverse reactions with INCRUSE ELLIPTA observed with an incidence <1% but more common than placebo included atrial fibrillation.

Once-daily INCRUSE ELLIPTA

Helps Improve Breathing in Patients With COPD

Primary Endpoint: Trough (Predose) FEV_1 at Day 169[1,2]



- Results from a 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that compared the efficacy and safety of INCRUSE ELLIPTA and placebo, each administered once daily by the ELLIPTA Inhaler. The primary endpoint was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168[1]

Provided improvement in health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ)

- In the same 6-month study, INCRUSE ELLIPTA demonstrated an improvement in health-related quality of life, as measured by a decrease in mean SGRQ total score of 4.69 units, compared with placebo at Day 168
- The proportion of patients with a clinically meaningful decrease (defined as a decrease of at least 4 units from baseline) at Week 24 was greater for INCRUSE ELLIPTA (42%; 172/410) compared with placebo (31%; 86/274)
- These endpoints were not adjusted for multiple comparisons
- The SGRQ is a respiratory disease-specific, patient-reported instrument that measures symptoms, activities, and impact on daily life[3]

Important Safety Information for INCRUSE ELLIPTA (cont'd)

ADVERSE REACTIONS (cont'd)

- In addition to the two placebo-controlled clinical trials with INCRUSE ELLIPTA, a 12-month trial evaluated the safety of umeclidinium 125 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and exceeded that in placebo) in subjects receiving umeclidinium 125 mcg were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

DRUG INTERACTIONS

- Avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

References: 1. Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546. **2.** Data on file, GSK. **3.** Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med.* 1991;85 (suppl B):25-31.

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

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INCRUSE® ELLIPTA®
(umeclidinium 62.5 mcg inhalation powder)

BRIEF SUMMARY

INCRUSE® ELLIPTA®
(umeclidinium inhalation powder)
FOR ORAL INHALATION USE
The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE
INCRUSE ELLIPTA is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

4 CONTRAINDICATIONS
The use of INCRUSE ELLIPTA is contraindicated in the following conditions: severe hypersensitivity to milk proteins or hypersensitivity to umeclidinium or any of the excipients *[see Warnings and Precautions (5.3), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Deterioration of Disease and Acute Episodes
INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. INCRUSE ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of INCRUSE ELLIPTA in this setting is not appropriate.
INCRUSE ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. INCRUSE ELLIPTA 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.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If INCRUSE ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of INCRUSE ELLIPTA beyond the recommended dose is not appropriate in this situation.

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

5.3 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of INCRUSE ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use INCRUSE ELLIPTA *[see Contraindications (4)]*.

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

5.5 Worsening of Urinary Retention
INCRUSE ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.2)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.4)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 1,663 subjects with COPD across 8 clinical trials (mean age: 62.7 years; 89% white; 65% male across all treatments, including placebo) received at least 1 inhalation dose of umeclidinium at doses of 62.5 or 125 mcg. In the 4 randomized, double-blind, placebo- or active-controlled, efficacy clinical trials, 1,185 subjects received umeclidinium for up to 24 weeks, of which 487 subjects received the recommended dose of umeclidinium 62.5 mcg. In a 12-month, randomized, double-blind, placebo-controlled, long-term safety trial, 227 subjects received umeclidinium 125 mcg for up to 52 weeks *[see Clinical Studies (14) of full prescribing information]*.
The incidence of adverse reactions associated with INCRUSE ELLIPTA in Table 1 is based upon 2 placebo-controlled efficacy trials: one 12-week trial and one 24-week trial.

Table 1. Adverse Reactions With INCRUSE ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Reaction	INCRUSE ELLIPTA (n = 487) %	Placebo (n = 348) %
Infections and infestations		
Nasopharyngitis	8%	7%
Upper respiratory tract infection	5%	4%
Pharyngitis	1%	<1%
Viral upper respiratory tract infection	1%	<1%
Respiratory, thoracic, and mediastinal disorders		
Cough	3%	2%
Musculoskeletal and connective tissue disorders		
Arthralgia	2%	1%
Myalgia	1%	<1%
Gastrointestinal disorders		
Abdominal pain upper	1%	<1%
Toothache	1%	<1%
Injury, poisoning, and procedural complications		
Contusion	1%	<1%
Cardiac disorders		
Tachycardia	1%	<1%

Other adverse reactions with INCRUSE ELLIPTA observed with an incidence less than 1% but more common than placebo included atrial fibrillation.
In a long-term safety trial, 336 subjects (n = 227 umeclidinium 125 mcg, n = 109 placebo) were treated for up to 52 weeks with umeclidinium 125 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the efficacy trials described above. Adverse reactions that occurred with a frequency greater than or equal to 1% in subjects

receiving umeclidinium 125 mcg that exceeded that in placebo in this trial were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

7 DRUG INTERACTIONS

7.1 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.4, 5.5), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with INCRUSE ELLIPTA in pregnant women. Because animal reproduction studies are not always predictive of human response, INCRUSE ELLIPTA 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 INCRUSE ELLIPTA.

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of INCRUSE ELLIPTA during labor and delivery. INCRUSE ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

It is not known whether INCRUSE ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when INCRUSE ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of INCRUSE ELLIPTA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue INCRUSE ELLIPTA, taking into account the importance of INCRUSE ELLIPTA to the mother.
Subcutaneous administration of umeclidinium to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

8.4 Pediatric Use

INCRUSE ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of INCRUSE ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.
Clinical trials of INCRUSE ELLIPTA included 810 subjects aged 65 years and older, and, of those, 183 subjects were aged 75 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

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment

Patients with severe renal impairment (creatinine clearance less than 30 mL/min) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with severe renal impairment and their healthy controls. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No case of overdose has been reported with INCRUSE ELLIPTA.
High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.
Treatment of overdosage consists of discontinuation of INCRUSE ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).
Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.
No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
Not for Acute Symptoms: Inform patients that INCRUSE ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.
Instruct patients to seek medical attention immediately if they experience any of the following:
- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with INCRUSE ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.
Paradoxical Bronchospasm: As with other inhaled medicines, INCRUSE ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue INCRUSE ELLIPTA.
Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

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Revised: 6/2014 INC:3BRS

Experts debate 'bare beneath the elbows'

BY AMY KARON
Frontline Medical News

SAN DIEGO – Going tieless and "bare beneath the elbows" has been touted for infection control. But while some clinicians endorse the practice, others call it inconvenient, unprofessional, and distracting. At an annual conference on infectious diseases, two specialists in the field debated going "BBE" and its evidence base.

Widespread practice of BBE dates to at least 2008, when the National Health Service in the United Kingdom mandated it as part of a set of measures to decrease nosocomial transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*. Clinicians at NHS were directed to leave jewelry, neckties, and wrist watches at

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home, hang up their lab coats, and wear short sleeves. The policy aims not only to reduce points of physical contact between providers and patients, but also to improve hand and wrist washing, said Dr. Michael Edmond, who is at the University of Iowa Hospitals and Clinics in Iowa City.

Some evidence supports going BBE, said Dr. Edmond. Pathogenic gram-negative rods have been cultured from neckties, scrubs, uniforms, and white coats in multiple studies, he added. Inadequate laundering is part of the problem – clinical faculty in one study reported washing their coats about once every 2 weeks, even less often than medical students did.

"So when is biological plausibility enough to support a change in practice?" Dr. Edmond asked. "There is a potential for benefit in going BBE. There is no risk for harm. And there is minimal cost. On the basis of the same evidence and assumptions, we are willing to wrap ourselves in plastic and confine patients to their hospital rooms – that is, to use contact precautions. And yet, we are not willing to eliminate white coats and ties."

Patient perception is not at issue, Dr. Edmond argued. Only about half of patients at one British hospital said they wanted physicians to wear traditional white coats, and that proportion dropped to 22% after patients received educational materials on clothing contamination, he noted. In another study, patients ranked their physician's appearance behind knowledge, compassion, and politeness when asked which characteristics they valued most.

"Without strong evidence for benefit, we should recommend – not mandate – this new practice," Dr. Edmond concluded.

But Dr. Neil O. Fishman disagreed, calling BBE "an evidence-free zone." Dr. Fishman, who is at the University of Pennsylvania in Philadelphia, noted a total lack of randomized, controlled trials or well-performed observational studies supporting BBE. "No clinical studies have demonstrated cross-transmission of health care–associated pathogens from a health care provider to a patient," he said.

Moreover, BBE does not prevent contamination, Dr. Fishman said. Bacterial cultures of the hands of BBE clinicians and controls revealed no differences in total bacteria counts or numbers of clinically significant pathogens, he said. Cultures of white coats and the undersides of wrists also were similar in terms of total bacteria and MRSA counts, he added.

Despite the lack of evidence, BBE has been implemented at NHS "mainly as a political gesture and has had unintended consequences," Dr. Fishman said. Informal attire has promoted a less-robust view of infection control, junior doctors have adopted scruffy attire and "slovenly" personal hygiene, and all the focus on clothing has distracted from hand washing, he added.

Furthermore, less than 12% of clinicians have complied with BBE, according to Dr. Fishman. Abstainers report feeling cold and not knowing what time it is. Women, in particular, say they have no pockets to carry work essentials. Dr. Edmond and Dr. Fishman reported no disclosures.

Malpractice premiums flat in 2015, but that could change

BY ALICIA GALLEGOS
Frontline Medical News

Physicians paid about the same in liability insurance premiums in 2015 as in 2014, and analysts don't see costs changing anytime soon. A nationwide survey of insurers by the Medical Liability Monitor shows that 71% of insurance premiums did not change this year, while 17% of rates rose and 12% fell.

'The claims counts are just not rising. Its great for the industry, it's great for physicians, but it is puzzling.'

MR. GREVE

Internists experienced an average premium increase of 0.6% in 2015, while general surgeons saw a 0.2% average rate decrease, and ob.gyns experienced an average 0.5% rate increase.

The static premium market is being largely driven by the low number of lawsuits filed by patients and family members in recent years, said survey coauthor Paul Greve Jr., executive vice president/senior consultant for the Willis Health Care Practice, a global risk management consultant firm.

"It's amazing to see the continuing stability in claim frequency," Mr. Greve said in an interview. "The claims counts are just not rising. Its great for the industry, and it's great for physicians, but it is puzzling because you wonder what has caused what amounts to a sea change in the attitudes of the general public toward malpractice litigation such that the claim counts were drop off."

Premiums continue to vary geographically. Southern Florida internists for example, will pay $47,707 for malpractice insurance this year, while their counterparts in Minnesota will pay $3,375. For ob.gyns., premiums range from $214,999 in southern New York to $16,240 in central California. General surgeons in Southern Florida will pay $190,829 this year, while Wisconsin surgeons will pay $10,868.

Various factors influence premium amounts, including the overall legal climate and the rate of insurer competition in each state, said Susan J. Forray, principal and consulting actuary with the Milwaukee office of Milliman, a global provider of actuarial services.

"The dollar amounts themselves are a function of the litigation environment and the cost of medicine or living within the state," Ms. Forray said in an interview. "In terms of rate changes, we are seeing certain environments where there is more competition."

On a regional basis, Southern physicians experienced the largest rate increases, while doctors in the Northeast, West, and Midwest continued to see decreases. The Midwest's 0.8% rate decrease was the largest decline, while Western states experienced a 0.2% average rate decrease. On average, the South showed a rate increase of 0.9% and the Northeast experienced a 0.1% average decrease. Doctors in Georgia, North Carolina, and Texas saw rate increases in excess of 5%, while Iowa physicians experienced an 11% rate decrease. Only three western states experienced rate increases: New Mexico at 2.5%, Oregon at 2%, and Idaho at 1%. Premium changes for Northeastern doctors fluctuated from Rhode Island's 7% increase to Pennsylvania's 8% decrease. Additionally, for the first time in 8 years, the premium market experienced an average overall increase of 0.3% in 2015, compared with an average overall decrease of 1.5% last year.

The jury is still out on how the Affordable Care Act and other health reforms will impact the malpractice premium market, Mr. Greve said. He said that he believes the majority of upcoming health reforms will improve patient safety, thus reducing liability for doctors. However, as more physicians become part of larger networks to deliver new models of care, their contractual liability spreads, he said.

"We're just beginning to see the tip of the iceberg here," Mr. Greve said. "In the past, it was overutilization, [the claim] that you did something in order to put money in your pocket. With putting providers at financial risk with capitated or bundled payments or global payments, then the argument is going to be, 'You didn't deliver enough care,' or 'You [used that device] because it was less expensive.' "

The MLM survey, published yearly in October, gathered July 1 premium data from the major malpractice insurers and examines rates for mature, claims-made policies with $1 million/$3 million limits for internists, general surgeons, and ob.gyns.

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Memorial Sloan Kettering Cancer Center

Chief, Pulmonary Service

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center (MSK) is seeking a Chief for the Pulmonary Service in the Division of General Medicine of the Department of Medicine. The Pulmonary Service at MSK consults on and manages all clinical problems within the full spectrum of benign and malignant pulmonary diseases. The Pulmonary Service encompasses the Interventional Pulmonology Program, inpatient consultative services, a busy outpatient program and Pulmonary Function Laboratories.

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Applicants must be ABIM-Certified in Pulmonary Medicine and preferably in Critical Care Medicine. This leader will be responsible for all aspects of the Pulmonary Service, including clinical programs, education, research (clinical, translational and basic) and strategic development. A record of productivity in research and educational activities is essential. Academic appointment at MSK will be at the rank of Associate Member or Member, commensurate with experience, training, and achievements. A parallel appointment as Associate Professor or Professor of Medicine at the Weill Cornell Medical College will be available.

Interested individuals should submit a **curriculum vitae *and* a cover letter outlining relevant prior experience and interests to**:

Hans Gerdes, MD, Chair, Pulmonary Service Search Committee, Division of General Medicine, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; email: **gerdesh@mskcc.org**

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About Memorial Healthcare System

Memorial Healthcare System is the third-largest public healthcare system in the United States. A national leader in quality care and patient satisfaction, Memorial has ranked 11 times since 2008 on nationally recognized lists of great places to work – including Modern Healthcare magazine, Florida Trend magazine and Becker's Hospital Review, to name just a few.

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Interested applicants may submit CV to Julia Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauver@cmhc.org . Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

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COMMENT: Responding to online physician review sites

BY JEFFREY BENABIO, M.D.
Frontline Medical News

Recently, Niam Yaraghi of the Brookings Institution caused quite a kerfuffle regarding the validity of online doctor reviews in a U.S. News and World Report op-ed piece titled, "Don't Yelp Your Doctor."

In it, he argues that customers are "generally qualified and capable" of reviewing a restaurant – anyone can tell if a steak is chewy or a server is rude, he says. (Of course, chefs may disagree.) Yet, when it comes to online physician reviews, Mr. Yaraghi argues that "patients are neither qualified nor capable of evaluating the quality of the medical services that they receive." I can see many of you nodding in vigorous agreement with that last sentence.


DR. BENABIO

Who among us hasn't felt indignant after reading a negative online review? Particularly one that criticizes our office decor or billing, yet makes no mention of our expert clinical abilities? But here's my advice. Have your moment of indignation, then start working on improving your online reputation, which may improve your actual practice as well.

Here are a few tips for optimizing online physician review sites:

- Google yourself and your practice to see which sites your patients are commonly using.
- Set up a Google Alert at https://www.google.com/alerts. Google Alerts are email updates that you receive based on your queries. Include your name and the name of your practice. This way, you'll receive notice when you're mentioned online.
- According to SoftwareAdvice.com, the most trusted review sites in descending order are: Yelp and Healthgrades (tied), RateMDs, Vitals, ZocDoc, and others. So familiarize yourself with these sites.
- Claim your page on review sites. Be sure all of the information listed is updated and correct.
- Upload a professional photo of yourself. It's much more effective to see a picture of you than an empty avatar.
- Be sure someone in your office is responsible for responding to comments online, particularly negative ones. It's best to respond promptly rather than have it linger without a response for weeks. If you don't write it, then at least approve it before it is posted.
- Respond to both positive and negative comments. Yelp, for instance, rewards business owners who maintain their site and actively respond to comments.
- For specific tips on how to respond to negative online reviews, see my column from July 2013 titled "How to handle negative reviews."

When it comes to online physician reviews, I want you to remember a few things:

- Physician reviews are usually favorable.
- Negative reviews are sometimes opportunities to improve your service.
- In the long run, we should want more, not fewer, reviews. Which would you rather have, two negative reviews, or two negative reviews and eight positive ones?
- The more reviews you have, the more credible you appear to prospective patients. This is particularly true for cosmetic practices.
- Patients are more likely to leave a positive review when they see other positive reviews posted about you.

Let's delve more deeply into the second point, "Negative reviews are opportunities for you and your staff to improve your service."

According to the 2014 "IndustryView report" from Software Advice, when it came to administrative issues such as wait times, billing, and staff friendliness, 25% of respondents cited wait times as the most important factor in their experience. Moreover, their 2013 report found that 41% of patients said they would consider switching doctors if it reduced their wait times!

We live in a consumer-centric society and service matters. For most patients, service equals quality. If you've got multiple negative reviews regarding your front desk staff, for instance, then address it directly with them. If you've got complaints about long wait times, then consider ways to improve it or improve the patient's experience of waiting. You might hire a consultant to help with reducing wait times or you might provide Wi-Fi or light refreshments in your waiting room to make the wait more pleasant.

Let's return to Mr. Yaraghi's contention that patients are unqualified to accurately assess our abilities. It is a moot discussion. Patients have, and will continue, evaluating us regardless of how qualified they are to do so. A restaurant patron may not be an expert of sous-vide cooking but can judge his or her experience of the meal and restaurant staff. Similarly, a patient may not be an expert in psoriasis, but he or she can accurately assess an experience in our office and with our staff.

The good news is that there are sites that are trying to incorporate more objective data in the reviews. For instance, Healthgrades lists doctors' board certifications, hospital affiliations, conditions treated, and procedures performed. The hope is that more objective criteria will improve the quality of the reviews and make the occasional angry and unwarranted rant less important.

One thing is for sure, there is much more discussion to come.

Dr. Benabio is a partner physician in the department of dermatology of the Southern California Permanente Group in San Diego, and a volunteer clinical assistant professor at the University of California, San Diego. Dr. Benabio is @dermdoc on Twitter.

Physician survey: 45% order tests to avoid lawsuits

BY RICHARD FRANKI
Frontline Medical News

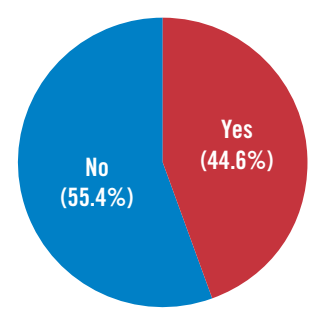
Almost 45% of physicians say that they have practiced defensive medicine, according to a survey of 1,001 physicians conducted by Physicians Practice, a practice management newspaper and website.

In addition, almost 44% of the physician respondents said that they had been threatened with a malpractice lawsuit, and nearly 32% reported that they had been the defendant in such a lawsuit Physicians Practice reported in its 2015 Great American Physician Survey.

rfranki@frontlinemedcom.com

Defensive medicine

Have you ordered procedures or tests that you "thought were probably not medically necessary just to avoid a potential lawsuit"?



FRONTLINE MEDICAL NEWS

Note: Based on a 2015 survey involving 1,001 physician respondents.

Source: Physicians Practice

California to allow physician-assisted suicide

BY ALICIA GALLEGOS
Frontline Medical News

California Gov. Jerry Brown (D) has signed into law a controversial measure that allows physicians to help terminally ill patients legally end their lives, making California the fourth state to permit doctor-assisted suicide through its legislature.

Gov. Brown, a former seminary student, approved the End of Life Option Act Oct. 5, after state lawmakers passed the bill Sept. 11.

In a signing message, Gov. Brown said that he had considered all sides of the issue and carefully weighed religious and theological perspectives that shortening a patient's life is sinful.

"In the end, I was left to reflect on what I would want in the face of my own death," Gov. Brown said in the message. "I do not know what I would do if I were dying in prolonged and excruciating pain. I am certain, however, that it would be a comfort to be able to consider the options afforded by this bill. And I wouldn't deny that right to others."

Modeled after Oregon's statute, California's law requires two doctors to determine that a patient has 6 months or less to live before doctors could prescribe life-ending medication. Patients must have the mental capacity to make medical decisions and would physically have to be able to swallow the drugs.

In addition, patients seeking physician aid in dying must submit two oral requests, a minimum of 15 days apart, and a written request to their physician. The attending physician must receive all three requests directly from the patient and not through a designee. Before prescribing end-of-life drugs, the attending physician must refer the patient to a consulting physician for confirmation of the diagnosis and prognosis and of the patient's capacity to make the decision.

Oregon, Vermont, and Washington each have laws permitting physician-assisted death. Court rulings in New Mexico and Montana have allowed for the practice, but litigation in those states is ongoing and the decisions have yet to be enforced.

'I am certain ... that it would be a comfort to be able to consider the options afforded by this bill.'

GOV. BROWN

The signing ends nearly a year of passionate debate in California that divided physicians, religious groups, lawmakers, and community members. In May, the California Medical Association (CMA) became the first state medical society to change its stance against physician-assisted suicide to that of being neutral.

"The decision to participate in the End of Life Option Act is a very personal one between a doctor and their patient, which is why CMA has removed policy that outright objects to physicians aiding terminally ill patients in end of life options," Dr. Luther F. Cobb, CMA president, said in a statement. "We believe it is up to the individual physician and their patient to decide voluntarily whether the End of Life Option Act is something in which they want to engage. Protecting that physician-patient relationship is essential."

The California law will take effect 90 days after the state legislature adjourns its special session on health care. The earliest likely enactment would be spring 2016.

agallegos@frontlinemedcom.com
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80% support Medicare coverage of end-of-life talks

BY JORDAN RAU, KAISER HEALTH NEWS

The public overwhelmingly supports Medicare's plan to pay for end-of-life discussions between doctors and patients, despite GOP objections that such chats would lead to rationed care for the elderly and ill, a poll finds.

About 8 of every 10 people surveyed by the Kaiser Family Foundation – in a nationally representative sample of 1,202 adults – supported coverage by the government or insurers for planning discussions about the type of care patients preferred in the waning days or weeks of their lives. (KHN is an editorially independent program of the foundation.) These discussions can include whether people would want to be kept alive by artificial means even if they had no chance of regaining consciousness or autonomy and whether they would want their organs to be donated. These preferences can be incorporated into advance directives, or living wills, which are used if someone can no longer communicate.

The Centers for Medicare & Medicaid Services earlier this year proposed paying doctors to have these talks with patients. A final decision is due out soon. The idea had been included in early drafts of the 2010 federal health care law, but former Alaska Gov. Sarah Palin and other opponents of the law labeled the counseling sessions and other provisions "death panels" motivated by desires to save money, and the provision was deleted from the bill.

The notion of helping patients prepare for death has support among many doctors, who sometimes see terminal patients suffer from futile efforts to keep them alive. Last year, the Institute of Medicine issued a report that encouraged end-of-life discussions beginning as early as age 16.

The Kaiser poll found that these talks remain infrequent. Overall, only 17% of those surveyed said they had had such discussions with their doctors or other health care professionals, even though 89% believe doctors should engage in such counseling. A third of respondents said they had talked to doctors about another family member's wishes for how they would want to be cared for at the end of life.

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While none of these proposals calls for the cost of care to weigh on these discussions, the final years of life are indeed expensive for America's health care system. The Dartmouth Atlas of Health Care has calculated that a third of Medicare spending goes to the care of people with chronic illnesses in their last 2 years of life. That is likely to increase as the population of those older than 65 increases. An analysis by the Kaiser foundation found that Medicare spending per person more than doubled from age 70 to 96, where it peaked at $16,145 per beneficiary in 2011.

The Kaiser poll found less public support for a cost-containment provision that did make it into the health law. The "Cadillac tax" begins in 2018 and will impose a tax on expensive insurance that employers provide to their workers. Sixty percent oppose the plan, which economists have long favored as a way to discourage lavish coverage and make people aware that extensive use of Medicare services is linked to premiums.

The poll also found that 57% of people favor repealing the medical device tax, another piece of the health law that Republicans in Congress are trying to repeal. The tax applies to artificial hips, pacemakers and other devices that doctors implant.

The poll was conducted from Sept. 17 through Sept. 23. The margin of error was +/– 3 percentage points.

Kaiser Health News is a nonprofit national health policy news service that is part of the nonpartisan Henry J. Kaiser Family Foundation.

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