VOL. 13 • NO. 2 • FEBRUARY 2018

CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Courtesy Dr. Peter Weina

Two trials involving ciprofloxacin had two "very different outcomes," noted Peter J. Weina, PhD, MD, at an FDA advisory committee meeting.

FDA panel does not back inhaled ciprofloxacin

BY IAN LACY
Frontline Medical News

HYATTSVILLE, MD. – A Food and Drug Administration advisory panel voted against recommending Linhaliq, ciprofloxacin dispersion for inhalation (cipro DI), to treat adult non–cystic fibrosis bronchiectasis (NCFBE) patients who have chronic lung infections with *Pseudomonas aeruginosa*.

At a meeting last month, the FDA's Antimicrobial Drugs Advisory Committee members voted 12-3 against recommending the drug, with 1 member abstaining. Data discrepancies between two phase 3 clinical trials, ORBIT-3 and ORBIT-4, were deciding factors for many of the members who voted against cipro DI.

"Two trials that have two very different outcomes – and no matter how we try and explain what the difference was, there was something really missing there," said advisory committee member Peter J. Weina, PhD, MD, chief of the department of research programs at Walter Reed National Military Medical Center, Bethesda, Md.

NCFBE is often treated with antibacterial drugs, which temporarily reduce inflammation and bacterial load. One of the most common

CIPROFLOXACIN WINS FEW VOTES // *continued on page 6*

LABA/ICS combos' boxed warning axed

BY KATIE WAGNER LENNON
Frontline Medical News

The Food and Drug Administration has eliminated the boxed warning for risk of asthma-related death from the labels of products containing both an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA), the agency announced.

In 2011, the FDA required companies manufacturing fixed-dose LABA-ICS combination products to conduct 26-week clinical safety trials to evaluate the risks of serious adverse asthma-related events in patients treated with these drugs. Specifically, the companies had to compare the risks of taking a LABA in combination with an ICS with the risks of taking an ICS alone.

The removal of the boxed warning follows the FDA's review of these trials, which found that treating asthma with LABAs in combination with ICS did not result in patients experiencing significantly more serious asthma-related side effects and asthma-related deaths, compared with those being treated with an ICS alone, according to the FDA announcement. "Results of subgroup analyses for gender, adolescents 12-18 years, and African Americans are consistent

CHANGES TO LABA/ICS LABELS // *continued on page 4*

INSIDE HIGHLIGHT

NEWS FROM CHEST

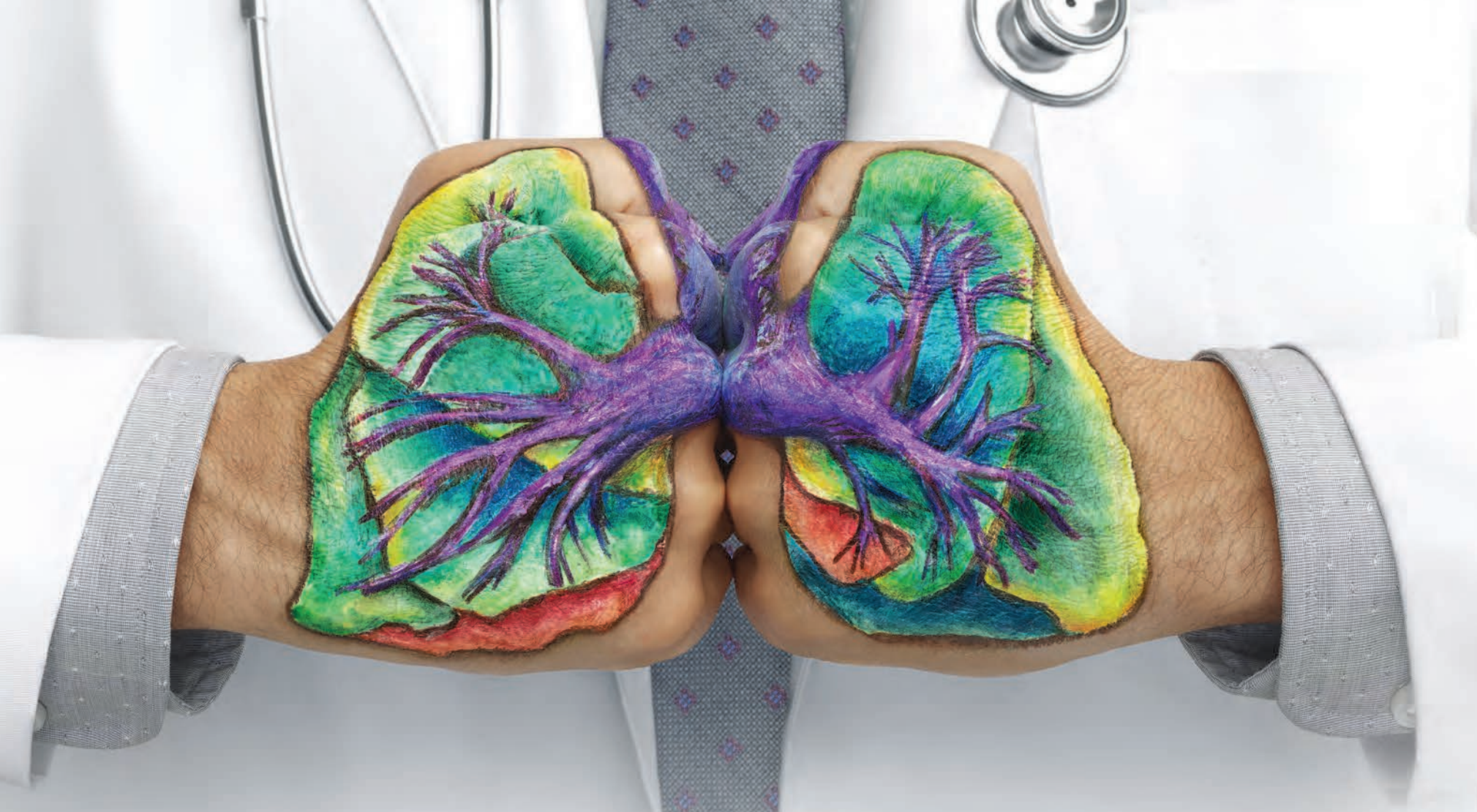
Critical Care Commentary

Page 49

CHEST Physician
151 Fairchild Ave.,
Suite 2,
Plainview, NY 11803-1709

CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY



Indication

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

Select Important Safety Information

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

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

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

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

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

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

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

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

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and

Genentech

A Member of the Roche Group

WE WON'T BACK DOWN FROM IPF

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

STUDIED IN A RANGE OF PATIENTS

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

DEMONSTRATED EFFICACY

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

ESTABLISHED SAFETY AND TOLERABILITY

The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[2†]

COMMITTED TO PATIENTS

Genentech offers a breadth of patient support and assistance services to help your patients with IPF[‡]

WORLDWIDE PATIENT EXPERIENCE

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

pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment.

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

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

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

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

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

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

IPF=idiopathic pulmonary fibrosis.

*The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).[2] In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide ($\%DL_{co}$) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[3] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[4] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[2,3] Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).[1,2,4] **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.[2,4]**

†In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[2]

‡Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[2]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

Changes to LABA/ICS labels // *continued from page 1*

with the primary endpoint results," the statement added.

"These trials showed that LABAs, when used with ICS, did not significantly increase the risk of asthma-related hospitalizations, the need to insert a breathing tube known as intubation, or asthma-related deaths, compared to ICS alone," the FDA said in the statement.

The trials also demonstrated that using the combination reduced asthma exacerbations, compared with using ICS alone, and that most of the exacerbations "were those that required at least 3 days of systemic corticosteroids" – information that is being added to the product labels, according to the FDA.

The products that will no longer carry this boxed warning in their labels include AstraZeneca's budesonide/formoterol fumarate dihydrate (Symbicort) and GlaxoSmithKline's fluticasone furoate/vilanterol (Breo Ellipta) and fluticasone propionate/salmeterol (Advair Diskus and Advair HFA).

The FDA also approved updates to the Warnings and Precautions section of labeling for the ICS/LABA class, which now includes a description of

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: Although these data have been available for some time, this action officially and definitely puts this issue to rest. This update by the FDA is unlikely to cause large changes in clinical practice since LABA/ICS combinations have been thought safe for some time but will serve to reassure the occasional patient who previously was reticent to use these medications after reading the package insert.

the four trials. Information on the efficacy of the drugs, found in the trials, has been added to the Clinical Studies section of the labels as well.

In a related safety announcement, the FDA stated the following: "Using LABAs alone to treat asthma without an ICS to treat lung inflammation is associated with an increased risk of asthma-related death. Therefore, the Boxed Warning stating this will remain in the labels of all single-ingredient LABA medicines, which are approved to treat asthma, chronic obstructive pulmonary disease (COPD), and wheezing caused by exercise. The labels of medicines that contain both an ICS and LABA also retain a Warning and Precaution related to the increased risk of asthma-related death when LABAs are used without an ICS to treat asthma."

klennon@frontlinemedcom.com

FDA approves starting dose of roflumilast

BY KATIE WAGNER LENNON
Frontline Medical News

The Food and Drug Administration has approved the use of a 250-mcg dose of roflumilast for patients with chronic obstructive pulmonary disease (COPD) for 4 weeks, followed by the use of 500-mcg therapeutic doses, according to a statement from the drug's marketer, AstraZeneca.

The larger doses of roflumilast (Daliresp) are currently indicated for reducing the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations, according to the statement. The selective phosphodiesterase-4 inhibitor, roflumilast, was approved for this use in 500-mcg doses in 2011. The new smaller doses of the drug are being offered to help reduce the rate of treatment discontinuation with use of the higher therapeutic dosing. The 250-mcg doses of roflumilast are not to be used as treatment for COPD.

The FDA confirmed its approval for the use of 250-mcg doses of roflumilast as described by the drug's marketer, in Section 2 of the FDA prescribing label.

The approval of use of the 250-mcg doses was based on data from the OPTIMIZE study, according to the statement.

In eight controlled clinical trials, the most common adverse effects were diarrhea, weight loss, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

klennon@frontlinemedcom.com

SOURCE: AstraZeneca press release, Jan 24, 2018.

Ciprofloxacin wins few votes // continued from page 1

colonizing bacteria in NCFBE infections is *P. aeruginosa,* which is often associated with increased risk of death and hospital admission.

Prior studies involving inhaled bacterial drugs such as gentamicin and colistin to treat NCFBE have yielded mixed results, and none has been approved for that indication by the FDA.

The FDA granted cipro DI orphan drug status in June 2011 and fast-track approval in August 2014. Cipro DI's developer, Aradigm, conducted two phase 3 clinical trials to support inhaled ciprofloxacin for the NCFBE indication.

"If I were to be a [statistically speaking] 'strict' person, I wouldn't be looking at the frequency of the [secondary] endpoints, because the primary [endpoint] failed," Dr. Tracy noted.

The two phase 3 clinical trials, ORBIT-3 and ORBIT-4, were nearly identical in design. Patients in both were randomized 2:1 to receive cipro DI or placebo once daily for six cycles of 56 days each.

The efficacy results of the ORBIT-3 and ORBIT-4 trials were mixed.

In ORBIT-3, there was very little difference between the treatment and placebo arms, with a median difference of 78 days for the primary endpoint of time to first pulmonary exacerbation (PE) (hazard ratio, 0.99; $P = .974$). ORBIT-3 also showed no difference between treatment and placebo in the frequency of PEs by week 48 of the study (incidence ratio, 0.852).

In contrast, a marginal treatment effect was observed in ORBIT-4, with a median time difference to first PE of 72 days between the placebo and treatment arms (HR, 0.71; $P = .032$). ORBIT-4 also demonstrated an ability to reduce the number of PEs (incidence ratio, 0.631) by approximately 36.9% by week 48.

Adverse events were the most common reason leading to patient discontinuation in both studies, accounting for 13.1% and 5.3% in the treatment arms of ORBIT-3 and ORBIT-4, respectively.

Despite some of the positive findings in ORBIT-4, FDA presenter LaRee Tracy, PhD, of the FDA's office of biostatistics voiced concerns about the trial data – specifically, the failure to reach the primary endpoint in ORBIT-3.

"If I were to be a [statistically speaking] 'strict' person, I wouldn't be looking at the frequency of the [secondary] endpoints, because the primary [endpoint] failed," Dr. Tracy noted. She also voiced concerns about a re-analysis Aradigm conducted after the trial data were unblinded, stating that the changes made to the original analysis plan "lend a lot of concerns for me."

Both ORBIT-3 and ORBIT-4 presented uncertainties related to the long-term use of cipro DI. The durability of efficacy and safety findings did not extend beyond a year, leaving some committee members wondering about the development of antibiotic resistance in cipro DI–treated patients. In addition, members were concerned that long-term use of cipro DI could limit the utility of systemic fluoroquinolones to treat severe bacterial and pneumonia infections in NCFBE patients.

The FDA usually follows the recommendations of its advisory panels, which are not binding.

ilacy@frontlinemedcom.com

VIEW ON THE NEWS

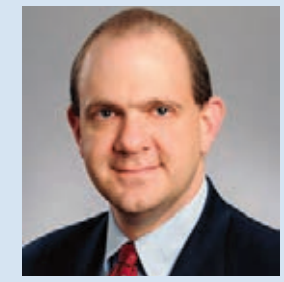
Daniel Ouellette, MD, FCCP, comments: My patients with bronchiectasis pose daily management problems. Symptoms of chronic cough with sputum production respond variably to inhaled bronchodilators. I reserve short-course oral antibiotics and glucocorticoids for exacerbations of disease, which seems to be effective. Some patients respond well to chest percussive and cough-assist devices. Select patients seem to respond well to chronic oral macrolides. Inhaled antibiotics intuitively appear attractive, and I have had patients with gram-negative colonization of the airways who I think respond to this treatment. However, I am forced to admit that good outcome data for these treatments are not available. Further research is needed.

NEWS FROM CHEST // 40

NETWORKS // 52

CHEST PHYSICIAN IS ONLINE

CHEST Physician is available at chestphysician.org.



David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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

E-mail: chestphysiciannews@chestnet.org

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for **CHEST PHYSICIAN** is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.

POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

EDITORIAL OFFICES 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

ADVERTISING OFFICES 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378

Scan this QR Code to visit chestnet.org/chestphysician

IN PATIENTS WITH ASTHMA

LOOK BEYOND EOSINOPHIL AND IgE LEVELS TO GET A CLEARER PICTURE OF TYPE 2 INFLAMMATION

Type 2 asthma encompasses a range of biomarkers and phenotypes driven by Type 2 inflammation.

Learn more at **UnderstandingType2Asthma.com**

SANOFI GENZYME

REGENERON

US-ILF-13910

Most influenza-related deaths occur after discharge

BY ELI ZIMMERMAN
Frontline Medical News

SAN DIEGO – More than half of hospitalized, influenza-related deaths occurred within 30 days of discharge, according to a study presented at an annual scientific meeting on infectious diseases.

As physicians and pharmaceutical companies attempt to measure the burden of seasonal influenza, discharged patients are currently not considered as much as they should be, according to investigators.

Among 968 deceased patients studied, 444 (46%) died in hospital, while 524 (54%) died within 30 days of discharge.

"Those who were admitted from the nursing home were almost exclusively discharged to either hospice care or back to a nursing home," Mr. McGowan said.

Investigators conducted a retrospective study of 15,562 patients hospitalized for influenza-related cases between 2014 and 2015, as recorded in Influenza-Associated Hospitalizations Surveillance (FluSurv-NET), a database of the Centers for Disease Control and Prevention.

The majority of the studied patients were women (55%) and the majority were white.

Those who died were more likely to have been admitted to the hospital immediately after influenza onset, with 26% of those who died after discharge and 22% of those who died in hospital having been admitted the same day. In contrast, 13% of those who lived past 30 days were admitted immediately after onset.

A total of 46% of those who died after hospitalization had a length of stay longer than 1 week, compared to 15% of those who lived.

Among patients who died after discharge, 356 (68%) died within 2 weeks of discharge, with the highest number of deaths occurring within the first few days, according to presenter Craig McGowan of the influenza division of the CDC.

Age also seemed to be a possible mortality predictor, according to Mr. McGowan and his fellow investigators. "Those who died were more likely to be elderly, and those who died after discharge were even more likely to be 85 [years or older] than those who died during their influenza-related hospitalizations," said Mr. McGowan, who added that patients aged 85 years and older made up more than half of those who died after discharge.

Patients who died in hospital were significantly more likely to have influenza listed as a cause of death. Overall, influenza-related and non–influenza-related respiratory issues were the two most common causes of death listed on death certificates of patients who died during hospitalization or within 14 days of discharge, while cardiovascular or other symptoms were listed for those who died between 15 and 30 days after discharge.

Admission and discharge locations among patients who did not die were almost 80% from a private residence to a private residence, while observations of those who died revealed a different pattern. "Those individuals who died after discharge were almost evenly split between admission from a nursing home or a private residence," Mr. McGowan said. "Those who were admitted from the nursing home were almost exclusively discharged to either hospice care or back to a nursing home."

Mr. McGowan noted rehospitalization to be a significant factor among those who died, with 34% of deaths occurring back in the hospital after initial discharge.

Influenza testing of studied patients was given at clinicians' discretion, which may make the sample not generalizable to the overall influenza population, and the investigators included only bivariate associations, which means there were likely confounding effects that could not be accounted for.

Mr. McGowan and his fellow investigators plan to expand their research by determining underlying causes of death in these patients, to create more accurate estimates of influenza-associated mortality.

Mr. McGowan reported no relevant financial disclosures.

ezimmerman@frontlinemedcom.com

SOURCE: McGowan C et al. ID Week 2017, Abstract 951.

Hyperbaric oxygen may cut CO deaths

BY ANDREW D. BOWSER
Frontline Medical News

FROM THE JOURNAL *CHEST*® ▪ In patients with carbon monoxide poisoning, hyperbaric oxygen therapy was associated with a lower rate of mortality, according to results of a recent retrospective study.

The mortality reduction was particularly evident among patients under 20 years of age and in patients with acute respiratory failure, authors of the study said in a report published in Chest (2017 Nov. doi: 10.1016/j.chest.2017.03.049).

"The results provide important references for decision making in the treatment of carbon monoxide poisoning," Chien-Cheng Huang, MD, department of emergency medicine, Chi-Mei Medical Center, Tainan, Taiwan, and colleagues wrote in their report.

While hyperbaric oxygen has been suggested for severe carbon monoxide poisoning, 100% normobaric oxygen is considered standard treatment, according to Dr. Huang and colleagues.

"There has been no consensus about whether hyperbaric oxygen therapy is better than 100% normobaric oxygen alone, or the number of sessions of hyperbaric oxygen therapy that are necessary regarding mortality and morbidity," they wrote.

In a Taiwanese nationwide poisoning database, Dr. Huang and colleagues identified 25,737 patients diagnosed with carbon monoxide poisoning between 1999 and 2012. Of those patients, 7,278 had hyperbaric oxygen therapy.

After researchers adjusted for variables including age, sex, and underlying comorbidities, the mortality rate was lower in patients who underwent hyperbaric oxygen therapy, compared with those who did not (adjusted hazard ratio, 0.74; 95% confidence interval, 0.67-0.81), data show.

The reduction in mortality was especially notable in patients younger than age 20 years (adjusted HR, 0.45; 95% CI, 0.26-0.80), according to the researchers.

A similarly greater magnitude of mortality benefit also was found for patients who had acute respiratory failure, "which supports acute respiratory failure being an indication for hyperbaric oxygen therapy," investigators wrote. "Further studies are warranted to clarify this issue."

The number of hyperbaric oxygen therapy sessions appeared to make a difference in mortality. Patients who received two or more sessions had a lower rate of mortality than did those who had only one session, according to the report.

Predictors of mortality, described in more detail in the published report, included older age, diabetes, alcoholism, and suicide attempts, among other factors.

"In addition to considering hyperbaric oxygen therapy for reducing mortality, control of other concomitant mortality predictors is necessary," the authors conclud-

Continued on following page

Inpatient antiviral treatment reduces ICU admissions among influenza patients

BY ELI ZIMMERMAN
Frontline Medical News

SAN DIEGO – Administering inpatient antiviral influenza treatment may reduce admissions to the ICU among adults hospitalized with flu, according to a study presented at ID Week 2017, an infectious diseases meeting.

While interventions did not directly affect flu-related deaths, lower ICU admission rates could reduce morbidity and ease the financial burden felt during influenza season.

Investigators retrospectively studied 4,679 influenza patients admitted to Canadian Immunization Research Network Serious Outcomes Surveillance (SOS) Network hospitals during 2011-2014. Of the 54% of patients given inpatient antiviral treatment, the risk of being admitted to the ICU was reduced by 90% (odds ratio, 0.10; 95% confidence interval, 0.08-0.13; *P* less than .001).

Antiviral treatment was not protective against death outcomes in patients with either influenza A or influenza B (odds ratio, 0.9; 95% confidence interval, 0.7-1.2; $P = .454$).

The median age of patients was 70 years, with a majority older than 75 years (41%); most presented with one or more comorbidities (89%) and had influenza A (72%).

Researchers found that, of the 4,679 patients studied, a total of 798 (16%) were admitted to the ICU, 511 (11%) required mechanical ventilation, and the average length of hospital stay was 11 days.

Of those, 444 (9%) died within 30 days of discharge.

Researchers also found that only 38% of those studied had received the current seasonal vaccine upon admittance. These numbers may be skewed from the general population, because unvaccinated patients are more likely to be hospitalized.

Along with the results of antivirals on hospitalized patients, researchers wanted to uncover how the effectiveness of inpatient vaccine administration would vary based on treatment timing, said presenter Zach Shaffelburg of the Canadian Center for Vaccinology, Dalhousie University, Halifax, N.S.

Even when administered 4.28 days after symptom onset, antiviral treatments in patients were associated with significant reductions in ICU admissions and the need for mechanical ventilation.

Even when administered 4.28 days after symptom onset, antiviral treatments in patients were associated with significant reductions in ICU admissions and the need for mechanical ventilation.

The investigators concluded that antivirals show a strong association with positive effects on serious, influenza-related outcomes in hospitalized patients and, while therapy remained effective with later treatment start, patients would benefit the most from initiation as soon as possible.

Currently, the U.S. Centers for Disease Control and Prevention and the Canadian Immunization Research Network (CIRN) have guidelines instructing best practice for inpatient antiviral treatment; however, the number of hospitalized patients given treatment has declined in Canada since 2009, according to Mr. Shaffelburg.

The reason more patients were not receiving inpatient antiviral treatment may be related to studies of different populations that failed to show significant impact, Mr. Shaffelburg suggested during a question and answer session following the presentation: "I think a lot of that comes from outpatient studies that involve patients who are younger and quite healthy [who received] antivirals, and it showed a very minimal impact," Mr. Shaffelburg said. "So a lot of people saw that study and thought, 'What's that point of giving it if it's not going to make an impact?' "

Mr. Shaffelburg and his colleagues are planning to continue their study of inpatient antiviral treatment, focusing more on the effectiveness of treatment in relation to time administered after onset.

Mr. Shaffelburg reported having no disclosures. The study was funded by the CIRN SOS network, Canadian Institutes for Health Research, and a partnership with GlaxoSmithKline Biologicals. Some of the investigators were GSK employees or received grant funding from the company.

ezimmerman@frontlinemedcom.com

SOURCE: Shaffelburg Z et al. IDWeek 2017, Abstract 890.

Continued from previous page

ed based on their results.

Accidental deaths from carbon monoxide poisoning also are a major issue in the United States, where each year, there are an estimated 1,000-2,000 cases, according to the authors. Additionally, accidental carbon monoxide poisoning has "increased greatly in the past 10 years," they said in the report.

Other studies have shown that, compared with normobaric oxygen, hyperbaric oxygen therapy did not reduce neurologic complications, the authors noted. Even so, that fact "does not suggest that hyperbaric oxygen therapy is not beneficial regarding mortality," they wrote. "In fact, it is possible that reducing mortality may increase morbidities such as neurologic sequelae."

Dr. Huang and coauthors reported no conflicts of interest related to the study, which was supported by Chi-Mei Medical Center in Taiwan.

VIEW ON THE NEWS

Data compelling, but "distant" from ideal

Use of hyperbaric oxygen therapy to treat carbon monoxide poisoning has been "controversial since its inception" since early promoters "tended to place hyperbaric treatment ahead of strong supporting data," wrote Clayton T. Cowl, MD, FCCP, in an editorial regarding the study by Dr. Huang and colleagues.

By contrast, the current study by Dr. Huang and colleagues includes data for more than 7,000 patients receiving hyperbaric oxygen therapy over a 13-year time span, compared with those who did not receive it. They found that mortality rates were significantly improved among patients who received hyperbaric oxygen therapy, "even after adjusting for multiple variables," Dr. Cowl remarked.

These data are compelling because they come from what is believed to be the first large-scale study that specifically examines mortality as an endpoint in an entire nation, as opposed to smaller cohorts in single centers or even multiple institutions, he said in his editorial.

"Have we reached the point of clearly establishing that delivery of pure oxygen in a high-pressure environment is more effective in treating patients who have carbon monoxide poisoning than is normobaric supplemental oxygen alone? Probably not," Dr. Cowl wrote.

"The retrospective database study by Huang et al, despite its large size and interesting findings, remains distant from the ideal of a large blinded multicenter randomized controlled trial using a standardized protocol to compare normobaric supplemental oxygenation with hyperbaric oxygen therapy delivery for this cohort," he explained. "However, its size, scale, and findings add credibility to the mounting data supporting HBOT [hyperbaric oxygen treatment] for this indication."

Dr. Cowl is with the division of preventive, occupational, and aerospace medicine and the division of pulmonary and critical care medicine, Mayo Clinic. His comments came from an editorial in the Journal Chest® (doi: 10.1016/j.chest.2017.07.022). He declared no financial or nonfinancial disclosures related to the editorial.

First month of LABA/LAMA ups cardiovascular risk

BY M. ALEXANDER OTTO
Frontline Medical News

New use of inhaled long-acting beta$_2$-agonists (LABAs) or long-acting antimuscarinic antagonists (LAMAs) was associated with a 1.5-fold increased cardiovascular risk within 30 days of initiation in patients with chronic obstructive pulmonary disease, irrespective of prior cardiovascular disease status and history of exacerbations, according to a review of more than 280,000 COPD patients in Taiwan.

The relationship between cardiovascular disease (CVD) and LABAs and LAMAs in chronic obstructive pulmonary disease has long been debated. The new study addressed some limitations of previous studies, which had found conflicting results ranging from no increased risk to up to a 4.5-fold increased risk of cardiovascular events when the medications were used for COPD.

Previous randomized trials haven't raised much concern, but they included prior users who may have developed tolerance to the heart effects and excluded patients with baseline CVD. "We caution physicians to closely monitor new users of LABAs or LAMAs for cardiovascular symptoms." Health care professionals should be vigilant for any cardiovascular symptoms during the first 30 days of inhalation therapy, said investigators led by Meng-Ting Wang, PhD, of the National Defense Medical Center, Taipei, Taiwan.

"We suspect that there may exist a subgroup of patients with COPD who are particularly at risk of CVD with initial exposure to LABAs or LAMAs. ... We suggest that the use of inhaled long-acting bronchodilators in COPD needs to be carefully assessed, and a thorough cardiovascular physical examination, especially heart rate measurement and electrocardiograms, needs to be performed" before prescribing LABAs and LAMAs, they wrote in JAMA Internal Medicine.

The team identified 284,220 COPD patients in the Taiwan National Health Insurance Research Database during 2007-2011 who were new to the medications. During a mean follow-up of 2 years, 37,719 developed severe CVD requiring hospitalization or emergency care.

The team compared their CVD subjects with controls who did not have a heart event and found that new LABA and LAMA use in COPD was associated with a 1.50-fold (95% confidence interval, 1.35-1.67; *P* less than .001) and a 1.52-fold (95% CI, 1.28-1.80; *P* less than .001) increased cardiovascular risk within 30 days of initiation, respectively.

The LABA- and LAMA-associated CVD risk remained significant, regardless of patients' CVD history and COPD exacerbations. Analyses of individual CVD outcomes revealed increased risks of coronary artery disease and heart failure with LABA and LAMA treatment and an increased risk for cardiac arrhythmias with LAMA therapy.

The cardiovascular risks peaked at around the 30th day of treatment, waned from 31 to 60 days of treatment, and fell below the baseline risk from 71 to 240 days.

"Given that CVD is highly prevalent among patients with COPD, clinicians should also pay attention to the management of CVD risk factors throughout the duration of LABA or LAMA therapy. ... If needed, a preventive therapy for CVD should be considered during the initial treatment of inhaled long-acting bronchodilators," the investigators said.

LABAs and LAMAs are believed to cause sympathetic overactivation by activating sympathetic beta$_2$ adrenergic receptors and suppressing parasympathetic muscarinic-3 receptors, which could contribute to the CVD risk. Also, LABA and LAMA use in COPD has been observed to increase inflammatory cytokine levels.

The subjects were 40 years or older; the mean age was 71.4 years and 68.9% of the participants were men.

The work was supported by Taiwan's Ministry of Science and Technology. The investigators had no disclosures.

Eli Zimmerman contributed to this report.

aotto@frontlinemedcom.com

SOURCE: Wang MT et al. JAMA Intern Med. 2018 Jan 2. doi: 10.1001/jamainternmed.2017.7720.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Long-acting beta-agonists (LABA) and long-acting muscarinic antagonists (LAMA) are agents commonly used to treat patients with chronic obstructive pulmonary disease (COPD). These inhaled medications have been generally considered to be safe and have a favorable side-effect profile. Although there have been some speculative data that suggest that these agents may be associated with increased cardiovascular risk, prospective, controlled studies have generally suggested that the cardiovascular risk is not increased with the use of these medicines.

A recent article in JAMA suggests that patients with COPD who have been initiated on LAMA and LABA agents may have an increased risk of cardiovascular events in the weeks following initiation. Using a large insurance database, investigators from Taiwan found that patients with new prescriptions for these drugs have increased cardiovascular events. These researchers further suggest that previous studies may have overlooked this phenomenon, as longitudinal studies would have studied cardiovascular risk among patients with established use patterns of LAMA and LABA agents, instead of just patients initiated upon therapy. They suggest that the longitudinal populations may therefore be censored and excluded patients who had effects shortly after commencing the medications.

One strength of this study is the size of the database, which is robust, and the novel treatment that this study uses to address the research question. Weaknesses include the study's necessarily retrospective design, and the fact that the population is from a single geographic area. Further research will be needed to understand whether or not the initiation of LABA and LAMA medications in COPD patients is associated with increased cardiovascular risk.

Influenza: All that and MI, too

BY RICHARD FRANKI
Frontline Medical News

Myocardial infarction admissions were six times more likely to occur in the week after a positive test for influenza than in the year before or the 51 weeks after the infection, according to analysis of a Canadian cohort that links laboratories with administrative databases.

The investigators used this cohort data to define definitions of "risk interval" – the first 7 days after flu detection – and a combined "control interval" – 52 weeks before the flu detection and 51 weeks after the end of the risk interval.

Among the total of 364 hospital admissions for MI in patients with confirmed influenza, 20 occurred during the defined 1-week risk interval (20 admissions/week) and 344 occurred during the control interval (3.3 admissions/week), giving an incidence ratio (IR) of 6.05, Jeffrey C. Kwong, MD, of the University of Toronto and his associates reported in the New England Journal of Medicine.

There was little difference between days 1 and 3 after flu confirmation (IR, 6.3) and days 4-7 (IR, 5.8), but risk dropped off quickly after that, with IRs of 0.6 at days 8-14 and 0.75 at days 15-28. Risk was increased for older adults, those with influenza B infection, and those who had their first MI, the investigators said.

MI incidence also was elevated after infection with noninfluenza respiratory viruses, although to a lesser extent than with influenza, which suggests that "influenza is illustrative of the role that acute respiratory infections have in precipitating acute myocardial infarction," Dr. Kwong and his associates wrote.

The study was supported by the Canadian Institutes of Health Research, by Public Health Ontario, and by the Institute for Clinical Evaluative Sciences. Dr. Kwong reported grants from Canadian Institutes of Health Research during the conduct of the study, as well as grants from Canadian Institutes of Health Research and University of Toronto.

rfranki@frontlinemedcom.com

SOURCE: Kwong JC et al. N Engl J Med. 2018. 378(4):345-53. doi: 10.1056/NEJMoa1702090.

Pay for performance not improving Medicare results

BY GREGORY TWACHTMAN
Frontline Medical News

Hospital pay-for-performance programs are not leading to significant improvements in clinical process scores or 30-day mortality rates for Medicare beneficiaries, according to an analysis of Medicare claims data.

"No evidence that hospitals [that were] operating under pay for performance programs for more than a decade had better process scores or lower mortality than other hospitals was found," Igna Bonfrer, PhD, of Erasmus University, Rotterdam, the Netherlands, and colleagues wrote in a study published Jan. 4, 2018, in BMJ.

"These findings suggest that, even among hospitals that volunteered to participate in pay for performance programs, having additional time is not likely to turn pay for performance programs into a success in the future," the investigators noted.

Researchers looked at Medicare claims data from nearly 1.4 million patients aged 65 years and older across 1,189 hospitals. That total included 214 hospitals that were early adopters of pay for performance programs, including the Hospital Quality Incentive Demonstration (HQID) and the current Hospital Value-Based Purchasing (HVBP) program, and 975 hospitals that adopted the programs at a later date. The study authors examined clinical process scores and 30-day mortality rates from 2003 to 2013.

Hospitals that were early adopters of a pay for performance program typically started from a higher baseline process measure score (91.5), compared with late adopters (89.9).

However, improvements among the early adopters "were smaller during the HQID period, although early adopters continued to perform at a slightly higher level than the late adopters during the pre-HVBP period," the researchers explained. "Over the HVBP period, early and late adopters no longer differed in their clinical process scores."

Indeed, a ceiling was ultimately reached, with early and late adopters approaching the same level (98.5 vs. 98.2).

For the 30-day mortality rates, both groups "started from a similar baseline (14.9% and 14.8% for the early and late adopters in the fourth quarter of 2003) and ended at the same rate of 9.9% for both groups in the fourth quarter of 2013," Dr. Bonfrer and colleagues wrote.

The researchers suggested that the programs did not yield better results because of small financial incentives, coupled with program complexities that made it "difficult for hospitals to meaningfully engage in the program." They also suggested that having to wait until year end to receive any financial incentives could have limited the impact.

"We found that hospitals that have been under financial incentives for more than a decade have not been able to reduce patient mortality more than late adopters, which had only been under financial incentives for less than 3 years," the researchers concluded. "Given its cost, policymakers in the [United States] should consider one of two things: revise the current program or potentially end it."

The changes suggested include increasing financial incentives and focusing on process measures that matter most to patients (mortality, patient experience, and functional status), rather than the current measure set that is larger and more difficult to track.

The researchers did not report any financial conflicts of interest.

gtwachtman@frontlinemedcom.com

SOURCE: Dr. Igna Bonfrer et al. BMJ 2018;360:j5622.

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: The most objective assessment of a process often comes from an independent review by an uninvolved party. This study using "Big Data" calls into question the hypothesis that the carrot may work more effectively than the stick, at least in the realm of hospital care. Sometimes the only way to know if something will work is to try it, but then make appropriate adjustments should the plan fail … a colloquial way to describe scientific method. It will be interesting to see if CMS responds to this information with an adjustment in policy.

CMS launches advanced alternative payment model

BY GREGORY TWACHTMAN
Frontline Medical News

The Centers for Medicare & Medicaid Services is launching a new voluntary bundled payment demonstration project that for the first time will qualify as an advanced alternative payment model under the Quality Payment Program.

The Bundled Payments for Care Improvement Advanced (BPCI Advanced) "builds on the earlier success of bundled payment models and is an important step in the move away from fee-for-service and towards paying for value," CMS Administrator Seema Verma said in a statement. "Under this model, providers will have an incentive to deliver high-quality care."

Medicare-certified acute care hospitals and physician group practices are eligible to take part in the BPCI Advanced, according to Medicare documentation. They will be categorized either as "conveners" – entities that bring together multiple parties for the purpose of coordinating care, as well as apportioning financial risks – or as "nonconveners" – those who bear financial risk for themselves only.

Both categories of participants may enter into agreements with individual physicians and nonphysician providers to furnish care under the bundled payment model.

The program will provide a single retrospective payment and one risk track, with a 90-day clinical episode duration. It will cover 29 inpatient episodes and three outpatient clinical episodes. Payment will be tied to performance on quality measures.

The 29 inpatient clinical episodes cover a range of conditions, including liver disorders (excluding malignancy, cirrhosis, and alcoholic hepatitis); various cardiac conditions; chronic obstructive pulmonary disease, bronchitis, and asthma; spinal fusion; joint replacements; femur, hip, or pelvis fractures; gastrointestinal hemorrhage or obstruction; renal failure; sepsis; simple pneumonia and respiratory infections; stroke; and urinary tract infections.

The three outpatient clinical episodes include percutaneous coronary intervention, cardiac defibrillator implantation, and back and neck surgery except spinal fusion.

Seven quality measures will be tracked as part of the payment. For all clinical episodes, measurement of all-cause hospital readmissions and advance care plan will be required.

The other five will be applied to the payment when appropriate, as follows:

- Perioperative care: selection of prophylactic antibiotic: first- or second-generation cephalosporin.
- Hospital-level risk-standardized complication rate following elective primary total hip arthroplasty and/or total knee arthroplasty.
- Hospital 30-day, all-cause, risk-standardized mortality rate following coronary artery bypass graft surgery.
- Excess days in acute care after hospitalization for acute myocardial infarction.
- AHRQ patient safety indicators.

CMS had an open-door forum on Jan. 30 for those who were interested in participating in BPCI Advanced.

Applications for participation will be accepted through March 12.

gtwachtman@frontlinemedcom.com

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: While this may not be a panacea for all of the ills of our expensive but broken health-care system, it is heartening to see CMS at least propose new models of health-care delivery. The move away from a fee-for-service model was inevitable for government-funded health care given the ever-increasing costs coupled with the dismal rankings when compared with other nations. The United States spends more than any other nation but is 37th in the WHO health-care performance ratings … ouch. Unfortunately, as long as health-care remains a political football, change for the better may be miserably slow.

Budesonide fails to cut deaths in preemies

BY JIM KLING
Frontline Medical News

The administration of inhaled budesonide to extremely preterm infants did not increase the risk of neurodevelopmental disability but did increase mortality, in a study by Dirk Bassler, MD, of the University of Zürich and his associates.

An older study led by Dr. Bassler and published in the New England Journal of Medicine (2015;373:1497-506) showed that inhaled budesonide significantly reduced the incidence of bronchopulmonary dysplasia, which has been linked to higher mortality and chronic respiratory and cardiovascular impairment.

Systemic glucocorticoids have been linked to greater risk of neurodevelopmental disability, but only a few studies have examined the effect of inhaled glucocorticoids, such as budesonide, in preterm infants. These studies, including the earlier one by Dr. Bassler and his colleagues, were either small, covered a short period of time, or involved late administration of the drug.

In the two studies by Dr. Bassler and his colleagues, 863 preterm infants between 23 weeks' and just under 28 weeks' gestation who required any form of positive-pressure respiratory support were randomized to receive inhaled budesonide (two puffs, 200 mcg per puff) or placebo every 12 hours. They began within 24 hours of birth and continued for the first 14 days of life. Following that, patients received one puff every 12 hours until they no longer required supplemental oxygen and positive-pressure support, or reached a postmenstrual age of 36 weeks.

"There was no significant difference between the groups in adverse long-term outcomes in our study. However, the fact that fewer infants died in the placebo group than in the budesonide group complicates the interpretation of the treatment of budesonide."

The treatment resulted in a significant reduction in bronchopulmonary dysplasia at a postmenstrual age of 36 weeks (28.2% in the budesonide group vs. 37.4%; $P = .01$), in the older study.

In the new study, which was also published in the New England Journal of Medicine, Dr. Bassler and his associates found higher mortality (19.9% vs. 14.5%; relative risk, 1.37; 95% confidence interval, 1.01-1.86; $P = .04$) in the group of patients who had received inhaled budesonide. Additionally, at a corrected age of 18-22 months, surviving infants who received inhaled budesonide had a similar risk of neurodevelopmental disability as those patients who took the placebo.

Broadly speaking, 48.1% of infants who received budesonide had a neurodevelopmental disability, compared with 51.4% of infants who received placebo (RR adjusted for gestational age, 0.93; 95% CI, 0.80-1.09; $P = .40$). The two groups also had no statistically significant differences in their frequencies of cerebral palsy, blindness, hearing loss, or cognitive delay.

"There was no significant difference between the groups in adverse long-term outcomes in our study. However, the fact that fewer infants died in the placebo group than in the budesonide group complicates the interpretation of the treatment of budesonide," the researchers wrote.

Supported by a grant from the European Union and by Chiesi Farmaceutici. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

SOURCE: N Engl J Med. 2018;378:148-57.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This is an important study regarding bronchopulmonary dysplasia prevention. The study suggests starting budesonide within 24 hours of life resulted in a lower rate of bronchopulmonary dysplasia than placebo but fewer infants died in the placebo group. A bigger question for me is "what is the evidence for starting inhaled steroids prior to neonatal intensive care unit discharge?" Pediatric pulmonologists would like to know if it decreases subsequent respiratory-related ER visits and readmissions.

Young e-cigarette users graduating to the real thing

BY RICHARD FRANKI
Frontline Medical News

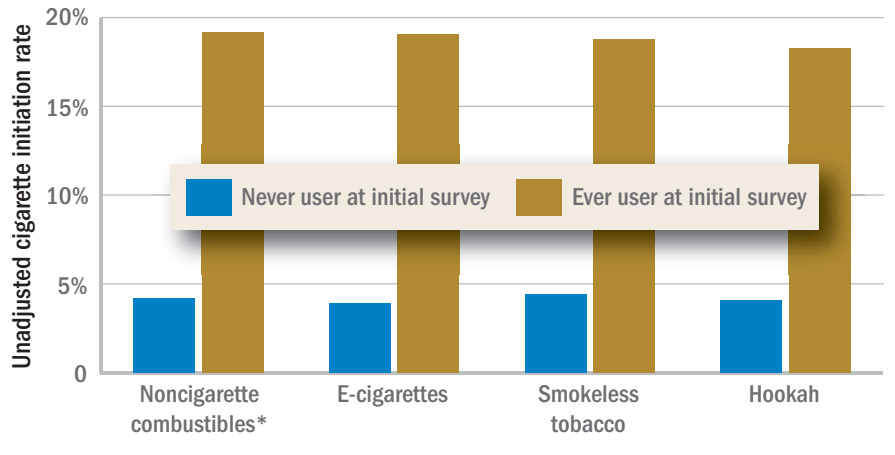
Children who use noncigarette forms of tobacco are significantly more likely to try cigarettes in the future, according to survey data from more than 10,000 young people aged 12-17 years.

An initial survey (wave 1) was conducted as part of the nationally representative Population Assessment of Tobacco and Health (PATH) study, with a follow-up (wave 2) administered to participants a year later. The analysis by Shannon L. Watkins, PhD, of the University of California, San Francisco, and her associates was based on data for 10,384 respondents who reported never smoking a cigarette in wave 1 and whose later cigarette use, which occurred in less than 5% overall, was reported in wave 2.

Among those who said that they had ever used an e-cigarette – the most popular of the noncigarette forms in wave 1 – 19.1% reported that they had tried a cigarette in the subsequent 12 months, compared with 3.9% who had never used an e-cigarette in wave 1. The results were similar (see graph) for the other forms of noncigarette tobacco: noncigarette combustibles (bidis, cigarillos, filtered cigars, kreteks, pipes, and traditional cigars), hookah (tobacco waterpipe), and smokeless tobacco (chewing tobacco, dissolvable tobacco, moist snuff, and snus).

RESULTS OF FOLLOW-UP SURVEY

Young people who tried cigarettes in the year after initial survey



Frontline Medical News

*bidis, cigarillos, filtered cigars, kreteks, pipes, and traditional cigars

Note: Based on data for 10,384 Population Assessment of Tobacco and Health respondents.

Source: JAMA Pediatr. 2018 Jan 2. doi: 10.1001/jamapediatrics.2017.4173

Those who used multiple noncigarette products were more likely than users of a single product to initiate cigarette use by wave 2. With never use of any tobacco as the reference, one model used by the investigators put the odds ratios of cigarette ever use at 4.98 for e-cigarettes only, 3.57 for combustibles only, and 8.57 for use of multiple products.

This study was supported by grants from the National Cancer Institute, Food and Drug Administration Center for Tobacco Products, National Institute on Drug Abuse, and National Center for Advancing Translational Sciences. No conflicts of interest were reported.

rfranki@frontlinemedcom.com

SOURCE: Watkins S et al. JAMA Pediatr. 2018 Jan 2. doi: 10.1001/jamapediatrics.2017.4173.

SYMBICORT— THE SPEED THEY WANT

WITH THE CONTROL THEY NEED

SPEED

– Majority of patients' FEV_1* improvement occurred at 5 minutes in COPD[1-3]

CONTROL

– Reduced COPD exacerbations[3]

*1-hour postdose FEV_1.

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

Please see study designs on following pages.

- SYMBICORT 160/4.5 for the maintenance treatment of COPD, and for reducing COPD exacerbations

IMPORTANT SAFETY INFORMATION

- Use of long-acting $beta_2$-adrenergic agonists (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA. When LABA are used in fixed dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone

Symbicort®
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

A reassuring sense of control

Please see additional Important Safety Information throughout and Brief Summary of full Prescribing Information on following pages.

SYMBICORT 160/4.5 for the maintenance treatment of COPD

THE SPEED THEY WANT...

BETTER BREATHING—FAST[1-3]

The majority of patients' FEV_1 improvement occurred at:

IN COPD[1-3]

- In a serial spirometry subset of patients taking SYMBICORT 160/4.5* (n=121) in the SUN Study, 67% of 1-hour postdose FEV_1 improvement occurred at 5 minutes on day of randomization, 83% at month 6, and 84% at end of treatment[1-3]
- Sustained improvement in lung function was demonstrated in COPD in a 12-month efficacy and safety study[1,2]

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

- The most common adverse reactions ≥3% reported in COPD lung function clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection

Study 2 (SUN): A 12-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1964 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=494), SYMBICORT pMDI 80/4.5 mcg (n=494), formoterol 4.5 mcg (n=495), and placebo (n=481), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD and symptoms for >2 years. The study included a 2-week run-in period followed by a 12-month treatment period. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1 (coprimary endpoints). The prespecified primary comparisons for predose FEV_1 were vs placebo and formoterol, and the primary comparison for 1-hour postdose was vs placebo.

COMPARATOR ARMS—Mean improvement in 1-hour postdose FEV_1 (mL/%) over 12 months (serial spirometry subset):

Day of randomization: SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (180 mL/20%), placebo (40 mL/5%).

6 months: SYMBICORT 160/4.5 mcg (270 mL/28%), formoterol 4.5 mcg (200 mL/23%), placebo (60 mL/7%).

End of month 12 (last observation carried forward [LOCF]):
SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (170 mL/19%), placebo (30 mL/5%).

SYMBICORT 160/4.5 mcg* (n=121)

Formoterol 4.5 mcg* (n=124)

Placebo* (n=125)

Please see additional Important Safety Information throughout and Brief Summary of full Prescribing Information on following pages.

*Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION (CONT'D)

- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- Lower respiratory tract infections, including pneumonia, have been reported following the administration of ICS
- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to ICS. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available ICS
- Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of ICS may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of ICS, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts

SYMBICORT 160/4.5 for reducing COPD exacerbations

THE CONTROL THEY NEED...

REDUCTION IN COPD EXACERBATIONS

In a 12-month exacerbation clinical trial (Study 4), SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations vs formoterol[3,4]

Annual rate estimate: **1.05**, formoterol 4.5 mcg* (n=403)

p<.0001 vs formoterol[4]
Estimate Rate Ratio=0.65; 95% CI: 0.53, 0.80

Annual rate estimate: **0.68**, SYMBICORT 160/4.5 mcg* (n=404)

In a second exacerbation clinical trial of 6-month duration (Study 3), SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations by 26% vs formoterol (Estimate Rate Ratio=0.74; 95% CI: 0.61, 0.91; *p*=.004)[3,4]

- Annual rate estimate was 0.94 for SYMBICORT 160/4.5 mcg* (n=606) vs 1.27 for formoterol 4.5 mcg* (n=613)

- In **Study 3**, COPD exacerbations were defined as worsening of ≥2 major symptoms (dyspnea, sputum volume, sputum color/purulence) or worsening of any 1 major symptom together with ≥1 of the minor symptoms (sore throat, colds [nasal discharge and/or nasal congestion], fever without other cause, increased cough or increased wheeze) for ≥2 consecutive days. COPD exacerbation severity was classified as moderate if symptoms required systemic corticosteroid (≥3 days) and/or antibiotic treatment, and severe if hospitalization was required
- In **Study 4**, COPD exacerbations were defined as worsening of COPD that required treatment with a course of oral steroids and/or hospitalization
- The safety findings from the two exacerbation clinical trials were consistent with the lung function studies

Study 3 (RISE): A 6-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 1219 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=606) with formoterol 4.5 mcg (n=613), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >1 year, and a history of ≥1 moderate or severe COPD exacerbation in the previous year requiring treatment with systemic corticosteroids or hospitalization. The study included a 4-week run-in period, a 26-week randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of moderate and severe COPD exacerbations for SYMBICORT vs formoterol.

Study 4: A 12-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 811 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=407) with formoterol 4.5 mcg (n=404), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >2 years, and a history of ≥1 COPD exacerbation in the previous year treated with a course of systemic corticosteroids and/or antibiotics. The study included a 2-week run-in period, a 12-month randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of COPD exacerbations for SYMBICORT vs formoterol.

*Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION (CONT'D)

- In rare cases, patients on ICS may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce COPD exacerbations.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

References: 1. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565. **2.** Data on file, 1084400, AZPLP. **3.** SYMBICORT [package insert]. Wilmington, DE: AstraZeneca; December 2017. **4.** Data on file, REF-16658, AZPLP.

Please see Brief Summary of full Prescribing Information on following pages.

AstraZeneca

Symbicort®
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol
A reassuring sense of control

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION. For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older.

SYMBICORT should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting beta$_2$-adrenergic agonist (LABA).

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. SYMBICORT 160/4.5 is also indicated to reduce exacerbations of COPD. SYMBICORT 160/4.5 is the only strength indicated for the treatment of COPD.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone (see *Serious Asthma-Related Events with ICS/LABA in the full Prescribing Information*).

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three trials included adult and adolescent patients aged ≥12 years: one trial compared budesonide/formoterol (SYMBICORT) to budesonide *[see Clinical Studies (14.1) in the full Prescribing Information]*; one trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder; and one trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric patients 4 to 11 years of age and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N =17,537)[1]	ICS (N =17,552)[1]	ICS/LABA vs ICS Hazard ratio (95% CI)[2]
Serious asthma-related event[3]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta$_2$-adrenergic Agonist
1. Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.
2. Estimated using a Cox proportional hazards model of time to first event with baseline hazards stratified by each of the 3 trials.
3. Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate / salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies

Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, 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.

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

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications 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 SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

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

Pneumonia and Other Lower Respiratory Tract Infections

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In a 6-month lung function study of 1704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month lung function study of 1964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6-month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe asthma attack or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe asthma attack, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma or COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

Hypercorticism and Adrenal Suppression

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

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

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

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

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

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

Reduction in Bone Mineral Density

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

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

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled

corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information]*.

Glaucoma and Cataracts

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

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

Eosinophilic Conditions and Churg-Strauss Syndrome

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

ADVERSE REACTIONS

LABA use may result in the following:

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- Cardiovascular and central nervous system effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

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

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

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

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

The incidence of common adverse events in Table 2 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 2 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 2 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 N = 277 %**	**160/4.5 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**

1. All treatments were administered as 2 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.

Pediatric Patients 6 to Less than 12 Years of Age

The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT 80/4.5 (n=92) or budesonide pMDI 80 mcg (n=92), 2 inhalations twice daily. The overall safety profile of these patients was similar to that observed in patients 12 years of age and older who received SYMBICORT 80/4.5 twice daily in studies of similar design. Common adverse reactions that occurred in patients treated with SYMBICORT 80/4.5 with a frequency of ≥3% and more frequently than patients treated only with budesonide pMDI 80 mcg included upper respiratory tract infection, pharyngitis, headache, and rhinitis.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The safety data described below reflect exposure to SYMBICORT 160/4.5 in 1783 patients. SYMBICORT 160/4.5 was studied in two placebo-controlled lung function studies (6 and 12 months in duration), and two active-controlled exacerbation studies (6 and 12 months in duration) in patients with COPD.

The incidence of common adverse events in Table 3 below is based upon pooled data from two double-blind, placebo-controlled lung function 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 2 inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 3 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 3 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[1]	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	**160/4.5 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**

1. All treatments were administered as 2 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, hematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

The safety findings from the two double-blind, active-controlled exacerbations studies (6 and 12 months in duration) in which 1012 adult COPD patients (616 males and 396 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily were consistent with the lung function studies.

Postmarketing Experience

The following adverse reactions have been identified 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.

Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.9) in the full Prescribing Information]*.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in adolescent and adult asthma patients 12 years of age and older, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur *[see Warnings and Precautions (5) in the full Prescribing Information]*. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France Rev. 12/2017 US-17406 1/18

HPV vaccine cuts juvenile respiratory papillomatosis numbers

BY BIANCA NOGRADY
Frontline Medical News

Introduction of a national human papillomavirus vaccination program in Australia has been associated with declines in the incidence of juvenile-onset recurrent respiratory papillomatosis, according to a nationwide study.

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare condition characterized by recurring growths in the larynx that often can require multiple operations to remove. The disease typically emerges around age 3-4 years and most cases are thought to be caused by human papillomavirus (HPV) subtypes 6 and 11, which are acquired from the mother during birth.

In this prospective study using data from the Australian Paediatric Surveillance Unit, researchers examined the incidence of juvenile-onset recurrent respiratory papillomatosis from October 2011 to December 2015, set against the background of the introduction of Australia's national HPV vaccination program between 2007 and 2009 (J Infect Dis. 2017 Nov 9. doi: 10.1093/infdis/jix498).

Overall, just 15 cases were reported during the course of the study; 7 in the first year, 3 in the second year, 2 each in the third and fourth years, and 1 case in the last year. The annual rates declined from 0.16 per 100,000 children aged 0-14 years in 2012 to 0.02 per 100,000 in 2016.

Of the cases identified, none of the mothers had been vaccinated against HPV before pregnancy and 20% had a history of genital warts. Seven cases were genotyped: Four were HPV-6 and three were HPV-11. Of the 15 cases, 13 were born vaginally.

"Our data strongly suggest that the previously documented impact of quadrivalent HPV vaccination in dramatically reducing the prevalence of HPV-6 and HPV-11 genital infection in the Australian population is translating to a reduction in the risk of transmission to infants intrapartum and subsequent development in some of these children of JORRP," wrote Daniel Novakovic, MD, of the University of Sydney Medical School, and his coinvestigators.

The authors noted that their initial estimate of infection rates was lower than that seen in other studies, such as the 0.5 per 100,000 rate seen in private health insurance data, and the 1.0 per 100,000 seen with Medicaid data in the United States.

Given that the study period started nearly 5 years after the vaccination program began, they suggested that this lower prevalence may reflect the early impact of the vaccine, particularly given that the prevalence of genital warts had already dramatically declined by that point.

However they also stressed that their study relied on clinicians actively reporting cases, and that given surveillance only began after the introduction of the vaccination program, no data were available on the incidence before that point.

The study was supported by a research grant from Merck and by the Australian Paediatric Surveillance Unit, which is supported by the Australian Government Department of Health. Three authors declared research funding from Merck/Seqirus for HPV studies. Two authors declared funding, speaking fees, and other support from a range of pharmaceutical companies.

Scrubbing homes of allergens may tame asthma, costs

BY DOUGLAS BIRCH, KAISER HEALTH NEWS

After years of studying the causes of asthma, a pediatrician turned public health sleuth thinks there's a way to substantially reduce its impact.

But the approach faces a big hurdle: getting someone to pay for it, said Elizabeth C. Matsui, MD, a professor at Johns Hopkins University in Baltimore.

Dr. Matsui, who suffered from asthma as a child, has spent much of her career studying the link between poor housing and asthma in low-income neighborhoods. In particular, she's looked at the effects of mouse allergens, typically found in high concentrations in urban homes.

Dr. Matsui cited a 2004 study in the New England Journal of Medicine that described measures to reduce home allergen levels and concluded that they were linked to reductions in asthma symptoms.

That research "was highly successful and impactful," but the approach wasn't widely adopted. "So here we have this trial that was published more than 10 years ago that shows [indoor allergen control] works," said Dr. Matsui, who did not participate in the study. "But the families who need it most can't afford to do these things, don't have control oftentimes over their home environment, and insurance or other payers don't cover these things."

Dr. Matsui has proposed new incentives for hospitals to provide home intervention, including Medicaid waivers. But, she said, scientists can't use research money for these programs. "Delivery of community health care programs would require a different type of funding."

As a result, doctors and scientists doubted if a plan to control home allergens would scale up, and insurers questioned whether benefits to their bottom line would justify the added cost.

"We have this enormous public health problem in that there are housing conditions that directly affect allergen exposure in this population of kids," Dr. Matsui said. "We have dedicated individuals and groups who are trying to solve the problem. But we don't have a system that is able to solve the problem."

A 2017 study by Dr. Matsui, published in JAMA, suggests that even without intensive professional cleaning services, families that receive some training can substantially reduce home allergens on their own.

That finding suggests health agencies should routinely offer to educate asthma-affected families in home allergen control. "There's potentially a large benefit," Dr. Matsui said.

In a separate study, Dr. Matsui's group is following 200 Baltimore children to see if those in homes scrubbed of allergens need fewer treatments with rescue inhalers. If they do, that could give health insurers an incentive to pay for the approach.

There's another incentive: Clearing the air in a child's home may be critical in cases where medications alone don't work. "We continue to see a lot of kids that, despite being on medication, don't have well-controlled asthma," Dr. Matsui said.

Asthma drugs can also have serious side effects, she said, especially at higher doses, and may suppress symptoms without halting lung damage.

Dr. Matsui's work on asthma began while working as a pediatrician at Baltimore's Franklin Square Hospital in 1998. As part of her job, she spent a half-day each week in a school health clinic in a low-income area.

Dr. Matsui was struck by the number of kids she saw with severe asthma, she said, and set up a home health visit program to help them. But she wasn't certain the program was working, so she consulted with experts at Hopkins.

In 2004, she earned a master's from the Johns Hopkins School of Public Health. Today, she is one of the nation's leading asthma researchers.

Dr. Matsui said her career was shaped by her own struggle with childhood asthma. "I think that that probably played a role, consciously or unconsciously," she said.

KHN's coverage of health disparities in east Baltimore is supported by The Annie E. Casey Foundation. Kaiser Health News is a nonprofit news service covering health issues. It is an editorially independent program of the Kaiser Family Foundation that is not affiliated with Kaiser Permanente.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Environment is certainly a factor in asthma control. We are lucky enough to have a network in our county that will take pediatric asthma cases to help with asthma education. The nurse will even accompany the child and parent to their outpatient visits to help advocate for help with their asthma management and go into the home to see if there is a cockroach problem or a dusty environment, for example. They will also help families learn how to better organize the child's bedroom so there is less dust! Some Medicaid HMOs will pay for this care management plan but not all of the insurances in our area.

Macrolide use cuts failure risk in pediatric CAP

BY ELI ZIMMERMAN
Frontline Medical News

SAN DIEGO – Macrolide use showed lower treatment failure rates than did amoxicillin or beta-lactam treatment for pediatric community acquired pneumonia (CAP) patients, according to a study presented at an annual scientific meeting on infectious diseases.

While guidelines recommend amoxicillin as the first-line therapy against CAP, investigators have noticed an increase in macrolide prescriptions to pediatric outpatients, despite reported shortcomings in its use against atypical pneumonia.

"Macrolides are probably prescribed out of proportion to the presence of atypical pneumonia in that practice setting," said Lori Handy, MD, of Children's Hospital of Philadelphia.

"We also know that, depending on the study, up to 40% of *Streptococcus pneumoniae* is resistant to macrolides, meaning there are children out there who may have *S. pneumoniae* who are receiving therapy not targeted at their disease pathogen," she said, during her presentation at the scientific meeting.

To examine the possible impact of an increase in macrolide prescriptions, the investigators conducted a retrospective cohort study of 10,470 CAP pediatric patients across 31 primary care practices in the Children's Hospital of Philadelphia network who were diagnosed between January 2009 and December 2013.

The studied cohort was split into three groups based on treatment options: amoxicillin monotherapy (4,252, 40.6%), macrolide monotherapy (4,459, 42.6%), and broad-spectrum beta-lactams (1,759, 16.8%).

Patient age ranged from 3 months to 18 years, the majority were white, with a roughly equal number of each sex. Of the children studied, 634 (6.1%) experienced treatment failure, defined as a change in antibiotics, an emergency department visit for related symptoms, or hospitalization for pneumonia, all of which had to occur more than 24 hours after a pediatric visit, according to Dr. Handy.

Of the children who failed treatment, 341 (54%) were in the amoxicillin group, 145 (23%) were in the macrolide group, and 147 (23%) were in the broad-spectrum group.

Patients younger than age 5 years who received macrolide therapy were half as likely to experience treatment failure compared with those given amoxicillin (odds ratio, 0.52; 95% confidence interval, 0.34-0.78).

"What this translates to in practice is that about 32 children would need to be treated with macrolides to prevent one failure in the amoxicillin group," said Dr. Handy.

Patients 5 years and older showed even lower odds of treatment failure, at approximately one-third the rate of amoxicillin-treated patients (OR .31 [95% CI, 0.23-0.92]).

Dr. Handy stated that the retrospective nature of the study and the possibility of changes in the epidemiology of CAP occurring since 2013 should be considered when evaluating the findings.

In addition, she pointed out, CAP is a clinical diagnosis, and there is generally no microbiological data associated with it in order to determine the etiology of the infection.

Dr. Handy and her colleagues reported having no relevant financial disclosures.

The event was 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.

ezimmerman@frontlinemedcom.com

Lung recovery high after ECMO in asthma

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Extracorporeal membrane oxygenation (ECMO) is associated with lung recovery rates as high as 90% in pediatric patients with near-fatal asthma, but complication risks were high and the cannulation technique employed made a significant difference to outcomes, according to a study presented at the CHEST annual meeting.

"ECMO for near-fatal asthma is a potentially life-saving intervention, however, clinicians should be aware of the potentially severe complications, particularly with venoarterial cannulation in this population," said Rebecca Kohlberg-Davis, MD, a pediatric resident at Connecticut Children's Medical Center, Hartford.

ECMO is being used in the setting of near-fatal pediatric asthma, but there are limited data on outcomes in this population. Dr. Kohlberg-Davis and her colleagues conducted a retrospective analysis of all children with asthma treated with ECMO using the Extracorporeal Life Support Organization registry.

During 1988-2016, 371 children with status asthmaticus underwent ECMO cannulation using one of two methods; 65% were treated with

Dr. Rebecca Kohlberg-Davis, a pediatric resident at Connecticut Children's Medical Center

ECMO using venovenous (VV) cannulation and 33% were treated using venoarterial (VA) cannulation. Both VV and VA require insertion of a cannula to take deoxygenated blood from a central vein or the right atrium. VA ECMO returns the oxygenated blood, under pressure, to the arterial side of the circulation (typically to the aorta), supporting cardiac output, while VV ECMO returns oxygenated blood back to a large vein and does not support circulation.

The median patient age was 7.5 years and 56% were male. The median ECMO run duration was 123 hours.

Overall, lung recovery was seen in 83% of patients, and 77% were discharged from the hospital. Of the children who received VV cannulation, 90% experienced lung recovery, while VA cannulation was associated with a 69% rate of lung recovery and significantly more complications. Among those who experienced lung recovery, those who received VV cannulation had a 3.6-fold higher likelihood of survival ($P = .006$), Dr. Kohlberg-Davis reported.

At presentation, 88% of patients had hypercarbic respiratory failure and were more likely to receive VV cannulation ($P = .003$); 34% had hypoxemic respiratory failure and 27% had mixed respiratory failure and were more likely to receive VA cannulation. Those with hypoxemic respiratory failure had a significantly lower likelihood of lung recovery (odds ratio, 4.9; P less than .0001), she said.

Eighty percent of runs had one or more complications and 20% had three or more. Of that 80%, most involved cardiovascular complications (53%), while 36% were hemorrhagic and 35% mechanical. The most common cardiovascular complications were the need for inotropic support (39%) and hypertension requiring vasodilators (18%). The most common hemorrhagic complications were bleeding at the cannula (23%) and surgical site (8%), while mechanical complications were mostly clots (19%) and cannulation problems (12%).

Children who received VA cannulation had a significantly higher rate of neurologic complications, compared with those who received VV cannulation (22% vs. 5%).

The authors reported having nothing to disclose.

chestphysician@frontlinemedcom.com

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This is a large study looking at the use of extracorporeal membrane oxygenation (ECMO) patients dying of status asthmaticus. It is interesting that the pCO_2 seemed to predict the type of ECMO used and outcomes. Of course, an ounce of prevention (i.e., appropriate asthma management) is the most important thing to say about any pediatric intensive care unit asthma study! Having said all of this, we have known that venovenous ECMO is preferred for a long time.

Varenicline reduces heavy drinking in male smokers

BY MADHU RAJARAMAN
Frontline Medical News

The smoking cessation aid varenicline tartrate is effective for reducing heavy drinking in men with alcohol use disorder and comorbid cigarette smoking, according to findings published Dec. 20, 2017. The drug also increased smoking abstinence in participants overall, reported Stephanie S. O'Malley, PhD, of the department of psychiatry at Yale University, New Haven, Conn., and her coauthors.

In a phase 2, randomized, double-blind study of 131 patients, varenicline treatment resulted in a significant decrease in the percentage of heavy drinking days (PHDD) at 9-16 weeks in men, compared with placebo (P = .09). Additionally, 29% of men taking varenicline had no heavy drinking days (NHDD) during the trial period. NHDD was defined as never drinking four or more drinks per day for women or five or more drinks per day for men, Dr. O'Malley and her colleagues wrote in JAMA Psychiatry.

Women had a smaller decrease in PHDD (P = .15), and 5% had NHDD, compared with 25% of the women on placebo.

The trial was conducted between September 2012 and August 2015 at research facilities affiliated with Columbia University in New York and with Yale. The study group was made up of 92 men and 39 women aged 18-70 years who met DSM-IV-TR criteria for alcohol dependence. Most of the respondents (52.7%) identified themselves as black. They reported heavy drinking at least twice per week for the preceding 90 days, having seven or fewer consecutive days of alcohol abstinence, and smoking at least twice per week, the investigators reported.

Among participants receiving varenicline, 13% achieved prolonged smoking abstinence at 13-16 weeks, the authors reported, whereas none of the participants on placebo quit smoking (P = .003).

The sex differences in the trial may be attributed to differences in baseline characteristics, such as greater alcohol dependence and lower nicotine dependence, Dr. O'Malley and her colleagues said.

Additionally, women were more likely to reduce or discontinue varenicline dose. "From a methodological perspective, we permitted dose reductions to minimize adherence problems because lower varenicline doses are effective for smoking cessation," they said.

"Individuals treated for alcoholism are more likely to die of smoking than from alcohol-related causes," they wrote, and "most smokers do not receive smoking-cessation assistance, yet heavy-drinking smokers see these behaviors as highly associated."

Continued on following page

VIEW ON THE NEWS

Study paves way for further research on substance use

Despite its limitations, this study provides an important contribution to the body of addiction research, wrote A. Eden Evins, MD, MPH, in an accompanying editorial.

"Outcome measures that take into account multiple addictions are largely unexplored," Dr. Evins said.

In addition to demonstrating its tolerability in patients with substance use disorders, the study makes "a creative contribution toward improved treatment trials for those who use multiple addictive substances by including an exploratory mixed outcome of no heavy drinking days and no tobacco use," she wrote.

Future research should further explore sex differences, as well as proactive treatment strategies for smokers who are not ready to quit but are willing to try medications to improve their chances of quitting, Dr. Evins concluded.

Dr. Evins is affiliated with the Center for Addiction Medicine at the department of psychiatry at Massachusetts General Hospital and with Harvard Medical School, both in Boston. She disclosed financial relationships with Forum Pharmaceuticals, Pfizer, and Brain Solutions.

Tracheobronchial tree size changes may predict IPF outcomes

BY HEIDI SPLETE
Frontline Medical News

FROM CHEST 2017 ▪ Changes in tracheobronchial tree size may serve as a practical and noninvasive method for predicting disease severity in patients diagnosed with idiopathic pulmonary fibrosis, according to data from 150 adults.

To determine the potential predictive value of tracheobronchial tree changes on mortality, Ankush Ratwani, MD, of Georgetown University, Washington, and colleagues reviewed data from adults with IPF seen at a single center between March 2012 and December 2016. The findings were presented at the CHEST annual meeting.

The researchers measured the tracheal diameters of the patients and used the GAP index, an established system for predicting mortality in IPF patients, to determine a relationship. Overall, they found a significant correlation between GAP index scores and increasing tracheobronchial tree size across eight measurements of different levels along the tracheobronchial tree "with an increase in GAP index stage for every level of increase in tracheal measurements (*P* less than .005)," they noted.

Measurements included the anterior-posterior diameter at the subglottic level, aortic arch, carina, right main stem bronchus, and left main stem bronchus, as well as transverse diameter assessment at the subglottis, aortic arch, and carina. The average anterior-posterior tracheal diameters were 21.77 mm for the subglottis, 21.84 mm for the aortic arch, 20.47 mm for the carina, 15.19 for the right main stem bronchus, and 14.21 mm for the left main stem bronchus.

No correlation appeared between tracheal size and lung volume, which suggests that enlargement of the trachea is likely caused by other factors beyond fibrosis, and next steps for research should determine whether tracheal size is an independent predictor of mortality in IPF patients, the investigators noted.

"With the field of treatment and management changing for IPF over the last few years, it has becoming increasingly important to prognose these patients in order to find where they fit in the spectrum for treatment or lung transplant," Dr. Ratwani said in an interview. "Additionally, there needs to be a noninvasive measure to show disease progression, such as with using CT scans, and correlate with other prognostic indicators to hopefully create a regression formula that encompasses multiple parameters," he explained.

"The results were surprising in that there was a correlation of a radiographic measure that has not been looked at previously with a validated measure of prognostication in IPF (GAP Index)," Dr. Ratwani said.

Although the findings do not imply more than a correlation, the results serve as "a good start to validate the theory that as the distal airways enlarge (traction bronchiectasis) in later stages of IPF, so may the proximal airways, which may be used to easily measure disease progression and guide the conversation for transplant or treatment," Dr. Ratwani noted. His next steps for research include studying transplant-free survival in correlation with tracheal size, as well as serial changes between CT scans with correlations of lung volumes and survival.

Dr. Ratwani and his coauthors reported having no disclosures.

chestphysician@frontlinemedcom.com

Continued from previous page

Lastly, the trial was limited by the small sample size of women.

"Future studies should evaluate the effectiveness and safety of varenicline in women and men separately in larger samples to establish whether the observed effects are of clinical significance," the authors concluded.

The study was funded by grants from the National Institutes of Health and from Connecticut's Department of Mental Health and Addiction Services. Pfizer, the manufacturer of varenicline under the name Chantix, provided varenicline and placebo pills.

The authors disclosed relationships with several companies, including Pfizer.

chestphysician@frontlinemedcom.com

SOURCE: O'Malley SS et al. JAMA Psychiatry. 2017 Dec 20. doi: 10.1001/jamapsychiatry.2017.3544.

Cancer screening needed earlier, more frequently in CF

BY MICHELE G. SULLIVAN
Frontline Medical News

Adults with cystic fibrosis (CF) should undergo screening colonoscopy for colorectal cancer every 5 years beginning at age 40 years, unless they have had a solid organ transplant – in which case, screening should begin at age 30 years. For both groups, screening intervals should be shortened to 3 years if any adenomatous polyps are recovered.

The new screening recommendation is 1 of 10 set forth by the Cystic Fibrosis Foundation, in conjunction with the American Gastroenterological Association. The document reflects the significantly increased risk of colorectal cancer among adults with the chronic lung disorder, Denis Hadjiliadis, MD, and his colleagues wrote in the February issue of Gastroenterology. CF patients face up to a 10-fold risk of colorectal cancer, compared with the general population; the risk approaches a 30-fold increase among CF patients who have undergone a lung transplant.

In addition to making recommendations on screening intervals and protocols, the document asks clinicians to reframe their thinking of CF as a respiratory-only disease.

"Physicians should recognize that CF is a colon cancer syndrome," wrote Dr. Hadjiliadis, director of the Adult Cystic Fibrosis Program at the University of Pennsylvania, Philadelphia, and his coauthors.

The increased colorectal cancer risk has become increasingly evident as CF patients live longer, Dr. Hadjiliadis and the panel wrote.

"The current median predicted survival is 41 years, and persons born in 2015 have an estimated average life expectancy of 45 years. The increasing longevity of adults with CF puts them at risk for other diseases, such as gastrointestinal cancer."

In addition to the normal age-related risk, however, CF patients seem to have an elevated risk profile unique to the disease. The underlying causes have not been fully elucidated but may have to do with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), which are responsible for the excess thickened mucosal secretions that characterize CF. CFTR also is a tumor-suppressor gene in the intestinal tract of mice, and is important in gastrointestinal epithelial homeostasis. "Absence of CFTR is associated with dysregulation of the immune response, intestinal stem cells, and growth signaling regulators," the authors noted.

In response to this observed increased risk of colorectal cancers among CF patients, the Cystic Fibrosis Foundation convened an 18-member task force to review the extant literature and compile colorectal cancer screening recommendations for CF patients who show no signs of such malignancies. The team reviewed 1,159 articles and based its findings on the 50 most relevant. The papers comprised observational studies, case-control studies, and case reports; there are no randomized clinical trials of screening for this population.

The American Gastroenterological Association reviewed and approved all of the recommendations:

- Screening decisions should be a collaborative process between the CF patient and clinician, taking into account comorbidities, safety, and quality of life. This should include a discussion of expected lifespan; patients with limited lifespan won't benefit from screening for a slow-growing cancer. Patients should also consider that the colonoscopy prep for CF patients is somewhat more complex than for non-CF patients. "Given these complexities, the task force agreed that individuals with CF and their providers should … carefully assess the risks and benefits of CRC screening and its impact on the health and quality of life for the adult with CF."
- The decision team should include an endoscopist. An endoscopist with CF training is preferred, but the panel noted these specialists are rare.
- Colonoscopy is the preferred method of screening for CF patients, since it can both detect and remove polyps. "This is one of the main reasons why colonoscopy is the screening procedure of choice for other high-risk groups," the panel noted.
- There is insufficient evidence to recommend alternative screening methods in CF patients, including CT scanning, colonography, stool-based tests, or flexible sigmoidoscopy.
- In CF patients without signs of CRC, screening should commence at age 40 years and be repeated every 5 years as long as the results are negative.
- Any CF patient who has had adenomatous polyps on a screening colonoscopy should have a repeat colonoscopy within 3 years, unless clinical findings support more frequent screening.
- For any adult CF patient older than age 30 years who has undergone a solid organ transplant, screening colonoscopy should commence within 2 years of transplantation. "Although the absolute risk of CRC in individuals with CF is extremely low for patients younger than 30 years, the risk … greatly increases after lung transplantation," to 25-30 times the age-ad-

Continued on page 29

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: According to the Cystic Fibrosis Foundation Patient Registry, more than 30,000 people are living with cystic fibrosis (CF) in the United States. More than half of the CF population is over 18 years of age! It is extremely important to talk to patients about preventative medicine which was not a topic of conversation CF healthcare providers were adding to their management plan in the past.

Flu season takes another turn for the worse

BY RICHARD FRANKI
Frontline Medical News

By one measure at least – the proportion of outpatient visits for influenza-like illness (ILI) – this flu season is now the worst in almost a decade, according to data from the Centers for Disease Control and Prevention.

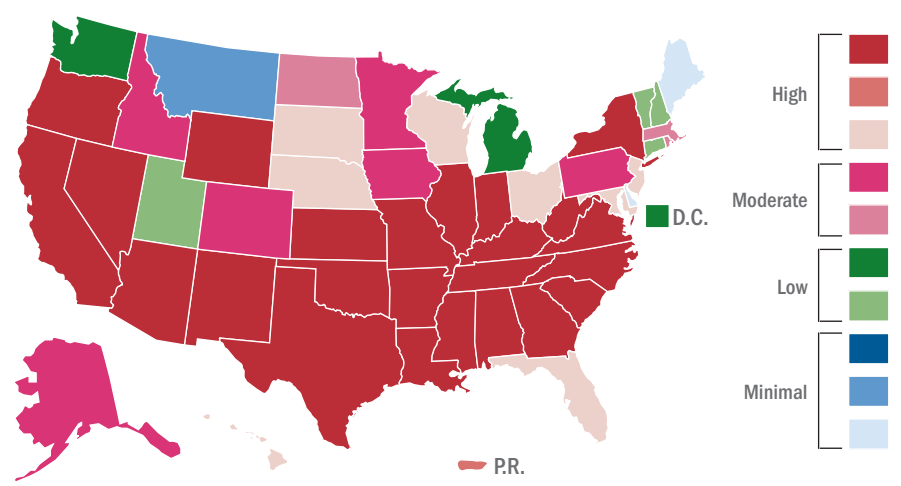
For the week ending Jan. 13, visits for ILI rose to 6.3% of outpatient visits nationwide – the highest figure reported since the 2009-2010 season, which hit an early peak of 7.7% in October of 2009. The slight pause that occurred in the first week of January as the rate rose only from 5.7% to 5.8% now looks more like the earlier trend from December, when the level of outpatient visits more than doubled over a 3-week period, data from the CDC FluView website show.

"The geographic spread of influenza in Puerto Rico and 49 states was reported as widespread" for the week ending Jan. 13, and 24 states had the highest level of ILI activity on the CDC's 1-10 scale, the CDC influenza division reported Jan 19.

There were 10 flu-related pediatric deaths reported during the week, with two occurring in the week ending Jan. 13. A total of 30 deaths in children have been associated with influenza so far for the 2017-2018 season, the CDC said.

rfranki@frontlinemedcom.com

Influenza-like illness activity level, week ending Jan. 13, 2018



Note: Based on data from the U.S. Outpatient Influenza-like Illness Surveillance Network.
Source: Centers for Disease Control and Prevention

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

NOW APPROVED

Visit TRELEGYHCP.com to learn more about this new therapy:

View Prescribing Information

Ask medical information questions

Live chat with GSK

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

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

Printed in USA. 824605R0 October 2017

BRIEF SUMMARY

TRELEGY ELLIPTA
(fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation
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), such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
TRELEGY is a combination inhaled corticosteroid/anticholinergic/long-acting beta$_2$-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.
Important Limitations of Use
TRELEGY is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of TRELEGY is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death.
A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in TRELEGY.
No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with TRELEGY has been conducted. The safety and efficacy of TRELEGY in patients with asthma have not been established. TRELEGY is not indicated for the treatment of asthma.
5.2 Deterioration of Disease and Acute Episodes
TRELEGY should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. TRELEGY has not been studied in subjects with acutely deteriorating COPD. The initiation of TRELEGY in this setting is not appropriate.
TRELEGY should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. TRELEGY 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 TRELEGY, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 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.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If TRELEGY 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 TRELEGY beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of TRELEGY and Use With Other Long-acting Beta$_2$-agonists
TRELEGY 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 TRELEGY should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Local Effects of Inhaled Corticosteroids
TRELEGY contains fluticasone furoate, an inhaled corticosteroid (ICS). Localized infections of the mouth and pharynx with *Candida albicans* have occurred in subjects treated with orally inhaled drug products, including fluticasone furoate. When such an infection develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while treatment with TRELEGY continues, but at times therapy with TRELEGY may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
5.5 Pneumonia
Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.
In two 12-week studies of subjects with COPD (N=824), the incidence of pneumonia was less than 1% for both treatment arms: umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg. Fatal pneumonia occurred in 1 subject receiving placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg.
In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 9 subjects receiving placebo, 10 subjects receiving fluticasone furoate 100 mcg, and 6 subjects receiving vilanterol 25 mcg (less than 0.2 per 100 patient-years for each treatment group).
5.6 Immunosuppression
Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.
ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
5.7 Transferring Patients From Systemic Corticosteroid Therapy
Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.
Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.
During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis), or other conditions associated with severe electrolyte loss. Although TRELEGY may control COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.
During periods of stress or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe COPD exacerbation.
Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRELEGY. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with TRELEGY. Lung function (forced expiratory volume in 1 second [FEV$_1$]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.
Transfer of patients from systemic corticosteroid therapy to TRELEGY may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (eg, rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).
During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (eg, joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.
5.8 Hypercorticism and Adrenal Suppression
Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of fluticasone furoate in TRELEGY. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.
Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with TRELEGY should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.
It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, appropriate therapy should be considered.
5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of TRELEGY 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 systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.
5.10 Paradoxical Bronchospasm
As with other inhaled medicines, TRELEGY can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with TRELEGY, it should be treated immediately with an inhaled, short-acting bronchodilator; TRELEGY should be discontinued immediately; and alternative therapy should be instituted.
5.11 Hypersensitivity Reactions, Including Anaphylaxis
Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY *[see Contraindications (4)]*.
5.12 Cardiovascular Effects
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY 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 *[see Clinical Pharmacology (12.2) of full prescribing information]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.
TRELEGY, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of adjudicated cardiovascular events (composite of myocardial infarction, stroke, unstable angina, transient ischemic attack, or on-treatment death due to cardiovascular events) was 2.5 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 2.7 for placebo, 2.4 for fluticasone furoate 100 mcg, and 2.6 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to cardiovascular events occurred in 82 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 86 subjects receiving placebo, 80 subjects receiving fluticasone furoate 100 mcg, and 90 subjects receiving vilanterol 25 mcg (annualized incidence rate ranged from 1.2 to 1.3 per 100 patient-years for the treatment groups).
5.13 Reduction in Bone Mineral Density
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, 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 TRELEGY and periodically thereafter. If significant reductions in BMD are seen and TRELEGY is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.
5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma
Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. TRELEGY should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms

cont'd

of acute narrow-angle glaucoma (eg, 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 healthcare provider immediately if any of these signs or symptoms develops. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, narrow- or open-angle glaucoma, and/or cataracts.

5.15 Worsening of Urinary Retention

TRELEGY, like all medicines containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

5.16 Coexisting Conditions

TRELEGY, 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.

5.17 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. TRELEGY 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:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10)]*
- Cardiovascular effects *[see Warnings and Precautions (5.12)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.14)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15)]*

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 safety of TRELEGY is based on the safety data from two 12-week treatment trials with coadministration of umeclidinium and the fixed-dose combination of fluticasone furoate and vilanterol and on the long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, the fixed-dose combination of umeclidinium/vilanterol, and umeclidinium monotherapy *[see Description (11), Clinical Pharmacology (12.3), and Clinical Studies (14.1) of full prescribing information]*.

Confirmatory Trials

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umeclidinium + fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol. A total of 824 subjects with COPD across two 12-week, randomized, double-blind clinical trials received at least 1 dose of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg administered once daily (mean age: 64 years; 92% white, 66% male across all treatments) *[see Clinical Studies (14.1) of full prescribing information]*. The incidence of adverse reactions associated with the use of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg presented in Table 1 is based upon the two 12-week trials.

Table 1. Adverse Reactions With Umeclidinium + Fluticasone Furoate/Vilanterol With ≥1% Incidence and More Common Than Placebo + Fluticasone Furoate/Vilanterol (Trials 1 and 2)

Adverse Reaction	Umeclidinium + Fluticasone Furoate/ Vilanterol (n=412) %	Placebo + Fluticasone Furoate/ Vilanterol (n=412) %
Nervous system disorders		
Headache	4	3
Dysgeusia	2	<1
Musculoskeletal and connective tissue disorders		
Back pain	4	2
Respiratory, thoracic, and mediastinal disorders		
Cough	1	<1
Oropharyngeal pain	1	0
Gastrointestinal disorders		
Diarrhea	2	<1
Infections and infestations		
Gastroenteritis	1	0

Supporting Long-Term Safety Data

The long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, umeclidinium/vilanterol, and umeclidinium monotherapy are similar to that reported in the 12-week clinical trials described in Table 1. *[See full prescribing information for BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder), ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder), and INCRUSE ELLIPTA (umeclidinium inhalation powder).]*

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also 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, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of TRELEGY with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.14, 5.15)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of TRELEGY or its individual components, fluticasone furoate, umeclidinium, and vilanterol, in pregnant women to inform a drug-associated risk. *[See Clinical Considerations.]* In an animal reproduction study, fluticasone furoate and vilanterol administered by inhalation alone or in combination to pregnant rats during the period of organogenesis produced no fetal structural abnormalities. The highest fluticasone furoate and vilanterol doses in this study were approximately 9 and 40 times the maximum recommended human daily inhalation doses (MRHDID) of 100 and 25 mcg in adults, respectively. *[See Data.]* Umeclidinium administered via inhalation or subcutaneously to pregnant rats and rabbits was not associated with adverse effect on embryofetal development at exposures approximately 50 and 200 times, respectively, the human exposure at the MRHDID.

The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the US general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Labor and Delivery: TRELEGY should be used during late gestation and labor only if the potential benefit justifies the potential for risks related to beta-agonists interfering with uterine contractility.

Data

Animal Data: The combination of fluticasone furoate, umeclidinium and vilanterol has not been studied in pregnant animals. Studies in pregnant animals have been conducted with fluticasone furoate and vilanterol in combination and individually with fluticasone furoate, umeclidinium or vilanterol.

Fluticasone Furoate and Vilanterol: In an embryofetal developmental study, pregnant rats received fluticasone furoate and vilanterol during the period of organogenesis at doses up to approximately 9 and 40 times the MRHDID, respectively, alone or in combination (on a mcg/m2 basis at inhalation doses up to approximately 95 mcg/kg/day). No evidence of structural abnormalities was observed.

Fluticasone Furoate: In 2 separate embryofetal developmental studies, pregnant rats and rabbits received fluticasone furoate during the period of organogenesis at doses up to approximately 9 and 2 times the MRHDID, respectively (on a mcg/m2 basis at maternal inhalation doses up to 91 and 8 mcg/kg/day). No evidence of structural abnormalities in fetuses was observed in either species. In a perinatal and postnatal developmental study in rats, dams received fluticasone furoate during late gestation and lactation periods at doses up to approximately 3 times the MRHDID (on a mcg/m2 basis at maternal inhalation doses up to 27 mcg/kg/day). No evidence of effects on offspring development was observed.

Umeclidinium: In 2 separate embryofetal developmental studies, pregnant rats and rabbits received umeclidinium via inhalation during the period of organogenesis at doses up to approximately 50 and 200 times the MRHDID, respectively (on an AUC basis at maternal inhalation doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). No evidence of teratogenic effects was observed in either species. In a perinatal and postnatal developmental study in rats, dams received umeclidinium during late gestation and lactation periods at doses up to approximately 26 times the MRHDID (on an AUC basis at maternal subcutaneous doses up to 60 mcg/kg/day). No evidence of effects on offspring development was observed.

Vilanterol: In 2 separate embryofetal developmental studies, pregnant rats and rabbits received vilanterol during the period of organogenesis at doses up to approximately 13,000 and 1,000 times, respectively, the MRHDID (on a mcg/m2 basis at maternal inhalation doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose in rats or in rabbits up to approximately 160 times the MRHDID (on an AUC basis at maternal doses up to 591 mcg/kg/day). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID (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. In a perinatal and postnatal developmental study in rats, dams received vilanterol during late gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a mcg/m2 basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in offspring development was observed.

8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRELEGY and any potential adverse effects on the breastfed child from fluticasone furoate, umeclidinium, or vilanterol, or from the underlying maternal condition.

Data

Animal Data: Subcutaneous administration of umeclidinium to lactating rats resulted in a quantifiable level of umeclidinium in 2 of 54 pups, which may indicate transfer of umeclidinium in rat milk.

8.5 Geriatric Use

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

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. 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.

cont'd

8.6 Hepatic Impairment
TRELEGY has not been studied in subjects with hepatic impairment. Information on the individual components is provided below.
Fluticasone Furoate/Vilanterol
Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.
Umeclidinium
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
TRELEGY has not been studied in subjects with renal impairment. Information on the individual components is provided below.
Fluticasone Furoate/Vilanterol
There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.
Umeclidinium
Patients with severe renal impairment (CrCl 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 human overdosage data has been reported for TRELEGY.
TRELEGY contains fluticasone furoate, umeclidinium, and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to TRELEGY. Treatment of overdosage consists of discontinuation of TRELEGY together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.
10.1 Fluticasone Furoate
Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*.
Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.
10.2 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 1000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.
10.3 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 (eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use *of full prescribing information*).
Asthma-Related Death
Inform patients that LABA, such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. TRELEGY is not indicated for the treatment of asthma.
Not for Acute Symptoms
Inform patients that TRELEGY is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting $beta_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.
Instruct patients to seek medical attention immediately if they experience any of the following:
- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with TRELEGY without physician/provider guidance since symptoms may recur after discontinuation.
Do Not Use Additional Long-acting $Beta_2$-agonists
Instruct patients not to use other LABA.
Local Effects
Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing therapy with TRELEGY, but at times therapy with TRELEGY may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.
Pneumonia
Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.
Immunosuppression
Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
Hypercorticism and Adrenal Suppression
Advise patients that TRELEGY may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to TRELEGY.
Paradoxical Bronchospasm
As with other inhaled medicines, TRELEGY can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue TRELEGY and contact their healthcare provider right away.
Hypersensitivity Reactions, Including Anaphylaxis
Advise patients that hypersensitivity reactions (eg, anaphylaxis, angioedema, rash, urticaria) may occur after administration of TRELEGY. Instruct patients to discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY.
Reduction in Bone Mineral Density
Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.
Ocular Effects
Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.
Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (eg, 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 (eg, difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
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.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 9/2017 TRL:1BRS

Printed in USA. 824605R0 October 2017

Shorter walk test predicts survival in IPF

BY HEIDI SPLETE
Frontline Medical News

FROM CHEST 2017 ▪ The 1-minute walk test is as effective as the 6-minute walk test at predicting transplant-free survival in patients with idiopathic pulmonary fibrosis (IPF), based on data from 179 adults. The findings were presented at the CHEST annual meeting.

The 6-minute test is often used to evaluate functional capacity in IPF patients, but is not always practical in a busy clinic setting, according to Flavia S. Nunes, MD, of Inova Fairfax Hospital in Falls Church, Va., and colleagues.

"Among the clinical and physiologic predictors associated with survival in IPF, the 6MWT [6-minute walking test] has been increasingly used over the past 5 years as a secondary endpoint in the efficacy analyses of potential therapies for IPF. Validation of shorter time of walking might make the test more feasible to be applied in routine clinical care," Dr. Nunes said in an interview.

To determine the predictive value of the first minute of the 6-minute test, the researchers reviewed data from 142 men and 37 women at a tertiary referral center between May 2010 and February 2017. The average age of the patients was 68 years, the average body mass index was 28.3 kg/m^2, and 27% used oxygen supplementation during the walk test.

Overall, the mean distance for the 6-minute test was 372 m, and the average distance for the 1-minute test was 65 m. Study participants who achieved a 6-minute walk distance greater than 372 m were defined as high walkers, and those with a 6-minute walk distance less than 372 m were defined as low walkers. A strong correlation appeared between the 6-minute distance and 1-minute distance in terms of predicting survival, and 1-year transplant-free survival was significantly better in high walkers than in low walkers (27 months vs. 22 months; $P = .015$).

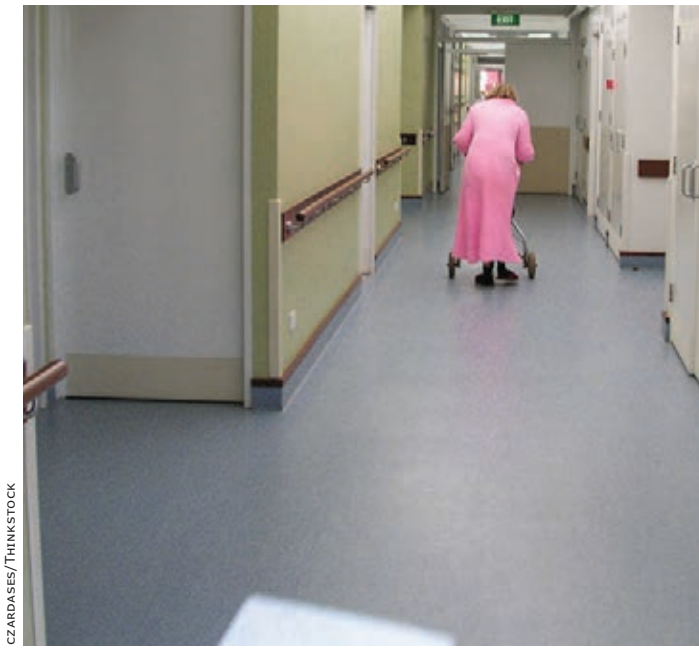
Dr. Nunes said she was not surprised by the results, in part because previous research has shown a strong correlation among 2-minute, 6-minute, and 12-minute walking tests.

Although more research is needed to validate the findings, the results suggest that the 1-minute test might be a practical substitute for the 6-minute test by providing similar prognostic information more quickly and easily than the 6-minute test, the researchers said.

"It is important for clinicians to know that the time chosen to assess exercise tolerance by walking tests might not be critical," said Dr. Nunes. "Shorter walks are not only less time consuming, and easier for both patients and clinicians, but are also reproducible and discriminatory of survival.

"We need to validate the test performance characteristics and prognostic value of distance walked in a 1MWT compared to the standard 6MWT in an independent cohort of patients with IPF," Dr. Nunes noted. "Additionally, the evaluation of alternate instruction, for example changing the wording from 'walk as far' to 'walk as fast' might facilitate a better effort, and a greater distance with improved reproducibility. Other novel parameters and modifications to the 6MWT or 1MWT might further improve the utility of these tests in the management of IPF and other patients," she added.

The researchers had no financial conflicts to disclose.



CZARDASES/THINKSTOCK

Continued from page 24

justed baseline, the panel wrote. "Increased posttransplantation survival means that many transplant patients will enter older age groups where there is an increased risk of cancer." Screening should be performed after recovery and within 2 years, unless there was a negative colonoscopy in the 5 years before transplant.

- Thereafter, patients who have had a solid organ transplant should undergo colonoscopy every 5 years, based on their life expectancy. "In cases where the expected survival time is limited (less than 10 years), screening should not be performed. For adults appropriately selected, lung transplantation usually increases survival probability. Therefore, a lung transplantation candidate with a short life expectancy is likely to become a screening candidate before and after transplantation at the appropriate ages described here, because the potential survival increases to approximately 10 years."
- Colonoscopy should be repeated every 3 years on CF patients with transplants with a history of adenomatous polyps. This interval may be as short as 1 year for patients with high-risk, large, or multiple polyps.
- CF patients should undergo more intense bowel prep for colonoscopy, with three to four washes of a minimum of 1 liter of purgative per wash; the last wash should occur 4-6 hours before the procedure. Split-prep regimens (several smaller-volume washes) are better than a single larger-volume wash. The panel suggested a sample CF-specific regimen available from the Minnesota Cystic Fibrosis Center.

The new document reflects expert consensus on the currently available data, the panel said. As more data emerge, the recommendations might change.

"It is possible that different subpopulations will need more or less frequent schedules for rescreening and surveillance. Our recommendations are making an effort to balance the risk of missing advanced colorectal cancer and minimizing the burden and risk of too frequent examinations."

None of the panel members had any financial disclosures.

msullivan@frontlinemedcom.com

SOURCE: Hadjiliadis D et al. Gastroenterology. 2017 Dec 28. doi.org/10.1053/j.gastro.2017.12.012.

Comparing arterial ratios may aid IPF risk assessment

BY HEIDI SPLETE
Frontline Medical News

FROM CHEST 2017 ▪ An arterial ratio can help identify idiopathic pulmonary fibrosis (IPF) patients with a poor prognosis, suggests the findings of registry data from 50 adults. Such patients might benefit from pharmacotherapy or transplants, the researchers noted.

The ratio of the main pulmonary artery diameter (PA) to the ascending aorta diameter (A) as seen on a chest CT correlates with pulmonary artery pressure, M. Faisal Siddiqui, MD, a pulmonologist in New York, and his colleagues wrote in an abstract from the agenda of the CHEST annual meeting. To determine whether higher PA:A ratios were associated with more biomarker abnormalities, the researchers reviewed 122 CT scans from 50 adults with IPF.

Overall, 48% of the patients had a PA:A ratio of at least 1, according to Dr. Siddiqui and his coauthors. These patients had significantly higher fibrosis scores ($P = .0006$), GAP index scores ($P = .0144$), brain natriuretic peptide scores ($P = .0046$), and pulmonary arterial systolic pressure ($P = .0063$) compared with patients who had PA:A ratios of less than 1, according to the Kruskal-Wallis test. This test also showed no significant differences on measures of coronary artery calcium, aortic value calcifications, mitral valve calcifications, bronchial wall thickening, emphysema, and spirometry data between the two patient groups, based on PA:A ratios.

Use of the Pearson correlation revealed a positive relationship between PA:A ratios greater than 1 and coronary artery calcium scores, fibrosis scores, and pulmonary arterial systolic pressure, but a negative relationship between a high PA:A ratio and both diffusing capacity and forced vital capacity.

Thee findings were limited by a small study population. Dr. Siddiqui and his coauthors had no financial conflicts to disclose.

RELEASE THE POTENTIAL OF NUCALA

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

Indication

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

Important Safety Information

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

ADVERSE REACTIONS

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

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

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

Benefits of NUCALA:

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

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

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

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

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

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

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

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

Visit **NUCALAHCP.COM** to learn more

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

BRIEF SUMMARY

NUCALA®
(mepolizumab) for injection, for subcutaneous use

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

1 INDICATIONS AND USAGE

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

Limitations of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

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

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

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

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-term Safety

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

6.2 Immunogenicity

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

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

6.3 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Clinical Considerations

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

Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

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

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

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

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

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

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

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

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

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

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

NUCALA is a registered trademark of GSK group of companies.

Manufactured by
GlaxoSmithKline LLC
Philadelphia, PA 19112
U.S. License No. 1727

Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 2/2017 NCL:2BRS

HRS: Consider ablation for asymptomatic atrial fib

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – When the Heart Rhythm Society and several collaborating groups published in October 2017 the first revised consensus statement on atrial fibrillation ablation in 5 years, the document included a novel and perhaps unexpected suggestion: Ablation for asymptomatic atrial fibrillation "may be considered."

This was "the first time" any group of experts suggested an indication potentially existed for ablating asymptomatic atrial fibrillation (AF), Hugh Calkins, MD, said at the annual International AF Symposium.

"You might say 'are you out of your mind recommending ablation for asymptomatic AF?' " conceded

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Hugh Calkins, noted that the statement was a "soft" recommendation.

Dr. Calkins, professor of medicine and director of the arrhythmia service at Johns Hopkins Medicine in Baltimore. But Dr. Calkins quickly added that this was a "soft" recommendation by being in the "may be considered" category, and he also noted that it received broad support from about 90% of the members of the statement's 60-member writing group (Heart Rhythm. 2017 Oct;14[10]:e445-e494).

In addition, he personally believed that an amber light for this strategy made a lot of sense.

"I have done it. I think that catheter ablation has gotten to the point in terms of safety and efficacy that this is reasonable," Dr. Calkins said in an interview.

He also acknowledged that this recommendation is sort of buried in the text of the consensus statement and does not appear in any summary diagram "because the reviewers wanted us to hide it. Only those who are passionate about ablation know about it.

"Our goal was not to send a message that this isn't for everyone. It's for very select patients and for very select operators after a very careful discussion" of the risks and potential benefits from performing the procedure on a truly asymptomatic patient.

The ideal candidate for this approach would be a relatively young patient, say someone in their 50s, who is identified as having AF incidentally, such as someone with an irregular pulse that's found during a routine examination that leads to an ECG and definitive identification

of AF despite the patient's complete denial of having symptoms.

The next step, Dr. Calkins suggested, would be to treat the patient with an antiarrhythmic drug, such as amiodarone or flecainide, and with cardioversion and see whether this stops the AF and makes the patient feel better. If the patient reports improvement, it suggests the AF really is symptomatic and management could then proceed as with any case of symptomatic AF. But if the patient perceives no change and the AF then recurs in a persistent presentation despite drug treatment, the cardiologist could then discuss with the patient the pros and cons of an ablative procedure.

The pros for immediate ablation are that, when left unablated, the patient will face a substantially increased lifetime risk for stroke, dementia, and new-onset heart failure.

The pros for immediate ablation are that, when left unablated, the patient will face a substantially increased lifetime risk for stroke, dementia, and new-onset heart failure, and after 2-3 years of continued

Continued on following page

Continued from previous page

persistent AF the left atrium would remodel and become much less likely to respond to ablation with little prospect for the patient ever returning to a normal sinus rhythm. "It's either a rhythm control strategy now, or we'll leave you in AF for the rest of your life," Dr. Calkins explained. "If I were 50 years old and had asymptomatic AF, there's no way I'd want to have AF for the rest of my life." The risks from ablation are that the procedure has about a 68% success rate and about a 1% rate of complications.

"A patient with asymptomatic paroxysmal AF doesn't have much to lose by waiting and seeing whether symptoms develop, but for the patient with persistent AF there is a penalty for allowing continuous AF, because after 2-3 years you won't be able to successfully ablate it. In the past, we left patients with asymptomatic AF that way for the rest of their life, but now we know that, if patients remain in AF over time, they will lose the option to have it ablated, and their risk of stroke, dementia, and heart failure will increase."

Dr. Calkins has been a consultant or adviser to or received honoraria from Abbott, AtriCure, Boehringer Ingelheim, Boston Scientific, iRhythm, Medtronic, Pfizer, St. Jude, and Toray, He has also received research funding from Boston Scientific and Medtronic.

mzoler@frontlinemedcom.com

Conflicting results for thrombolysis treatment

BY ANDREW D. BOWSER
Frontline Medical News

In patients with acute proximal deep vein thrombosis who were undergoing anticoagulation, adding pharmacomechanical catheter–directed thrombolysis did not reduce risk of the postthrombotic syndrome, according to results of a phase 3, randomized, controlled trial.

Moreover, addition of pharmacomechanical thrombolysis increased risk of major bleeding risk, investigators wrote in a report published in the New England Journal of Medicine (2017;377:2240-52).

The trial results contrast with recent reports from another randomized trial, known as CAVENT, which suggested that pharmacomechanical thrombolysis might help reduce incidence of postthrombotic syndrome (Lancet Haematol. 2016;3[2]:e64-71).

"Our trial, for uncertain reasons, did not confirm these findings," wrote Suresh Vedantham, MD, of Washington University, St. Louis, and his coauthors.

Postthrombotic syndrome is associated with chronic limb swelling and pain and can lead to leg ulcers, impaired quality of life, and major disability. About half of patients with proximal deep vein thrombosis (DVT) will develop the postthrombotic syndrome within 2 years, despite use of anticoagulation therapy, Dr. Vedantham and his colleagues noted.

Pharmacomechanical thrombosis is the catheter-directed delivery of a fibrinolytic agent into the thrombus, along with aspiration or maceration of the thrombus. The goal of the treatment is to reduce the burden of thrombus, which in turn might reduce risk of the postthrombotic syndrome.

However, in their randomized trial known as ATTRACT, rates of postthrombotic syndrome between 6 and 24 months after intervention were 47% in the pharmacomechanical thrombolysis group and 48% in the control group (risk ratio, 0.96; 95% confidence interval, 0.82-1.11; P = .56). Control group patients received no procedural intervention.

Major bleeds within 10 days of the intervention were 1.7% and 0.3% for the pharmacomechanical thrombolysis and control groups (P = .049).

Dr. Vedantham and his coauthors suggested that perhaps the number of patients enrolled (692 in ATTRACT, versus 209 in CAVENT) or the greater use of mechanical therapies in ATTRACT versus longer recombinant tissue plasminogen activator infusions in CAVENT accounts for the differences.

The study was supported by multiple sources, including the National Heart, Lung and Blood Institute, Boston Scientific, Covidien (now Medtronic), Genentech, and others. Dr. Vedantham reported receiving grant support from Cook Medical and Volcano. Some of the other authors reported financial ties to Abbott Vascular, Boston Scientific, Medtronic, and other pharmaceutical and device companies.

chestphysician@frontlinemedcom.com

SOURCE: Vedantham S et al. N Engl J Med. 2017;377:2240-52.

DAPT duration: How low can you go?

BY BRUCE JANCIN
Frontline Medical News

DENVER – Six months of dual-antiplatelet therapy proved equivalent in terms of safety, efficacy, and bleeding risk to the guideline-recommended standard 12 months in ST-elevation MI patients after primary percutaneous coronary intervention (PCI) with a second-generation drug-eluting stent in the randomized DAPT-STEMI trial.

"This trial, for the first time, showed that in the modern DES [drug-eluting stent] era, event-free STEMI patients do not benefit from a prolonged DAPT [dual-antiplatelet therapy] beyond 6 months, as currently recommended, and sets the stage for further dedicated research in this important topic," Elvin Kedhi, MD, PhD, declared in presenting the DAPT-STEMI results at the Transcatheter Cardiovascular Therapeutics annual educational meeting.

DAPT-STEMI was a prospective randomized international study that enrolled 1,100 STEMI patients who underwent primary PCI with the second-generation Resolute Integrity zotarolimus-eluting stent and were placed on 6 months of DAPT. After that truncated period of DAPT, patients who had not had an ischemic or bleeding event or other reason for ineligibility during the initial 6 months were then randomized to continue DAPT for another 6 months in accord with current guidelines or were switched to single-antiplatelet therapy (SAPT) with aspirin.

Among the 861 completers, the composite primary outcome of death, MI, revascularization, stroke, and major bleeding during months 6-24 occurred in 4.8% of the SAPT group, a 27% relative risk reduction compared with the 6.6% rate in the DAPT group. Thus, 6 months of DAPT met the prespecified endpoint of noninferiority compared with the standard 12 months of DAPT, reported Dr. Kedhi, head of interventional cardiology and clinical research and innovation at the Isala Heart Center in Zwolle, The Netherlands.

The secondary composite endpoint of death, MI, stroke, stent thrombosis, or TIMI major bleeding occurred in 3.2% of the SAPT group and 4.3% of the DAPT group, for a 25% relative risk reduction.


DR. KEDHI


DR. KEREIAKES

All individual components of the composite endpoints occurred at the same or lower rate in the SAPT group compared with the DAPT arm, he noted at the meeting, which was sponsored by the Cardiovascular Research Foundation.

At a press conference where Dr. Kedhi presented the DAPT-STEMI results, discussant Dean J. Kereiakes, MD, explained why he didn't find the study results surprising.

"The second- and third-generation stents are better. They're safer. And in STEMI, where you may have multicentric disease and an acute systemic inflammatory process, the other treatments that we're giving – statins, ACE inhibitors, etc. – are also preventing ischemic events," said Dr. Kereiakes, medical director of the Christ Hospital Heart and Vascular Center in Cincinnati.

Press conference moderator Gary S. Mintz, MD, put the DAPT-STEMI findings in perspective: "The need for DAPT has decreased along with all the stent-related complications. There's always been a greater focus on DAPT for preventing events and a relatively lesser focus on the adverse consequences of DAPT. And anybody who's a clinician who takes care of patients knows that drug-related bleeding after stent implantation is not a trivial occurrence," observed Dr. Mintz, chief medical officer at the Cardiovascular Research Foundation in Washington.

DAPT-STEMI isn't the final word on DAPT duration

At a late-breaking clinical trials session, comoderator Eric D. Peterson, MD, noted that, in earlier megatrials such as PEGASUS, DAPT, and PLATO, there were signals that extending DAPT beyond 12 months might be even more beneficial than the guideline-recommended 12 months.

"It seems somewhat counterintuitive that now you have better results with less. Any speculation as to why?" asked Dr. Peterson, executive director of the Duke Clinical Research Institute and professor of medicine at Duke University in Durham, N.C.

"It's true that DAPT reduces the general risk of thromboembolic events, but it does so at a relative risk reduction rate of about 20%, while it augments the bleeding risk by over 200%. And ask yourself, what is the benefit of this 6 months of extra DAPT on the lifelong process of atherosclerosis? It's almost invisible," Dr. Kedhi explained.

Although Dmitriy N. Feldman, MD, of Cornell University in New York, noted that DAPT-STEMI was statistically underpowered to be definitive, he found the results encouraging.

"It's very reassuring that the stent thrombosis rates are quite low: 0.7% and 0.9%. ... This is a very select group – patients had to tolerate the first 6 months of DAPT without MACE events or bleeding. But it is reassuring that in patients who are able to do well at 6 months, this is an option," the interventional cardiologist said.

Session moderator Gregg W. Stone, MD, called DAPT-STEMI "hypothesis generating" in light of its limited size and statistical power.

"At least it raises the concept of shorter-duration DAPT, whereas I'd say before today it was not a concept. We were always talking about prolonging DAPT in the highest-thrombotic risk STEMI patients, and now we can at least think about shortening it, whether for all patients or for higher-bleeding-risk patients," observed Dr. Stone, a professor of medicine at Columbia University in New York.

As a matter of fact, DAPT durations even briefer than 6 months are under active investigation. Dr. Kedhi is co-principal investigator in the Onyx ONE clinical trial, a new prospective, 85-center, randomized, single-blind trial of a mere 1 month of DAPT in 2,000 high-bleeding-risk coronary artery disease patients undergoing PCI with the Resolute Onyx DES or the BioFreedom drug-coated stent.

The DAPT-STEMI trial was funded by Maasstad Cardiovascular Research. Dr. Kedhi reported receiving consultant fees and/or institutional grants from Medtronic, Abbott Vascular, Meril. OrbusNeich, Boston Scientific, AstraZeneca, and Pfizer.

bjancin@frontlinemedcom.com

SOURCE: Kedhi E. TCT 2017.

PCI outcomes not better at top-ranked hospitals

BY ANDREW D. BOWSER
Frontline Medical News

Outcomes after percutaneous coronary intervention (PCI) are not superior when performed in U.S. hospitals ranked as "best" in a prominent national rating system as compared with nonranked hospitals, according to results of a recent retrospective analysis.

Rates of in-hospital mortality, acute kidney injury, and bleeding were similar for hospitals in the 2015 U.S. News & World Report's "Best Hospitals" rankings and nonranked hospitals, Devraj Sukul, MD, reported at the American Heart Association Scientific Sessions.

"These findings should reassure patients that safe and appropriate PCI is being performed across the country," said Dr. Sukul of the division of cardiovascular medicine, University of Michigan, Ann Arbor.

The findings were based on a retrospective analysis of PCIs documented in the National Cardiovascular Data Registry CathPCI Registry.

Dr. Sukul and his colleagues limited their analysis to hospitals that both participated in that registry and performed at least 400 PCIs during July 2014–June 2015. That narrowed it down to 654 hospitals, including 44 out of the 50 hospitals ranked by U.S. News & World Report in 2015.

A total of 509,153 PCIs were performed over the 1-year study period, including 55,550 (10.9%) performed at the top-ranked hospitals.

After adjustment for patient risk, there was no difference in post-PCI in-hospital mortality between top-ranked and nonranked hospitals investigators reported (adjusted odds ratio, 0.96; $P = .64$).

There were also no differences in acute kidney injury (aOR, 1.10; $P = .1$) or bleeding (aOR, 1.15; $P = .052$) for top-ranked vs. nonranked hospitals, according to investigators.

In addition, top-ranked hospitals had a "slightly lower proportion" of appropriate PCI, Dr. Sukul reported.

Continued on following page

Transcatheter valve-in-ring a winner in mitral disease

BY BRUCE JANCIN
Frontline Medical News

DENVER – Transseptal mitral valve implantation of an off-the-shelf, commercially available transcatheter aortic valve replacement (TAVR) in high-surgical-risk patients with a failing surgically implanted mitral ring prosthesis has become a reasonable treatment strategy in light of the interim findings of the ground-breaking MITRAL trial, Mayra E. Guerrero, MD, said at the Transcatheter Cardiovascular Therapeutics annual educational meeting.

Her presentation of the preliminary results of the MITRAL (Mitral Implantation of Transcatheter Valves) trial showed this valve-in-ring (ViR) treatment strategy using the Sapien 3 valve was associated with low 30-day morbidity and mortality rates and impressive symptomatic improvement.

In contrast, another arm of the MITRAL trial showed that placement of the Sapien 3 TAVR valve in high-surgical-risk patients with severe mitral stenosis caused by mitral annular calcification (MAC) of their native valve is a treatment strategy that's not yet ready for prime time, she added at the meeting, which was sponsored by the Cardiovascular Research Foundation.

The ViR arm of the observational multicenter prospective MITRAL trial included 30 patients with extremely high surgical risk and either severe mitral stenosis as defined by a mitral valve area of 1.5 cm^2 or less or moderate mitral stenosis plus severe mitral regurgitation. Access for transcatheter mitral valve replacement (TMVR) was transseptal in 100% of patients.

The technical success rate at exit from the catheterization lab was 70%. The procedural success rate at 30 days was 62%.

Six patients required a second valve. This was mainly because of malpositioning of the first valve with resultant mitral regurgitation; however, this problem became a nonissue as operator experience grew. All six affected patients were alive at 30 days, and four of the six were New York Heart Association (NYHA) functional class I or II.


DR. GUERRERO

In-hospital and 30-day mortality rates were low. There was one cardiovascular death and one noncardiac death in hospital, with no additional deaths through 30 days. No cases of stroke, acute MI, or valve embolization or thrombosis occurred. The mean mitral valve area at 30 days was 2.1 cm^2, although three patients still had a mitral valve area of less than 1.5 cm^2. Three patients experienced acute renal failure requiring hemodialysis. Seventy-five percent of patients had no or only trace mitral regurgitation by echocardiography; the rest had mild regurgitation.

At baseline more than 60% of the patients were NYHA class III, 10% were class IV, and the rest were class II; at 30 days, more than 30% were NYHA class I, 40% were class II, and the rest were class III.

Heart valve design changes, such as a longer inner skirt, might further improve the technical success rate for ViR, according to Dr. Guerrero, an interventional cardiologist at NorthShore University HealthSystem in Evanston, Ill.

Picking the right ring

Studies have shown one-third of recipients of a surgical mitral ring or valve repeat interventions within 10 years, so she made a plea to surgeons: "If we are going to be treating patients with valve-in-ring TMVR, that means when surgeons do a repair they should pick a ring that is amenable to a ViR procedure. So don't use flexible incomplete bands or very rigid rings because those are really difficult to treat later on. We should pick a ring thinking of the future. That ring is going to fail at some point, and when it fails it's going to make our lives much easier if we'd picked the right ring."

MAC TMVR needs more work

In the MAC arm of the MITRAL trial, 96 patients were screened so the researchers could find 30 candidates for TMVR. The 61 rejections were for high risk of left ventricular outflow tract obstruction (LVOTO), embolization, or both.

The technical success rate at exit from the cath lab in the MAC patients was 73%, with a 30-day procedural success rate of 46% and a 19% 30-day mortality. Three patients developed severe LVOTO with hemodynamic compromise.

One transseptal and one transapical TMVR were complicated by LVOTO, both treated by bailout alcohol septal ablation. This led Dr. Guerrero and her co investigators to the concept of preemptive alcohol septal ablation, which they used in seven patients deemed at high risk for LVOTO an average of 6 weeks prior to transseptal TMVR as a successful risk reduction strategy.

Survival climbing with operator experience

"In the early days of the TMVR MAC registry, the 30-day mortality rate was 37%. It came down to 22% in the middle third of the registry, then about 18% in the final third. Now we've got it down in MITRAL to 16.7%, but when you separate the rate in the transseptal versus the transatrial patients, it's 13% versus 20%. The difference is not statistically significant, but it's promising, and I think we are making great progress," Dr. Guerrero said.

The MITRAL trial was partially supported by Edwards Lifesciences. Dr. Guerrero reported receiving a research grant from that company and serving as a consultant to Tendyne Holdings/Abbott and on a speakers bureau for Abiomed.

bjancin@frontlinemedcom.com

SOURCE: Guerrero M. TCT 2017.

Continued from previous page

Appropriate PCIs – defined as those performed according to evidence-based indications – have been increasingly emphasized over the past decade.

Though rates of appropriate PCI were relatively high in both groups, the odds of having an appropriate PCI were nevertheless significantly higher at nonranked hospitals (89.2% for ranked and 92.8% for nonranked hospitals; *P* less than .001).

Although some recent reports suggest hospital-level appropriateness may not necessarily correlate with clinical outcomes, Dr. Sukul remarked, "we believe that PCI appropriateness is an important indicator of quality, serving as a measure of physician decision making when faced with treating the vast array of coronary artery disease presentations."

Dr. Sukul is supported by a National Institutes of Health postdoctoral research training grant.

chestphysician@frontlinemedcom.com

SOURCE: Sukul D. AHA Scientific Sessions 2017.

VIEW ON THE NEWS

Local hospitals do PCI well

It should be welcome news to the public that outcomes of PCI conducted at top-ranked hospitals were not superior to those of procedures performed at nonranked hospitals.

This study addresses what is often the foremost question of a patient and their family in their hometown: Is my local hospital doing a good job? To the extent measured by the variables in this study, it is reassuring that the answer appears to be "Yes."

It is hard to argue that health care should be immune from rankings in an era where consumers have access to ratings for just about every product and service available.

However, the public may be confused regarding the multiple national hospital ranking systems that are available today, particularly since these rating systems do not consistently identify hospitals as top performers.

Each rating system uses different data sources, has its own rating methodology, defines different measures of performance, and has a different focus. Many have argued that transparency will improve health care but, for the public, this is getting to the point of "too much information."

Gregory J. Dehmer, MD, of the Department of Medicine (Cardiology Division) Texas A&M University, and Baylor Scott & White Health, Temple, made the comments above in an accompanying editorial (JACC Cardiovasc Interv. 2017 Nov 1. doi: 10.1016/j.jcin.2017.11.001). He reported no financial relationships relevant to the topic.

Pulmonary Perspectives®

Postoperative pulmonary complications of cardiac surgery

BY CHRISTOPHER NOEL, MD

Cardiac surgery patients are sicker today than in previous decades due to an aging population and a rising complexity in medical care. There is an increasing reliance on noncardiac surgeons to care for these patients. The optimal postoperative providers and structure of the ICU where patients are cared for remain unclear, but what is irrefutable is patients' increased postoperative morbidity. Pulmonary complications are a leading cause of morbidity in these patients, occurring in up to one-fifth of cases (Szelowski LA, et al. *Curr Probl Surg.* 2015;52[1]:531). Common pulmonary complications of cardiac surgery are listed in Table 1. Those complications, captured by The Society of Thoracic Surgeons (STS) Cardiac Surgery Database, include receiving ventilation longer than 24 hours, pneumonia, pulmonary embolism, and pleural effusion requiring drainage (The Society of Thoracic Surgeons. STS National Database. https://www.sts.org/registries-research-center/sts-national-database. Accessed January 9, 2018).

Table 1

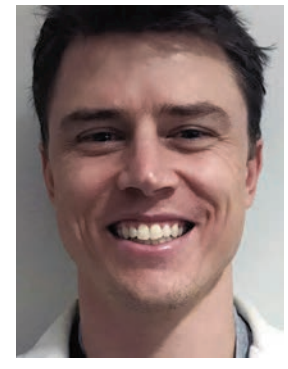
Pulmonary Complications Following Cardiac Surgery

Atelectasis
Pneumonia
Pleural effusion
Pulmonary edema
Phrenic nerve injury
Pneumothorax
Prolonged mechanical ventilation

It should come as no surprise that cardiac surgery can have pronounced effects on lung function. The anesthetic agents, chest wall alteration, and direct lung manipulation can all affect pulmonary parameters. Functional residual capacity (FRC) can decrease by up to 20% with anesthesia (Szelowski LA, et al. *Curr Probl Surg.* 2015;52[1]:531), and the thoracic manipulation and alteration of rib cage mechanics with a classic median sternotomy approach can lead to decreases in forced vital capacity (FVC) and expiratory volume in the first second of forced expiration (FEV_1) that can last for months after surgery. Use of the cardiopulmonary bypass circuit can also lead to bronchoconstriction. These changes in pulmonary function are less pronounced in alternative surgical approaches, such as partial sternotomies (Weissman C. *Seminars in Cardiothoracic and Vascular Anesthesia: Pulmonary Complications After Cardiac Surgery*. Glen Head, NY: Westminister Publications; 2004).

The most frequent pulmonary consequence of cardiac surgery is atelectasis, seen on postoperative chest radiographs in approximately 50% to

Continued on following page



Dr. Noel is a Critical Care Fellow, Cooper Medical School of Rowan University, Camden, New Jersey.

President's Report

As I sit here and write this article, it is hard to fathom that a quarter of my year as the President of CHEST has passed by. Thanks again for this incredibly humbling opportunity to serve as your President.

JOHN STUDDARD, MD, FCCP

I hope many who read this were able to get to Toronto and experience CHEST 2017. Special thanks to our Program Chair, Peter Mazzone, and to his Co-Chair Diane Lougheed from the Canadian Thoracic Society; the Scientific Program Committee; our excellent and committed CHEST 2017 faculty, who give their valuable time to ensure we are delivering the best clinical education possible; and our incredibly talented CHEST staff for all their work to make this meeting a reality.

What a great opportunity to learn and stay up to date while exposed to such meaningful content from so many outstanding clinical educators in so many traditional and innovative ways. For those who were able to be there, I hope you were able to experience the value of learning in a highly interactive setting while taking the opportunity to build and nurture old and new friendships and relationships.

As we move forward, there is so much going on:

1. The Editor in Chief Search Task Force, under the leadership of Dr.. David Gutterman and Nicki Augustyn, is hard at work with their diverse and talented colleagues on this critically important task.

2. The Scientific Program Committee, under Dr. David Schulman's direction, is hard at work building October's CHEST 2018 in San Antonio. It is so exciting to watch this group plan and create, in new and innovative ways, the content for this meeting to be held October 6-10.

3. By the publication date of this article, your Board of Regents most likely will have put the finishing touches, under the leadership of Jenny Nemkovich, our Chief of Staff, on our next 5-year strategic plan.

4. The Board of Regents is also moving forward with a uniform, business-like process and approach in delivering international education offerings and meeting opportunities. Special thanks to Bob Musacchio, our COO and the SVP of Strategy and Innovation, Sue Reimbold, wearing her hat of Market Growth; and Chad Jackson, VP of Innovation and Development, for their direction in this area.

5. Thanks to the Diversity/Inclusion Task Force for their continued work to ensure that the principles of diversity of thought and inclusion permeate all of our conversations and work on the volunteer and professional sides of CHEST.

6. Thanks also to our Training and Transitions Committee and their leadership, Drs. Gabe Bosslet and Matt Miles, and the support of Dr. Richard Irwin and our CHEST® journal for the introduction of the CHEST Teaching, Education, and Career Hub in the journal, which made its debut in January.

7. Also, emphasizing the critical importance of relationships, thanks to our colleagues and partners with so many sister societies with whom we are working closely to help advance the practice of chest medicine. I am confident that we are building better relationships built on common goals, transparency, communication, and trust than we have in many years.

8. Last, and certainly not least, one of the jobs of President I am most looking forward to is serving on the Board of Trustees of the CHEST Foundation as an ex officio member. Having served on this Board for about 10 years, I am so glad to be joining my CF family once again. What an amazing group of volunteers, leaders, and staff serving CHEST and our patients in such amazing ways.

These are but a few of so many things that are transpiring at CHEST. People have asked me if it is intimidating to take on this responsibility. With the support of such diversely talented leaders in our Presidential line; an incredibly mature and engaged BOR; and a CEO, senior leadership, and diverse and talented staff that we have at CHEST, all characterized by incredible intellect and energy, it is pretty easy to be just another member of a great team.

Thanks again for your unwavering support of CHEST and our mission.

Continued from previous page

90% of patients (Szelowski LA, et al. *Curr Probl Surg.* 2015;52[1]:531). Induction, apnea during cardiopulmonary bypass, manual compression of the lungs for surgical exposure, internal mammary harvesting, and pleurotomy can lead to atelectasis in the intraoperative setting while weak cough, poor inspiratory efforts, interstitial edema, and immobility further contribute postoperatively (Weissman 2004). While frequently seen, clinically significant pulmonary consequences from this radiographic finding alone are rare (Weissman 2004).

Pleural effusions are seen on immediate postoperative chest radiographs in the majority of patients. Additionally, 10% to 40% of patients develop pleural effusions 2 to 3 weeks after surgery secondary to postpericardiotomy syndrome. While some effusions require drainage and further intervention (eg, hemothorax), most effusions require no specific treatment and resolve over time (Weissman 2004).

The prevalence of pneumonia following cardiac surgery varies based on differences in study populations and diagnostic criteria, but it remains an important source of morbidity and mortality. In one series, postoperative pneumonia occurred in 3.1% of patients, with higher rates observed in patients who were older, had worse left ventricular ejection fraction, had COPD, experienced longer bypass times, and received more red blood cell transfusions in the operating room (Allou N, et al. *Crit Care Med*. 2014;42[5]:1150). A meta-analysis found that an average of 6.37% of patients developed ventilator-associated pneumonia (VAP), and this rose to 35.2% in those receiving ventilation for greater than 48 hours. Those who developed VAP had an odds ratio of dying of 15.18 (95% CI 5.81-39.68) compared with those who did not (He S, et al. *J Thorac Cardiovasc Surg.* 2014;148[6]:3148).

A small proportion of patients go on to develop ARDS. While relatively uncommon, ARDS carries a high mortality rate. Many possible etiologies for ARDS in cardiac surgery patients have been proposed, including an inflammatory response related to the cardiopulmonary bypass circuit, reperfusion injury secondary to reduced pulmonary blood flow during bypass, protamine administration, transfusion, hypothermia, and lack of ventilation during bypass (Weissman 2004); (Stephens RS, et al. *Ann Thorac Surg.* 2013;95[3]:1122). Type of surgery may also play a role, as patients who undergo aortic surgery are at an even greater risk (Stephens 2013). As with other cases of ARDS, treatment is supportive: low tidal volume ventilation and careful management of fluid balance, as well as paralysis, prone positioning, and consideration for extracorporeal membrane oxygenation (ECMO), as appropriate (Stephens 2013).

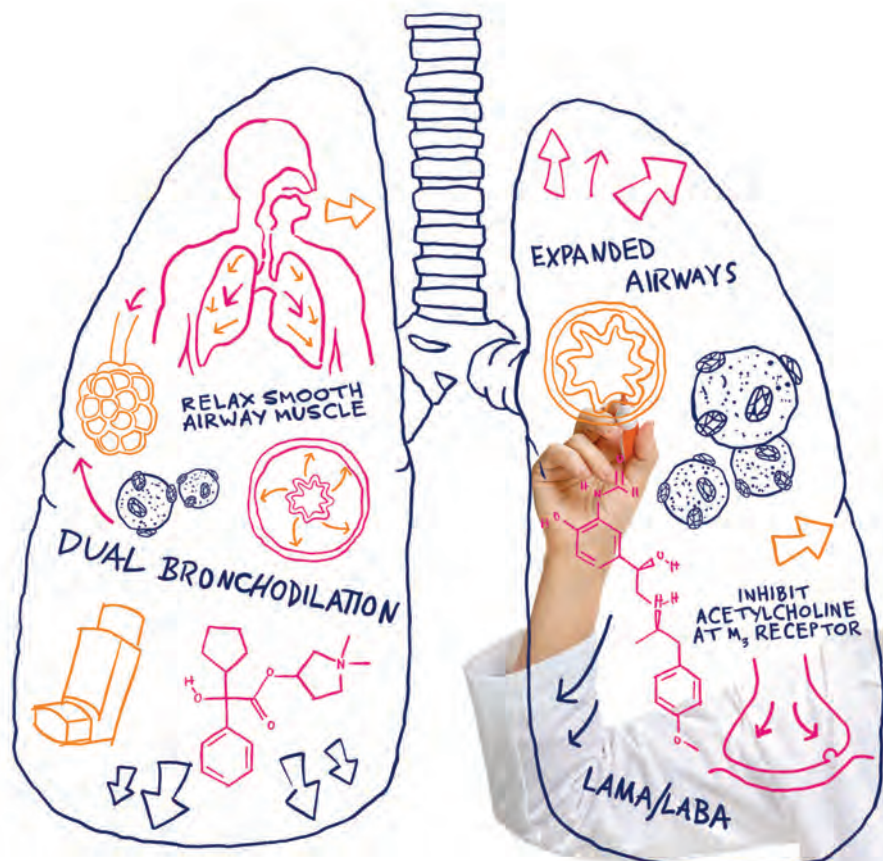
Therapies to prevent postoperative pulmonary complications have included early extubation, aggressive pain control, deep breathing, physical therapy, early mobilization, and noninvasive ventilation in the form of CPAP and intermittent positive pressure breathing. A meta-analysis of 18 trials looking at the use of various forms of prophylactic postoperative physiotherapy did not show a difference in any measured clinical outcome (Pasquina P, Walder B. *Br Med J.* 2003;327[7428]:1379).

However, the heterogeneity, short follow-up, and low quality of included studies made it difficult to draw meaningful conclusions on the benefit or lack thereof for these therapies. More recent studies have shown promise for chest physiotherapy started several weeks prior to elective coronary bypass graft surgery and extended CPAP via nasal CPAP mask immediately following extubation (Hulzebos EH. *JAMA*. 2006;296[15]:1851), (Stephens 2013).

Ongoing areas for improvement include further clarification and standardization of best practices for postcardiac surgery patients, including blood product transfusion, optimal tidal volumes for surgical and postsurgical ventilation, timing of extubation, and the use of preventive therapies in the pre- and postsurgical periods. As providers who care for these patients, understanding how we can improve their postoperative pulmonary recovery will allow us to enhance our patient's experience.

BEVESPI AEROSPHERE®

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



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

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting $beta_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

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

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

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating chronic obstructive pulmonary disease (COPD), which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions occur, in particular, angioedema, urticaria, or skin rash, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction, and instruct patients to contact a physician immediately if symptoms occur

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

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

2017 GOLD Report

LAMA/LABAs RECOMMENDED

1ST-LINE FOR MOST PATIENTS*

MAXIMIZE BRONCHODILATION[1,2†]

Improved lung function including predose FEV_1 and peak FEV_1 at 24 weeks[1,2‡]

In a separate study vs placebo, improvement in peak inspiratory capacity at Day 29[3§‖]

INTELLIGENT FORMULATION[1¶]

Intelligent formulation for a pMDI using patented, phospholipid-based AEROSPHERE™ Delivery Technology[1]

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

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

*Initial treatment in Group B patients with severe breathlessness and in Group D patients.

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

‖In a separate Phase IIIb trial (n=35), there was a significant improvement in the primary endpoint, FEV_1 $AUC_{0\text{-}24}$, on Day 29 vs placebo. Peak inspiratory capacity after the evening dose on Day 29 was a secondary endpoint. Similar results seen in a second Phase IIIb trial (n=75).

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

by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore, BEVESPI should be used with extreme caution in patients being treated with these agents

- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

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

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

‡**PINNACLE 1 & 2 Pivotal Trials:** Two 24-week efficacy and safety studies were conducted in patients with moderate to very severe COPD (n=3699). Inclusion criteria: A clinical diagnosis of COPD; between 40-80 years of age; history of smoking ≥10 pack-years; post-albuterol FEV_1 of <80% of predicted normal values, and FEV_1/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI 18 mcg/9.6 mcg BID compared with placebo BID (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; *P*<0.0001 for all treatment comparisons.[1,2] Trial 1 also included an open-label active control.[1] Statistically significant results were also seen in Trial 2.[1,2] Secondary endpoints included change from baseline in peak FEV_1 at Week 24 for BEVESPI BID compared with placebo BID (291 mL), glycopyrrolate 18 mcg BID (133 mL), and formoterol fumarate 9.6 mcg BID (93 mL); results are from Trial 1; *P*<0.0001 for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[1,2]

§**Separate Phase IIIb Trials (Study A & B):** Two Phase IIIb crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI 18 mcg/9.6 mcg BID compared with placebo BID in patients with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and Study B). Study B also included an open-label active control.[3] Inclusion criteria were consistent with the two 24-week pivotal trials.[1,3] Adverse events were numerically similar across treatment arms.[3] Primary endpoint, FEV_1 $AUC_{0\text{-}24}$: Study A – BEVESPI (n=35) vs placebo (n=31) = 249 mL (baseline FEV_1 1.382 L and 1.345 L, respectively); Study B – BEVESPI (n=65) vs placebo (n=65) = 265 mL (baseline FEV_1 1.328 L and 1.333 L, respectively); both *P*<0.0001.[4] Secondary endpoint, Peak IC (evening): Study A – BEVESPI (n=34) vs placebo (n=30) = 381 mL (baseline IC [evening], 1.980 L and 1.939 L, respectively); Study B – BEVESPI (n=62) vs placebo (n=63) = 312 mL (baseline IC [evening] 1.877 L and 1.913 L, respectively); both *P*<0.0001.[4]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2017. **2.** Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357. **3.** Reisner C, Gottschlich G, Fakih F, et al. 24-h bronchodilation and inspiratory capacity improvements with glycopyrrolate/formoterol fumarate via co-suspension delivery technology in COPD. *Respir Res*. 2017;18:157. **4.** Data on File, 3270300, AZPLP.

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

Learn more at DUALBRONCHODILATION.COM

AstraZeneca

BEVESPI AEROSPHERE™

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

BEVESPI AEROSPHERE contains 28 or 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Asthma-Related Death

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

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

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

Deterioration of Disease and Acute Episodes

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

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

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

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

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

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

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

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

Cardiovascular Effects

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

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

ADVERSE REACTIONS

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

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

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

Clinical Trials Experience

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

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

24-Week Trials

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

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

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

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

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

Long-Term Safety Extension Trial

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

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

DRUG INTERACTIONS

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

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

Non-Potassium Sparing Diuretics

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

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

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

Beta-Blockers

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

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

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

Glycopyrrolate

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

Formoterol Fumarate

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

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom
or By: AstraZeneca Dunkerque Production (AZDP), Dunkerque France

06/17 US-15356 10/17

How Will You Champion Lung Health in 2018?

Our CHEST Foundation grantees are doing amazing research and community service projects that are paving the way for change and improvements in chest medicine. How will you help champion lung health?

"This award carries great importance to me as a young clinician who is in the early phase of my career. I'm driven by my passion for researching this disease (PAH). This award helps establish me as a strong clinical researcher – where I see my career heading. It also helps us identify those clues that can lead to changing how this disease state is treated. Everything starts with an idea."

DR. SAHAY

Sandeep Sahay, MD, FCCP
Houston Methodist Hospital – Houston, Texas
CHEST Foundation Research Grant in Pulmonary Arterial Hypertension
Title: *Alterations of Estrogen Metabolism in the Development of Portopulmonary Hypertension*

"This grant has allowed me to do this project, period. Having support from the CHEST Foundation automatically gives me credibility at my new institution. As I would meet with people to discuss my project, they would see that a big organization is supporting me, and that is the outside validation to show that this must be a useful project. The grant really helps me hit the ground running, and plants the seed to help us do a larger project in the future."

DR. HARRIS

Drew Harris, MD
Yale University – New Haven, Connecticut
CHEST Foundation Research Grant in Asthma
Title: *Utilizing Medical-Legal Partnership to Promote Asthma Health Equity*

"I recently completed my MD, and because of this grant, I am able to do a completely independent research study. I've also been recently short-listed for a clinical lecturer post at my university...which positions me to be the lead for quantitative imaging should I receive the post. This grant added gravitas to my project, and, without it, I don't think I would have had as big of a boost."

"As I would meet with people to discuss my project, they would see that a big organization is supporting me, and that is the outside validation to show that this must be a useful project. The grant really helps me hit the ground running, and plants the seed to help us do a larger project...," said Drew Harris, MD.

Diana Crossley, MBChB
University Hospital Birmingham – Birmingham, England
CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
Title: *Functional Magnetic Resonance Lung Imaging Using Inhaled Hyperpolarised 129Xenon: A Pilot Study of the Clinical Utility in Alpha One Antitrypsin Deficiency (AATD).*

DR. SILVERMAN

"Because of this grant, we are able to be effective teachers to Haitian pediatricians, so they can more effectively intervene and save childrens' lives. We are able to translate these critical care materials into French and provide the best opportunity for learning to our colleagues there."

Adam Silverman, MD
Connecticut Children's Medical Center – Hartford, Connecticut
CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP
Title: *Haitian Pediatric Critical Care Collaborative Training Course*

The CHEST Foundation is accepting grant applications now until March 31 in the following areas:

- CHEST Foundation Research Grant in Lung Cancer – $50,000 - $100,000 2-year grant*
- CHEST Foundation Research Grant in Asthma - $15,000 - $30,000 1-year grant*
- CHEST Foundation Research Grant in Pulmonary Arterial Hypertension - $25,000 - $50,000 1-year grant*
- CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency - $25,000 1-year grant
- CHEST Foundation Research Grant in Pulmonary Fibrosis – $50,000 1-year grant
- CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease – $50,000 1-year grant
- CHEST Foundation Research Grant in Venous Thromboembolism - $15,000 – $30,000 1-year grant*
- CHEST Foundation Research Grant in Nontuberculous Mycobacteria Disease - $30,000 1-year grant
- CHEST Foundation Research Grant in Women's Lung Health - $10,000 1-year grant
- CHEST Foundation Research Grant in Cystic Fibrosis – $15,000 – $30,000 1-year grant
- CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP - $2,500- $15,000 1-year grant

*Amount contingent on funding.

Go to chestfoundation.org/grants to apply now.

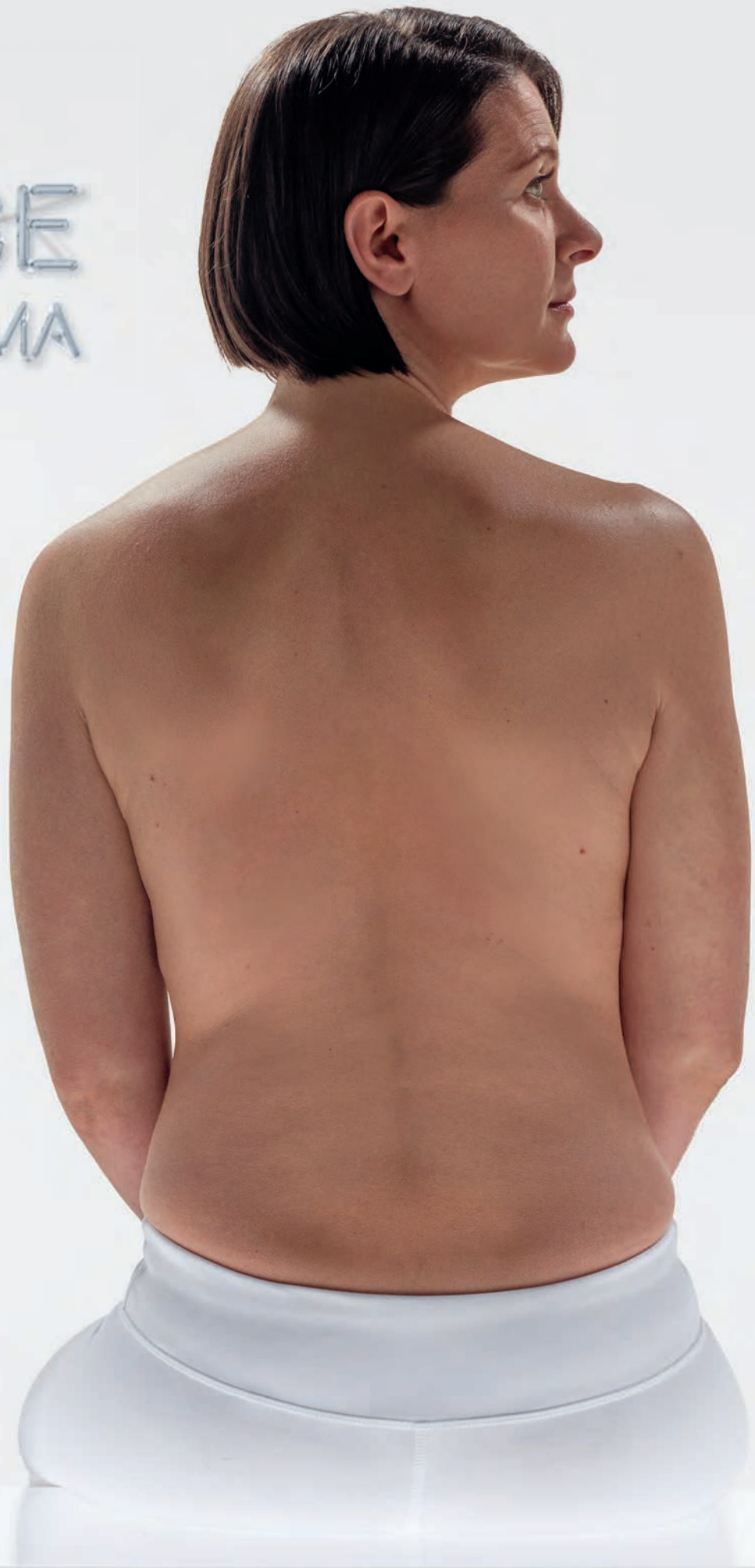
Meet Our CHEST President-Designate

Stephanie M. Levine, MD, FCCP, is an expert in lung transplantation, pulmonary and critical care issues in pregnancy and women's lung health, and eosinophilic lung disorders. She is a Professor of Medicine in the Division of Pulmonary Diseases and Critical Care Medicine at the University of Texas Health Science Center in San Antonio, Texas; the Program Director of the Pulmonary and Critical Care Fellowship at the University of Texas Health Science Center; and the Director of the Medical Intensive Care Unit and Bronchoscopy Laboratory at the University Hospital. She also is a staff physician at the Audie Murphy Veteran Administration Hospital. Dr. Levine has authored or co-authored over 270 manuscripts, chapters, reviews, editorials, and abstracts, primarily in her major field of interest, lung transplantation. She has been Editor of both Critical Care SEEK and Pulmonary SEEK. In 2009, she received the CHEST Presidential Citation Award; in 2010, the CHEST Distinguished Service Award; and in 2017, the Master Clinician Educator Award. Dr. Levine has been active in CHEST international activities with CHEST World Congress meetings, the 2017 Basel Joint CHEST/SPG Congress in collaboration with the Swiss Lung Association, and with the pulmonary/critical care subspecialty training programs being developed in China. She was President and Chair of the CHEST Foundation from 2010-2014 and is currently on the CHEST Board of Regents. Dr. Levine's presidential term will begin in October 2019.

DR. LEVINE

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

Do you know what's driving her **severe asthma?**



AstraZeneca

ILLUMINATEOSINOPHILS

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

Elevated eosinophils are seen in the airways of approximately 50% of patients with severe asthma, and are a **direct cause of chronic inflammation**, which can lead to progressive damage in the airways.[1-3]

Patients with eosinophilic asthma (e-asthma) can experience frequent exacerbations requiring oral corticosteroid (OCS) use, emergency visits, or hospitalizations.[3,4,5] Use of OCS may leave patients susceptible to **steroid-associated adverse events and comorbidities**.[6]

Learn more about how testing patients for e-asthma can help inform clinical decision making at illuminatEOS.com

References: 1. Wenzel S. Severe asthma in adults. *Am J Respir Crit Care Med*. 2005;172:149-160. **2.** Trivedi SG, Lloyd CM. Eosinophils in the pathogenesis of allergic airways disease. *Cell Mol Life Sci.* 2007;64(10):1269-1289. **3.** de Groot JC, Ten Brinke A, Bel EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res.* 2015;1:1-11. **4.** de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res.* 2016;2(2):1-8. **5.** Zeiger RS, Schatz M, Li Q, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract*. 2014;2:741-750. **6.** Lefebvre P, Duh MS, Lafeuille MH, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol.* 2015;136(6):1488-1495.

AstraZeneca

Critical Care Commentary

On Diagnosing Sepsis

BY STEVEN Q. SIMPSON, MD, FCCP

Two years ago, a panel appointed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, referred to as a consensus conference, proposed a new definition for sepsis and new diagnostic criteria for sepsis and septic shock, known as Sepsis-3 (Singer M, et al. *JAMA*. 2016;315[8]:801). The panel proposed that sepsis be defined as life-threatening organ dysfunction due to a dysregulated host response to infection. Upon reflection, one could see that what we had called definitions of sepsis, severe sepsis, and septic shock for over 2 decades actually represented diagnostic criteria more than concise definitions. In that regard, a concise definition is a useful addition in the tool kit for training all health-care professionals to recognize sepsis and to treat it early and aggressively.

However, the diagnostic criteria leave something to be desired, in terms of both practicality and sensitivity for detecting patients whose infection has made them seriously ill. Those who participate in quality improvement efforts in their own hospitals will recognize that to promote change and to achieve a goal of better, higher quality care, it is important to remove obstacles in the system and to structure it so that doing the right thing is easier than not doing it. For sepsis, the first step in the process, recognizing that sepsis is present, has always been complex enough that it has been the bane of the enterprise. As many as two-thirds of patients with sepsis presenting to the ED with severe sepsis never receive that diagnosis while in the hospital. (Deis AS, et al. *Chest.* 2018;153[1]:39). As any sepsis core measure coordinator can attest, diagnostic criteria that are readily visible on retrospective examination are often unnoticed or misinterpreted in real time.

The crux of this issue is that the very entity of sepsis is not a definite thing but a not-quite-focused idea. Much is known of pathophysiologic features that seem to be important, but there is no one unifying pathologic condition. Contrast that with another critical illness, myocardial infarction. The very name states the unifying pathology. Our predecessors were able to work backward from an understanding that acute blockage of a small artery led to ischemia and infarction, in order to identify methods to detect it while it is happening—measuring enzymes and evaluating an ECG. For sepsis, we don't even understand why patients are sick or why they die. There is a complex interaction of inflammation, microcirculatory thrombosis, mitochondrial dysfunction, immune suppression, but there is no one combination of those things that is yet understood in a way that lends itself to diagnostic testing. The best we can say is that the patient reacted to their infection in a way that was detrimental to their own body's functioning. Rather than recognizing a few symptoms and sending a confirmatory test, with sepsis, we must tote up the signs and symptoms in the domains of recognizing infection and recognizing organ dysfunction, then determine whether they are present in sufficient amounts; it is an exercise that requires mental discipline.

The very entity of sepsis is not a definite thing but a not-quite-focused idea. Much is known of pathophysiologic features that seem to be important, but there is no one unifying pathologic condition.

If the diagnostic criteria we use, whether Sepsis-1, 2, or 3, are all gross descriptions of complex internal interactions that are not specific, then the syndrome that any of these criteria identifies is also not specific for anything particular. It falls to the medical community, as a whole, to determine exactly what it is that we desire a given syndrome to be indicative of. The Sepsis-3 authors decided that the appropriate syndrome should predict death or prolonged ICU stay. They used several large data sets to develop and validate infection-associated variables that would have good predictive ability for that outcome, and they compared what they found with sepsis by the Sepsis-1 definition, infection plus SIRS (Seymour C, et al. *JAMA*. 2016;315[8]:762). Infection + SIRS is a strawman in this comparison, because they tested its predictive ability for the outcome against that of the Sequential Organ Failure Assessment (SOFA) and the Logistic Organ Dysfunction Score (LODS). These two scoring systems were developed as severity of injury scales and validated as mortality predictors; the higher the score, the likelier mortality, whereas SIRS clearly contains no information about organ dysfunction. The comparator of interest for this outcome is actually severe sepsis, infection plus SIRS plus organ dysfunction.

Although the criteria the Sepsis-3 investigators used for defining patients with suspected infection were novel and reasonable, we lack additional important information about the patients they studied. They did not report the spectrum of treatments for sepsis in their cohort, whether early or late, adequate or inadequate, so it is impossible to determine whether the criteria address patients who are undertreated, patients who are treated late, patients who will die regardless of adequate therapy, or some combination. In other words, there is no way to tell whether patients who were recognized early in their course via Sepsis-1 criteria and treated aggressively and effectively may have avoided shock, ICU admission, and death. It is, of course, the business of physicians and nurses to help patients avoid exactly those things. Multiple studies have now demonstrated that SIRS criteria are more sensitive than SOFA-based screens, specifically qSOFA, for identifying infection with organ dysfunction, and that qSOFA is more specific for mortality (Serafim, et al. *Chest.* 2017; http://dx.doi.org/10.1016/j.chest.2017.12.015).

Dr. Simpson is Professor, Interim Director; Division of Pulmonary and Critical Care Medicine, University of Kansas, Kansas City, Kansas.

In contrast, the Sepsis-1 authors proposed infection plus SIRS as a sensitive screening tool that could warn of the possibility of an associated organ dysfunction (Sprung, et al. *Crit Care Med.* 2017;45[9]:1564). Previous to the Sepsis-1 conference, Bone and colleagues had defined the sepsis syndrome, which incorporated both SIRS and organ dysfunction (Bone, et al. *Crit Care Med.* 1989;17[5]:389). It was the collective insight of the Sepsis-1 participants to recognize that SIRS induced by infection could be a harbinger of organ failure. The Sepsis-3 authors believe that SIRS is a "normal and adaptive" part of infection and that it is "not useful" in the diagnosis of sepsis. That analysis neglects a couple of important things about SIRS. First, numerous studies demonstrate that infection with SIRS is associated with a mortality rate of 7% to 9%, which is by no means trivial (Rangel-Frausto MS, et al. *JAMA*. 1995;273[2]:117). Second, the components of SIRS have been recognized as representative of serious illness for millennia; the assertion that the Sepsis-1 definitions are not evidence-based is mistaken and discounts the collective experience of the medical profession.

Finally, SIRS is criticized on the basis of being nonspecific. "If I climb a flight of stairs, I get SIRS." This is clearly a true statement. In fact, one could propose that the name could more accurately be Systemic Stress Response Syndrome, though "scissors" is certainly less catchy than "sirs" when one says it aloud. However, the critique neglects an important concept, encapsulated in Bayes' Theorem. The value of any positive test result is largely dependent on the prevalence of the disease being tested for in the population being tested. It is unlikely that the prevalence of sepsis is very high among patients whose SIRS is induced by climbing a flight of stairs. On the other hand, tachycardia and tachypnea in a patient who is indulging in no activity while lying on a bed feeling miserable should prompt a search for both the infection that could be causing it and the organ dysfunction that could be associated with it. The specificity of SIRS derives from the population in which it is witnessed, and its sensitivity is to be respected.

To quote a friend, the remarkable CEO of a small Kansas hospital, "If a patient with an infection feels bad enough that they climb up on that gurney and place themselves at our mercy, we

Continued on following page

Continued from previous page
owe it to them to prove why they don't have sepsis, rather than why they do."

Editor's Comment

The progress made in the last several years emphasizes the importance of early identification and aggressive treatment of sepsis. The Third International Consensus Definitions (Sepsis-3) have sparked great controversy in the sepsis community, because they delay the recognition of sepsis until organ damage occurs. In this Critical Care Commentary, Dr. Steven Q. Simpson asserts with solid arguments that the use of a screening tool with higher specificity for mortality, at the expense of sensitivity, is not a step in the right direction. Moving away from criteria that have been widely adopted in clinical trials and quality improvement initiatives throughout the world can be a setback in the battle to improve sepsis outcomes. Until prospectively validated criteria that allow earlier identification of sepsis are developed, there is no compelling reason for change.

Angel Coz, MD, FCCP
Section Editor

This Month in the Journal CHEST®

Editor's Picks

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

Giants In Chest Medicine
Professor Nan-shan Zhong, MD. By Wei-jie Guan.

Original Research
Long-term Use of Inhaled Corticosteroids in COPD and the Risk of Fracture. By Dr. A. V. Gonzalez, et al.
Cardiac Troponin Values in Patients With Acute Coronary Syndrome and Sleep Apnea: A Pilot Study. By Dr. A. Sánchez-de-la-Torre, et al.
CA-125 in Disease Progression and Treatment of Lymphangioleiomyomatosis. By Dr. C. G. Glasgow, et al.

Evidence-Based Medicine
Cough Due to TB and Other Chronic Infections: CHEST Guideline and Expert Panel Report. By Dr. S. K. Field, et al, on behalf of the CHEST Expert Cough Panel.

Shop the CHEST Store

Have you shopped at the CHEST Store lately? We've recently updated our merchandise to include several new items perfect for staff gifts or for yourself. Along with our old standbys, including lab coats and scrubs, we now feature CHEST-branded scarves, knit caps (perfect for winter), and insulated hot and cold drink mugs. And don't forget, most items are customizable for a small, additional fee. For the more education-inclined, the store also features the best in CHEST print, including CHEST SEEK™ volumes, *Coding for Chest Medicine*, patient education guides, and much more.

Products can be ordered online, and most items are sold onsite at our live learning and board review courses and at the CHEST Annual Meeting. If you can't purchase in person, visit the store at chestnet.org/store to stock up.

CHEST NetWorks

Adult bronchiectasis, asthma therapy, frailty in ILD

Clinical Research

New guidelines for adult bronchiectasis

Clinically significant bronchiectasis is a combination of radiologic bronchial dilatation with clinical symptoms. Guidelines on management of adult bronchiectasis were recently published (*Eur Respir J.* 2017; Sep 10;50[3]).

For all adult patients with clinically significant bronchiectasis, the guidelines suggest standardized minimum testing with differential blood count, serum immunoglobulins, and testing for allergic bronchopulmonary aspergillosis with any further workup on an individual basis. Annual sputum surveillance is suggested for clinically stable adult patients; however, the evidence for this recommendation came from studies done on patients with cystic fibrosis.

Inhaled bronchodilators are suggested as the first-line treatment in symptomatic patients. Long-term antibiotics (greater than 3 months) are recommended in patients with greater than 3 exacerbations/year after optimizing airway clearance and disease-specific treatment.

Continued on following page

In Memoriam

CHEST has been informed of the following members' deaths. We extend our sincere condolences.

Nagesh V Salian, MD, FCCP (2016)
Ted A Calinog, MD, FCCP (2017)
Azam Ansari, MD (2017)
Arthur E. Schmidt, MD, FCCP (2017)

INDEX OF ADVERTISERS

Continued from previous page

Pseudomonas aeruginosa infections are to be treated with inhaled antibiotics (colistin or gentamicin) (Charles SH, et al. *Am J Respir Crit Care Med.* 2014;189[8]975; Murray P, et al. *Am J Respir Crit Care Med.* 2011;183[4]:491; and nonpseudomonal infections are to be treated with macrolides (Conroy W, et al. *Lancet.* 2012;380[9842]:660; Altenburg J, et al. *JAMA.* 2013;309[12];1251), although interchangeable for intolerance. Sputum cultured early will guide therapy among poor responders. Long-term mucolytic agents are suggested in appropriate tolerating patients. Pulmonary rehabilitation for 6-8 weeks is strongly recommended in adult bronchiectasis with impaired exercise capacity. Surgical interventions for bronchiectasis are reserved for a small group of patients who have localized disease and high exacerbation rates despite maximal medical therapy. Inhaled corticosteroids are suggested not to be used in adult bronchiectasis. Guidelines recommend against the use of statins and recombinant human DNase as it increases exacerbations (*Chest.* 1998;113[5]:1329. The task force acknowledged the low quality of evidence for their recommendations requiring more research in the field of adult bronchiectasis.

DR. BAJANTRI

Bharat Bajantri, MD
Fellow-in-Training Member

Airways Disorders

ICS/LABA combo therapy: black box warning removed

Publication of the Salmeterol Multicenter Asthma Research Trial (SMART) in 2006 caused panic among asthmatics and the physicians who treat them (Nelson et al. *Chest*. 2006;129[1]:15). The study suggested that the long-acting beta-2-agonist (LABA) salmeterol leads to an increased risk of asthma/respiratory-related deaths compared with placebo. This finding was more pronounced in the African American subpopulation. The study left many questions unanswered, including whether or not this risk is present when LABA therapy is combined with inhaled corticosteroids (ICS) (O'Byrne. *Chest*. 2006;129[1]:3). Subsequent meta-analyses confirmed the increased risk with LABA monotherapy but not with LABA/ICS (Salpeter et al. *Ann Inter Med*. 2006;144[12]: 904; Jaeschke et al. *Am J Respir Crit Care Med.* 2008;178[10]:1009). Still, a black box warning relating LABA to asthma-related death was applied to LABA/ICS products.

Now that tiotropium is included in the 2017 GINA guidelines, it's only a matter of time before we're debating whether LABA/long-acting muscarinic antagonist is safe for asthmatics.

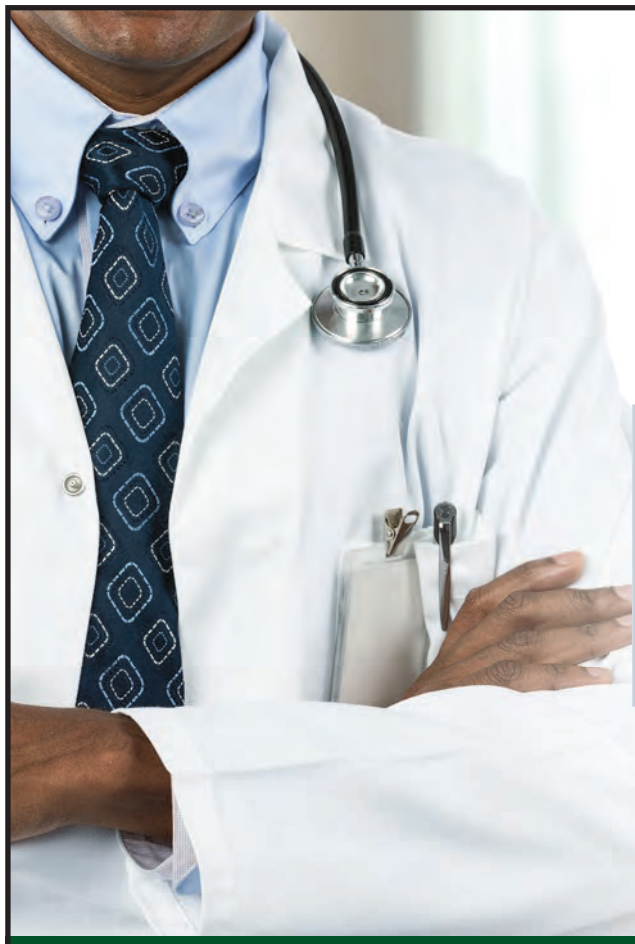
In 2011, the Food and Drug Administration (FDA) mandated large, randomized controlled trials be performed for LABA/ICS products to assess safety. These trials were recently completed, showing no difference in asthma-related deaths between LABA/ICS and ICS alone. There were 41, 297 patients across four trials, three included teenagers and adults (age ≥ 12) and one enrolled children (ages 4-11). These studies prompted the FDA to remove the black box warning from salmeterol/fluticasone, formoterol/budesonide, and formoterol/mometasone (https://wwwfdagov/downloads/Drugs/DrugSafety/UCM589997pdf).

Conclusion: Because LABA/ICS therapy is effective for asthma, most pulmonologists continue to prescribe it despite the SMART study results and FDA warning. In a practical sense, we don't expect the FDA findings to radically change asthma care. Still, it seems we can finally put this question to rest – LABA/ICS is indeed safe for asthmatics. Most physicians will continue to avoid LABA monotherapy, and now that tiotropium is included in the 2017 GINA guidelines, it's only matter of time before we're debating whether LABA/long-acting muscarinic antagonist (LAMA) is safe for asthmatics.

Aaron Holley, MD, FCCP
Steering Committee Member

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

Continued on page 55



Summit Inpatient Pulmonary Services

NOW HIRING

Summit Medical Group, East Tennessee's leading primary care organization, is seeking well-qualified **pulmonary- and critical care-trained physicians** to join our team in Knoxville.

Compensation package

- High income potential
- Employed status and full benefits
- Sign-on bonus and relocation allowance
- 401(k) match, pension plan, CME allowance and paid malpractice
- Health, dental, vision and life insurance group participation
- Flexible, day-shift predominant schedule with minimum night callbacks
- Leadership opportunities

Nestled in the foothills of the beautiful Great Smoky Mountains, Knoxville offers amenities such as no personal or state income tax, low cost of living, excellent schools, outdoor recreational activities, arts, culture and more.

For more information, contact: Jason Edwards
865-584-4747, ext. 7311 • jredwards@summithealthcare.com

To apply, visit SummitMDJobs.com.

Yale University
School of Medicine

THE SECTION OF PULMONARY, CRITICAL CARE & SLEEP MEDICINE IS SEEKING OUTSTANDING INDIVIDUALS

Yale School of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, is seeking candidates to be members of our Pulmonary Vascular Disease (PVD) Center. This academic position will be filled at a rank of: Instructor, Assistant Professor, Associate Professor with qualifications. Experienced candidates who have a specific career interest in advancing PVD research and clinical programs are encouraged to apply. Candidates are expected to have outstanding skills in the clinical and educational arena and will have the opportunity to take an active role teaching and mentoring fellows and residents in clinical & translational research. Successful applicants are expected to make a significant contribution to the clinical, educational, and research missions of the section. The PVD Center at Yale is rapidly expanding clinically, is accredited by the Pulmonary Hypertension Association as a Comprehensive Care Center, and is involved in basic science, translational, and clinical research. The candidates are expected to evaluate and manage all groups of pulmonary hypertension, and should have experience in all forms of PAH management, including oral, inhaled, and infused therapies. Research experience and proven productivity are an advantage. Minimum requirements include: board certification in pulmonary diseases and critical care medicine. All application materials should be submitted electronically to: **http://apply.interfolio.com/46514**

Review of applications will begin immediately, and will continue until the position is filled.

Yale University is an affirmative action/equal opportunity employer and welcomes applications from women, persons with disabilities, protected veterans and members of minority groups.

Continued from page 53

Critical Care

Standardized handoffs in the ICU: room for improvement?

Transitions in patient care are commonplace in the ICU. But handoffs are particularly susceptible to error given the complexity of the patient population. Impacts of less-than-ideal handoffs likely include adverse events, delays in medical diagnosis and treatment, redundant communications, redundant activities such as additional procedures and tests, lower provider and patient satisfaction, higher costs, longer hospital stays, more hospital admissions, and less effective training for health-care providers. Yet, there is great heterogeneity in handoff practiced, and the impact of standardized handoffs in the ICU is unclear (Cochran A. *JAMA Surg.* 2018 Jan 3. doi: 10.1001/jamasurg.2017.5468. [Epub ahead of print]).

DR. GADRE

In a survey of over 600 academic intensivists, 55% of the participants stated that attending handoffs in the ICU should be standardized, yet, only 13% of those participating in handoffs reported using a standardized process (Lane-Fall M. *Crit Care Med.* 2016;44[4]690). Clinician miscommunication contributes to an estimated 250,000 deaths in US hospitals per year (Makary M. *BMJ.* 2016 May 3;353:i2139. doi: 10.1136/bmj.i2139). Standardized handoffs may improve outcomes in the ICU.

In many ICUs that do use standardized sign-out templates, higher clinician satisfaction and fewer unexpected patient events have been reported (Bavare AC. *J Healthc Qual.* 2015;37[5]:267; Nanchal R. *BMJ* Qual Saf. 2017;26[12]:987). In a recent randomized controlled trial, use of a standardized handoff curriculum in the ICU resulted in a significant 3% decrease in communication errors, without any change in the duration of the handoff. There also was a clinician-reported improvement in team communication and patient safety; but no changes in ICU length of stay, duration of mechanical ventilation, or number of re-intubations were noted (*JAMA Surg.* 2018 Jan 3. doi: 10.1001/jamasurg.2017.5440. [Epub ahead of print]).

Unfortunately, despite interest in improving patient handoffs, there are few tools to evaluate the effectiveness of different handoff strategies. Most studies report clinician perceptions rather than patient-centered outcomes. Further research is required to examine the optimal approach to handover communication. However, based on the available evidence, a standardized approach to handoffs is likely better than a nonstandardized format.

Shruti Gadre, MD
Fellow-in-Training Member

Christopher Carroll, MD, FCCP
Vice-Chair

Home-Based Mechanical Ventilation and Neuromuscular Disease

Update on two recent FDA-approved therapies for ALS and SMA

Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are neuromuscular diseases often deteriorating to progressive respiratory failure. Two medications received recent FDA approval and are now available in clinical practice – edaravone for ALS and nusinersen for SMA. We present a balanced overview of the favorable data along with realistic challenges.

DR. LEE

Edaravone (Radicava) is the second FDA-approved medication for management of ALS (Riluzole was approved over 20 years ago). Edaravone is a free radical scavenger that reduces oxidative stress, resulting in a protective effect on neuronal cells. It originally showed promise in acute ischemic stroke in Japan and was subsequently studied for ALS. A phase 3 randomized, double-blind placebo-controlled study performed in Japan (*Lancet Neurol.* 2017;16[7]:505) compared ALSFRS-R scores of a specific subset of ALS patients receiving edaravone vs placebo. This study revealed that patients with early ALS (2 years duration or less) with rapid progression (ALSFRS-R score of 7.5 in 6 months) had a 33% decrease in their degree of progression (reducing their ALSFRS-R score to 5) in the edaravone group. Of note, there was also slowing in the decline of FVC, though not clinically significant. Although the drug was rapidly approved by the FDA, there are obvious challenges that must be recognized. First, it is unclear if patients will discern such a mild degree of slowing of disease progression. In addition, the annual cost may be prohibitive, and lifelong IV administration of the medication for 10 days every month may pose logistical barriers.

Nusinersen (Spinraza) is the first FDA-approved therapeutic medication for spinal muscular atrophy (SMA). SMA is a hereditary neuromuscular disorder leading to degeneration of motor neuron cells and ultimately diffuse muscle weakness and often respiratory failure. Nusinersen is an antisense oligonucleotide that modifies splicing of the *SMN-2* gene to increase production of normal, full-length SMN protein, which is deficient in SMA. The ENDEAR trial (Finkel RS, et al. *N Engl J Med.* 2017;377[18]:1723) was a phase 3, multicenter, double-blind study that enrolled SMA infants to receive nusinersen vs sham. Infants who received treatment had improvements in motor milestones (41% vs 0%) and less permanent-assisted ventilation or death in the nusinersen group (39% vs 68%), a 47% reduction in risk of death. The therapy is safe and tolerable, although there is reported risk of bleeding abnormalities, renal toxicity, and constipation. Administered intrathecally, there is a series of four loading doses, followed by maintenance doses every 4 months – presumably lifelong. Although FDA approved all three SMA subtypes, the eventual impact is uncertain, especially in cases of advanced muscle weakness. There are realistic challenges: the high cost ($125,000/dose), limited longitudinal evidence, technical administration, and limited access.

Pulmonologists should be aware of both medications as new therapeutic options for ALS and SMA; however, the long-term impact is yet to be determined.

Ashraf Elsayegh, MD, FCCP
Steering Committee Member

Won Y. Lee, MD
Steering Committee Member

Interstitial and Diffuse Lung Disease

Frailty as a measure of disease activity in ILD

Frailty is a systemic geriatric syndrome characterized by age-related accumulation of physiologic deficits across several systems with an attenuated response to biological stress. Considering that interstitial lung disease (ILD), particularly, idiopathic pulmonary fibrosis (IPF), is a disease of the aging population, frailty is an emerging area of clinical interest. The biological pathways driving the association of frailty with worse prognosis are complex but hinge on cellular senescence, systemic inflammation, and sarcopenia.

There is a high prevalence of frailty in adults with chronic lung diseases and is associated with worse prognosis. The current literature, though, is mostly derived from patients with COPD. Frailty

Frailty is an emerging area of clinical interest. The biological pathways driving the association of frailty with worse prognosis are complex but hinge on cellular senescence, systemic inflammation, and sarcopenia.

measured using the 42-item patient-reported frailty index is associated with dyspnea severity in patients with fibrotic ILD (Milne et al. *Respirology.* 2017;22[4]:728) and systemic sclerosis-associated ILD (Guler et al. *Respir Med.* 2017 Aug;129:1-7. doi: 10.1016/j.rmed.2017.05.012. Epub 2017 May 25.). The SHARE-Frailty and the Edmonton Frail Scale instruments utilized to measure frailty in the University of Alabama at Birmingham IPF cohort detected a high-percentage of frail and pre-frail patients (Luckhardt et al. *Am J Respir Crit Care Med.* 2017;195:A7012). However, there are differences in targeted domains between the various frailty instruments, and this could affect the identification of the frailty syndrome in patients.

Frailty as a measure of disease activity and progression is not currently employed in clinical trials for ILD, primarily due to lack of standardized tools for this patient population. Future studies designed to utilize the frailty syndrome as outcome measures may further our understanding of the clinical manifestations and underlying mechanisms, as well as identify potential therapeutic interventions for patients with ILD.

Tejaswini Kulkarni MD, MPH
Fellow-in-Training Member

EKOS®

One year later, still faster and even safer.

Very low 2% mortality at one year and continued patient improvement.[1]

Get the same EKOS® efficacy in as little as 2-hr treatment duration, with bilateral total tPA doses as low as 8mg.[2,3] The 2017 OPTALYSE PE randomized, multi-center study showed EKOS® two, four and six-hour treatments all relieved right heart strain, with efficacy similar to EKOS® current treatment and r-tPA doses as low as 8 mg total.[2,3] Now long-term data further proves the efficacy and safety of the EKOS® treatment.[1] Visit www.ekoscorp.com to learn more about the only endovascular device cleared by the FDA for the treatment of pulmonary embolism.

EKOS® — Setting the standard in PE treatment.

1 Sterling, K. "Long-term Results of the OPTALYSE PE trial" as presented at the International Symposium on Endovascular Therapy (ISET) meeting, Hollywood, FL Feb 2018

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

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

The EkoSonic™ Endovascular System is not available for sale in Canada.

FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician.

THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS: Peripheral Vasculature: The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. Pulmonary Embolism: The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25mmHg) or echocardiographic evaluation.

Imagine where we can go.

BTG

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