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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Mitchel L. Zoler/Frontline Medical News

Balanced crystalloids protect kidney better than saline

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Treatment with balanced crystalloid intravenous fluids cut adverse renal events modestly but with statistical significance, compared with 0.9% saline in hospitalized patients in a pair of single-center randomized trials with more than 29,000 total patients.

Despite showing a number needed to treat with balanced crystalloids of roughly 100 to prevent one major renal event, compared with saline, the scope of intravenous fluid use makes even this relatively small improvement potentially important to tens of thousands of patients annually.

"It's a small but clinically important difference," Wesley H. Self, MD, said at the CHEST annual meeting.

"These fluids are used every day and in millions of patients annually in the United States and worldwide. There is no functional cost difference between them, and now we have the data to show that [balanced crystalloid fluids] produce a better patient outcome. It's reasonable to consider changing practice," based on the results, said Matthew W. Semler, MD, a pulmonologist at Vanderbilt University Medical Center in Nashville, Tenn., who led one of the two trials.

At Vanderbilt, where the two studies ran,

IN-HOSPITAL DEATHS REDUCED // *continued on page 4*

Nebulized glycopyrrolate improves lung function in COPD

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Glycopyrrolate, a novel nebulized long-acting muscarinic antagonist (LAMA) in development, was well-tolerated and significantly improved lung function and health status in COPD patients regardless of baseline lung function or age, according to a subgroup analysis of pooled results from two randomized trials.

There are currently no nebulized LAMAs approved for use in the U.S.

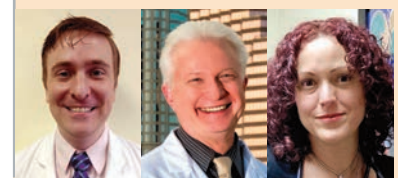
Jill Ohar, MD, FCCP, from Wake Forest University School of Medicine (Winston-Salem, N.C.), presented this secondary analysis of the GOLDEN-3 and GOLDEN-4 trials at the CHEST annual meeting. She and her colleagues evaluated the efficacy and safety of glycopyrrolate in patients with a forced expiratory volume (FEV_1) % predicted of less than 50 and an FEV_1 % predicted of greater than or equal to 50, in age ranges of less than 65 years, greater than or equal to 65 years and at least 75 years, as measured by trough FEV_1.

NEW FORM OF DRUG UPS FEV_1 // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Critical Care Commentary:



***Clostridium difficile* in the ICU**

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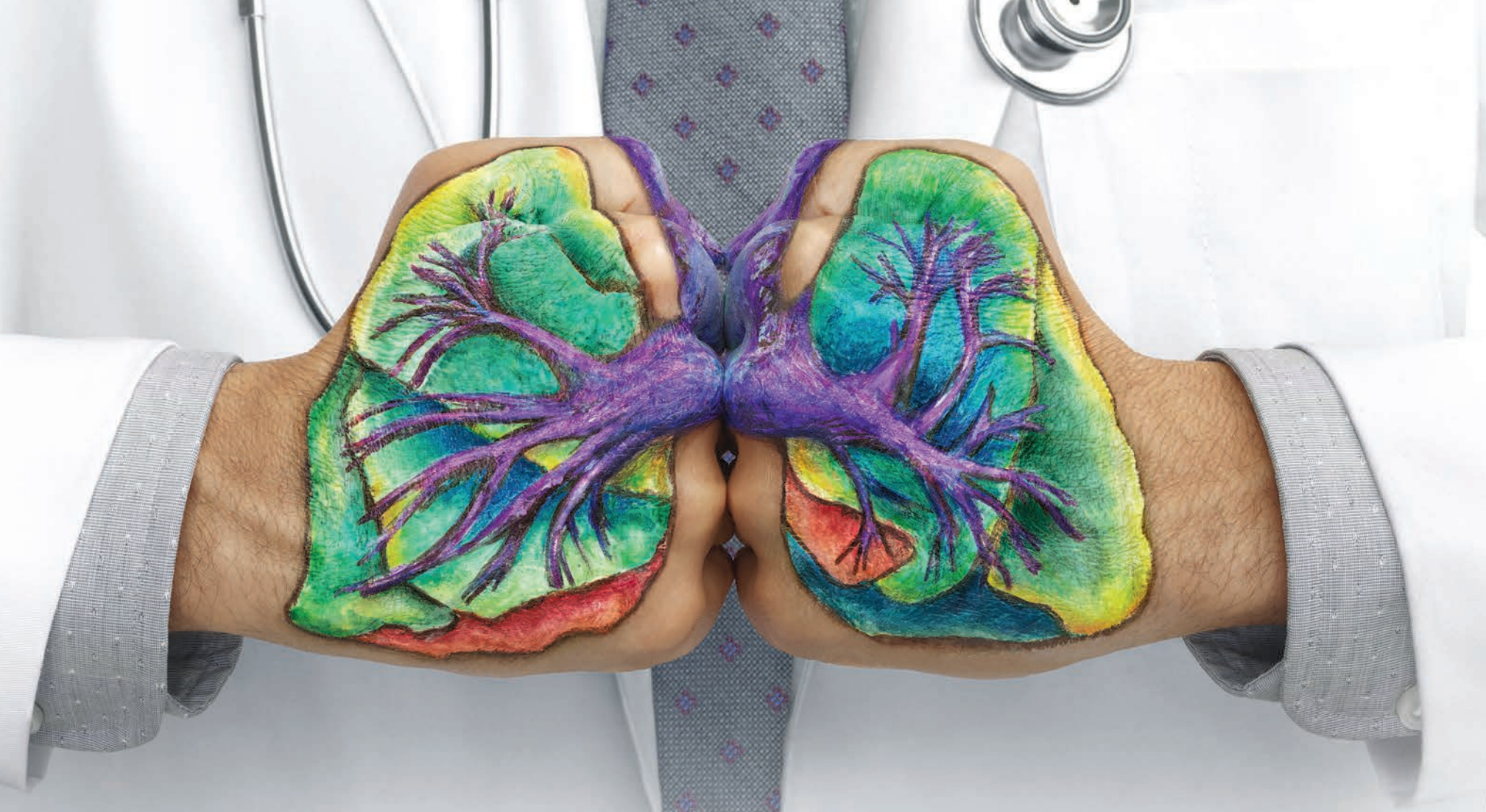

Indication

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

Select Important Safety Information

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

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

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

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

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

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

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

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

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

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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

In-hospital deaths reduced // *continued from page 1*

"we've changed our practice and are transitioning from primarily using saline to primarily balanced crystalloid," Dr. Semler said in a video interview available on www.mdedge.com/chestphysician. The main limitation to changing practice now because of the results is that the two trials both ran at a single center.

The findings Dr. Semler reported came from the Isotonic Solutions and Major Adverse Renal Events Trial (SMART). In this study, 7,860 intensive care unit (ICU) patients were randomized to be treated with a 0.9% saline intravenous fluid, while 7,942 ICU patients were randomized to be given a balanced crystalloid intravenous fluid, either lactated Ringer's or Plasma-Lyte A. The study's primary endpoint was the combined 30-day rate of in-hospital death, incident need for renal replacement therapy, or at least a doubling of the patient's baseline creatinine level, a marker of persistent renal dysfunction.

This outcome occurred in 14.3% of patients on balanced crystalloid fluid and 15.4% on saline, a 1.1% statistically significant ab-

solute difference. The endpoint components showed that patients treated with balanced crystalloid had 0.8% less in-hospital death and 0.4% less incident renal replacement therapy; both of these between-group differences were close to having statistical significance. The two treatment groups showed less difference in the rate of persistent renal dysfunction.

The second trial had an identical design but ran instead in the emergency department. The Saline Against Lactated Ringers or Plasmalyte in the Emergency Department (SALT-ED) trial randomized 6,708 to receive balanced crystalloid and 6,639 to receive saline. The combined primary renal endpoint was 0.9% less frequent with balanced crystalloid fluid, a statistically significant difference, Dr. Self, an emergency medicine physician at Vanderbilt, reported at the meeting. In this study the between-group differences for both incident renal replacement therapy and persistent renal dysfunction were statistically significant in favor of balanced crystalloid, but the between-group mortality difference was not significantly different.

The reason why balanced crystalloid fluid produced better renal outcomes than saline remains unclear. Both Dr. Semler and Dr. Self noted that the two balanced crystalloid fluids used in the study have chloride levels that closely match normal plasma levels, but the chloride concentration in 0.9% saline is about 50% higher than plasma. Some researchers have hypothesized, based on animal findings, that this difference may influence inflammation, blood pressure, acute kidney injury, and renal vasoconstriction.

The SMART and SALT-ED trials received no commercial funding. Dr. Semler had no disclosures. Dr. Self has been a consultant to Abbott Point of Care, BioTest, Cempra, Fering, Gilead, and Pfizer.

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VIEW ON THE NEWS

Fluid switch has big impact for small cost

The SMART and SALT-ED trials were awesome and beautifully planned. The researchers used a pragmatic design that is the wave of the future. The incremental benefit from balanced crystalloid fluids was small, about 1%, but it's a cheap solution. If you administer 7 L of fluid to a patient the incremental cost compared with 0.9% saline is about $45. Based on the number needed to treat that the studies found, this means it would cost less than $5,000 extra to prevent one major adverse kidney event. Nothing else in the ICU or ED compares with that. It's a phenomenal impact from a low-tech intervention.

Bennett P. deBoisblanc, MD, FCCP, is professor of medicine at Louisiana State University Health and director of Critical Care Services at the Medical Center of Louisiana in New Orleans. He had no disclosures. He made these comments from the floor during discussion of the two reports.

New form of drug ups FEV_1

// continued from page 1

"Glycopyrrolate works," reported Dr. Ohar. "It improves FEV_1 [at week 12], not only in the statistically significant manner but in a clinically significant manner, both at the 25-microgram and 50-microgram dose…And when you cut the data according to FEV_1, you again see a statistically significant improvement regardless [of whether] your FEV_1 at baseline was less than 50% of predicted versus greater than or equal to 50%."

DR. OHAR, FCCP

Similarly, both glycopyrrolate doses produced significant (*P* less than .05) and clinically meaningful lung function improvements vs. placebo in participants less than 65 years of age, at least 65 years, and greater than or equal to 75 years.

Glycopyrrolate use for 12 weeks led to greater improvements over placebo in St. George's Respiratory Questionnaire (SGRQ) total score, in patients in both lung function classes. There were a higher percentage of SGRQ responders in the treatment arms, compared with placebo arms.

The highest improvement in SGRQ (−6.287) was seen in the 47 patients that comprised the at-least-75 years of age subgroup receiving glycopyrrolate 25 mcg BID. "It's a small number of people, but I think it's [valuable] to see if the very aged act in any way differently than the entire greater than or equal to 65-year-old group," said Dr. Ohar.

Adverse event rates were similar for placebo and both glycopyrrolate doses, with no safety signals seen according to baseline lung function or age. Few cardiovascular events of special interest were seen.

"Looking at major adverse cardiovascular events, such as fatal MIs, other cardiovascular deaths, arrhythmias, etc., we see nothing that would suggest that the drug overall is associated with an undue number of these versus placebo," reported Dr. Ohar.

Glycopyrrolate use for 12 weeks led to greater improvements over placebo in St. George's Respiratory Questionnaire total score, in patients in both lung function classes. There were a higher percentage of SGRQ responders in the treatment arms, compared with placebo arms.

GOLDEN 3 and 4 were replicate, 12-week, phase 3, randomized, double-blind, placebo-controlled studies that evaluated glycopyrrolate solution administered by an investigational eFlow Close System (eFLOW CS) nebulizer in individuals with moderate-to-very severe COPD, including those with continued background use of a long-acting beta2-agonist (LABA), with or without an inhaled corticosteroid (ICS). In each of the trials, about 30% of patients were on LABA ICS, noted Dr. Ohar in her presentation. A total of 653 subjects were randomized in GOLDEN 3 and 641 in GOLDEN 4.

Its manufacturer, Sunovion Pharmaceuticals, resubmitted the product to the FDA in June 2017 in response to a Complete Response Letter received from the FDA in May 2017. The FDA is expected to act on the new submission on December 15, 2017. The novel agent is being considered for the long-term, maintenance treatment of airflow obstruction in people with COPD, including chronic bronchitis and/or emphysema.

Dr. Ohar reported that she serves on the advisory boards of several pharmaceutical companies. The other three authors are employees of Sunovion Pharmaceuticals Inc.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: If approved, this would represent the first nebulized LAMA available in the U.S. – so in the small population of patients that is unable to utilize standard delivery devices, this would provide an option. It is unclear if this medication must be administered via the proprietary nebulizer that was used in the study – but if so, this would certainly add to the already extremely high cost of respiratory medications and further limit access for many patients.

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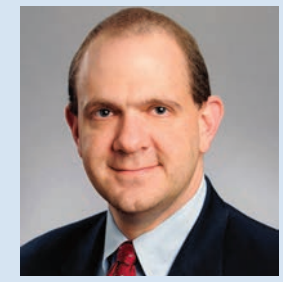
CHEST Physician is available at chestphysician.org.



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

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Revised guidelines raise lung cancer screening age

BY MITCHEL L. ZOLER
Frontline Medical News

Photos Mitchel L. Zoler/Frontline Medical News

Dr. Peter J. Mazzone, FCCP

Dr. Gerard A. Silvestri, FCCP, and Dr. Renda Soylemez Wiener

EXPERT ANALYSIS FROM CHEST 2017 ▪ TORONTO – A proposed change to CHEST's lung cancer screening guideline calls for raising the upper age for screening recent cigarette smokers to 77 years of age from 74 years of age.

This proposal is part of draft guideline that was unveiled during the CHEST annual meeting but is still subject to tweaking by peer review until formal release in early 2018. The draft also offers expanded guidance on how to implement screening, containing three times as many recommendations as the current lung cancer screening guidelines (Chest. 2013 May; 143[5 Suppl]:e78S-e92S).

"We want screening to expand in a safe and effective way," said Peter J. Mazzone, MD, FCCP, chair of the expert panel that is preparing the revision for CHEST and a pulmonologist at the Cleveland Clinic. "We are less restrictive with these guidelines" than in the 2013 version.

Dr. Mazzone cited two major changes that will produce modest broadening of the criteria that determine which patients can appropriately get screening. The clearest change was the age range, which expanded from 55-74 years of age set in 2013 to reflect the age criterion for enrollment in the National Lung Screening Trial (New Engl J Med. 2011 Aug 4; 365[5]:395-409). The panel raised the upper age limit to 77 years of age to coincide with what Medicare covers, Dr. Mazzone explained, though it remains short of the 80-year old ceiling recommended by the U.S. Preventive Services Task Force.

The second, subtler change eased back on the outright ban that the 2013 guidelines placed on screening anyone who falls outside the target age range and smoking history (at least 30 pack years and either being a current smoker or having recently quit within the past 15 years) and who is without severe comorbidities.

The guidelines from 2013 said that screening people who fell outside these limits "should not be performed." In contrast, the new draft guideline simply said that people who fall outside of the age and smoking-history criteria but who are still considered high risk for lung cancer based on a risk-prediction calculator should not "routinely" undergo screening. Additionally, exceptions could be made for certain patients whose high risk appears to warrant screening, Dr. Mazzone and others from the expert panel noted.

The revision specified that a high-risk person outside of the core criteria might still be a reasonable candidate for screening if this person tallies at least a 1.51% risk of developing lung cancer during the next 6 years according to the $PLCO_{M2012}$ risk calculator (New Engl J Med. 2013 Feb 21; 368[8]:728-36).

"Some of the evidence allowed us to be a little more flexible," though not to the point of "opening screening widely" to people who fall outside the core target population; rather, clinicians get to have a little more discretion, said Dr. Mazzone, who directs the Cleveland Clinic's Lung Cancer Program. "We hope this will lead to more patients being screened in a high quality way," he said in an interview. The panel strove to "look beyond the National Lung Screening Trial and find other groups of patients who could benefit" from screening. "We say that other high-risk people should not, on the whole, be screened" but that clinicians could consider individuals as appropriate for screening on a case-by-case basis.

The revision "fills in the outline" for screening that was established in the 2013 guidelines, said Gerard A. Silvestri, MD, FCCP, a member of the revision panel, in a video interview, which is available at mdedge.com/chestphysician.

In addition to four evidence-based recommendations that help define who is and isn't an appropriate screening candidate, the revised guideline also included 11 mostly consensus-based "suggestions" about how screening programs should ideally operate.

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Rapid influenza test obviates empiric antivirals

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – A test that only requires a maximum 2-hour wait for results was highly accurate at detecting influenza and respiratory syncytial virus infection in lung transplant patients, according to research presented at the CHEST annual meeting on Oct. 30.

This rapid and highly accurate test for detecting three common respiratory viruses has dramatically cut the need for empiric treatments and the risk for causing nosocomial infections in lung transplant patients who develop severe upper respiratory infections, Macé M. Schuurmans, MD, FCCP, noted during the presentation.

This study involved 100 consecutive lung transplant patients who presented at Zurich University Hospital with signs of severe upper respiratory infection. The researchers ran the rapid and standard diagnostic tests for each patient and found that, relative to the standard test, the rapid test had positive and negative predictive values of 95%.

The number of empiric treatments with oseltamivir (Tamiflu) and ribavirin to treat a suspected influenza or respiratory syncytial virus infection (RSV) has "strongly diminished" by about two-thirds, noted Dr. Schuurmans, who is a pulmonologist at the hospital.

Until the rapid test became available, Dr. Schuurmans and his associates used a standard polymerase chain reaction test that takes 36-48 hours to yield a result. Using this test made treating patients empirically with oseltamivir and oral antibiotics for a couple of days a necessity, he said in a video interview available on www.mdedge.com/chestphysician. The older test also required isolating patients to avoid the potential spread of influenza or RSV in the hospital.

Mitchel L. Zoler/Frontline Medical News

Dr. Macé M. Schuurmans, FCCP

The rapid test, which became available for U.S. use in early 2017, covers influenza A and B and RSV in a single test with a single mouth-swab specimen.

"We now routinely use the rapid test and don't prescribe empiric antivirals or antibiotics as often," Dr. Schuurmans said. "There is much less drug cost and fewer potential adverse effects from empiric treatment." Specimens still also undergo conventional testing, however, because that can identify eight additional viruses that the rapid test doesn't cover.

Dr. Schuurmans acknowledged that further study needs to assess the cost-benefit of the rapid test to confirm that its added expense is offset by reduced expenses for empiric treatment and hospital isolation.

He had no disclosures. The study received no commercial support.

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Government uncertainty drives jump in ACA silver plan insurance premiums

BY GREGORY TWACHTMAN
Frontline Medical News

Silver plans on the Affordable Care Act insurance exchanges in 2018 will see an average premium increase of 34% nationwide, according to new research from Avalere Health.

"Plans are raising premiums in 2018 to account for market uncertainty and the federal government's failure to pay for cost-sharing reductions," Caroline Pearson, senior vice president at Avalere, said in a statement. "These premium increases may allow insurers to remain in the market and enrollees in all regions to have access to coverage."

Other drivers of this increase include lower than anticipated enrollment in the marketplace, limited insurer participation, insufficient action by the government to reimburse plans that cover higher-cost enrollees, and general volatility around the policies governing exchanges, according to the Avalere research.

The expected premium changes are highly variable by state. Iowa has the highest change in its silver plans, with an average premium increase of 69% for its silver plans, while at the other end of the spectrum, Alaska is actually seeing a 22% decrease.

"These rates may change prior to open enrollment depending on how states respond to the elimination of CSR [cost-sharing reduction] funding for the 2018 plan year," Avalere notes in its new analysis, adding that states may allow plans to refile for rate hikes now that CSR funding is likely dead. "In states where this occurs, it is expected that the newly updated rates will be substantially higher for the 2018 plan year."

There was a glimmer of hope that the CSR payments would resume after a compromise was reached in the Senate Health, Education, Labor & Pensions Committee by Chairman Lamar Alexander (R-Tenn.) and ranking member Patty Murray (D-Wash.) that would offer 2 years of funding along with flexibility in the waiver program to allow states to tweak Affordable Care Act requirements. However, Speaker Paul Ryan (R-Wis.) said the House would not be taking on any more health care action for the remainder of the year.

A spokeswoman from America's Health Insurance Plans said in an interview that, although the CSR payments are no more, premium tax credits still exist to help lower-income individuals obtain insurance coverage.

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VIEW ON THE NEWS

Mike Nelson, MD, FCCP, comments: One need not "google" too long to find that the United States performs quite poorly in overall health care when compared with other nations, despite spending more than any of the comparators...we're 37th this year. This information from Avalere Health portends a further drop in our ranking next year. The privilege of good health is a responsibility of the individual, but the right to affordable health care is a responsibility of the government. It is time for our legislators to stop playing partisan politics and start communicating to propose a workable and affordable solution.

Docs to receive better Medicare pay bump than proposed

BY GREGORY TWACHTMAN
Frontline Medical News

Physicians will see a 0.41% increase to their payments under the Medicare physician fee schedule in 2018, a slight increase from the proposed 0.31% uptick but still short of the 0.5% increase promised under the Medicare Access and CHIP Reauthorization Act (MACRA).

Officials at the Centers for Medicare & Medicaid Services were unable to find adequate funding in so-called misvalued codes to back the larger increase, as required by law, according to the final version of the 2018 physician fee schedule, released Nov. 2 and scheduled for publication in the Federal Register on Nov. 15.

The agency finalized a number of other provisions, including the rollback of reporting requirements for the recently completed Physician Quality Reporting System to better align those reporting requirements with the Merit-based Incentive Payment System requirements of the Quality Payment Program created by MACRA. Similar changes were made to the reporting requirements under the Medicare Electronic Health Record Incentive Program.

"We finalized these changes based on stakeholder feedback and to better align with the MIPS data submission requirements for the quality performance category," CMS said in a fact sheet detailing the provisions of the final rule.

CMS also is delaying the start of the appropriate use criteria (AUC) for imaging services, a program that would deny payments for imaging services unless the ordering physician consulted appropriate use criteria. The program will begin with an educational and operational testing year in 2020. Physicians will be required to start using AUCs and reporting this information on claims, but CMS will pay claims regardless of whether they correctly contain the required AUC data.

"This allows both clinicians and the agency to prepare for this new program," the agency said in the fact sheet. The CMS had proposed 2019 be the educational and operational testing year.

In response to comments submitted to the agency, CMS is changing its policy on billing codes for biosimilars administered under Medicare Part B.

"Effective January 1, 2018, newly approved biosimilar products with a common reference product will no longer be grouped in the same billing code," the agency said in the fact sheet. "By encouraging innovation and greater manufacturer participation in the marketplace, we believe that this policy change will result in the licensing of more biosimilar products, thus creating a stable and robust market, driving market competition, and decreasing uncertainty about access and payment."

The final rule implements proposed expansion of the Medicare Diabetes Prevention Program from a demonstration project to a nationwide program in 2018, however the implementation will be delayed for three months until April 1, 2018, rather than start at the beginning of the year. The program provides payments to physicians based on performance goals being met by patients, including meeting certain numbers of service and maintenance sessions with the program and achieving specific weight-loss goals.

CMS also finalized a number of new telemedicine payment codes.

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VIEW ON THE NEWS

Mike Nelson, MD, FCCP, comments: I always appreciate someone who has the time and willingness to read through, understand and succinctly summarize pertinent points of the Medicare Physician Fee Schedule (MPFS). The good news is that physicians will receive a pay increase and some of the increase in administrative burdens are being delayed. The bad news is that CMS admits that it is not yet ready to act upon some of the changes required by recent law. How do they expect clinicians, who have many fewer resources, to comply with these changes? There are defined comment periods to the MPFS each year and I would encourage all readers to comment. Like voting, it is one of the few ways to have one's voice heard.

More physicians excluded from MIPS

BY GREGORY TWACHTMAN
Frontline Medical News

More doctors will be exempt from participation in the Merit-Based Incentive Payment System in 2018, under a final rule issued by the Health & Human Service Department.

Health care providers will be excluded from MIPS if they have $90,000 or less in Medicare Part B billings, or if they see 200 or fewer Medicare patients next year. These reporting thresholds are higher than the ones from 2017, which were $30,000 or 100 patients, respectively. Providers participating in an advanced alternative payment model also will not be a part of the MIPS track. The "increase in the low-volume threshold is expected to exclude 540,000 clinicians who do not exceed that threshold," officials from the Centers for Medicare & Medicaid Services wrote in the final rule released Nov. 2.

Health care providers will be excluded from MIPS if they have $90,000 or less in Medicare Part B billings, or if they see 200 or fewer Medicare patients next year.

In comments when the rule was a draft, many organizations suggested that CMS allow clinicians who are ready to participate in MIPS to opt in even if they fall into the MIPS low-volume threshold category. While the agency did not codify this suggestion, officials noted that they intend to "revisit this policy in future rule making and are seeking comment on methods to implement this policy in a low-burden manner."

Medical societies were generally in favor of the new higher threshold, but it was met with resistance from associations representing group practices.

"The transition to value is challenging and CMS understandably wants to ease providers into value," Jerry Penso, MD, president and CEO of the American Medical Group Association, said in a statement. "But excluding providers isn't the same as learning how to deliver care in a value-based world. Taking accountability for the quality and cost of care requires years of experience. Despite CMS' intentions to ensure a smooth transition, AMGA is concerned that this rule actually hinders the prospects for value-based care."

CMS is providing a number of enhancements for small practices participating in MIPS.

Small practices (15 or fewer providers) will get five bonus points under MIPS and will continue to earn points for partial data reporting of quality measures. They also will be able to join virtual groups to help aggregate their reporting and improve

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abilities to access payment bonuses.

CMS also is slowly phasing in the cost performance category, which will account for 10% of a MIPS score and will include Medicare spending per beneficiary and total per capita cost measures. These measures are carried over from the Value Modifier program and will require no action from providers to calculate. CMS will measure the performance in this category.

Finally, the agency included a hardship exemption for those affected by major hurricanes in the Gulf Coast and Puerto Rico in 2017. Currently, those who lost access to their EHRs because of the hurricanes, other natural disasters, or public health emergencies can file a hardship exemption to have their Advancing Care Information (formerly the meaningful use program) score reweighted to reflect the issues. Applications must be filed by Dec. 31, 2017.

The final rule extends the reweighting policy to the other three categories (quality, cost, and improvement activities) through the 2018 performance year, with a deadline of Dec. 31, 2018, to file for a hardship exemption.

"Because our policies relating to reweighting the quality, cost, and improvement activities performance categories are not effective until next year, we are issuing an interim final rule for automatic extreme and

uncontrollable circumstances where clinicians can be exempt from these categories in the transition year without submitting a hardship exception application," CMS noted in the fact sheet. For 2017, that means clinicians in areas affected by the hurricanes who do not submit data will not receive any negative adjustment. Clinicians who do submit data will be scored as usual.

"The transition to value is challenging and CMS understandably wants to ease providers into value," said Jerry Penso, MD, president and CEO of the American Medical Group Association.

On the advanced APM track, under which physicians take on more risk in exchange for a potential for greater bonus payments, CMS said it is making it easier for clinicians to participate, including extending for an additional 2 years certain revenue and expenditure provisions that are used to determine nominal risk, changing the medical home models to slow the increase of the minimal amount of financial risk taken on, and making it easier for clinicians to earn bonus payments for APMs that begin or end mid-year.

The final rule was scheduled for publication in the Federal Register on Nov. 16.

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Caprini model is not a good predictor of PE

BY MARK S. LESNEY
Frontline Medical News

The Caprini score, commonly used to risk-stratify patients for the development of venous thromboembolism and to determine the optimal dose of prophylaxis, failed to predict the development of pulmonary embolism and hemodynamically significant PE in patients presenting with deep vein thrombosis (DVT), according to the results of a large, retrospective single-center study.

Recent surgery was not associated with the development of hemodynamically significant PE, but the presence of proximal DVT was, according to a report published

online in the Journal of Vascular Surgery: Venous and Lymphatic Disorders (2017. doi: 10.1016/j.jvsv.2017.08.015).

Nancy Huynh and her colleagues at the Yale University School of Medicine, New Haven, performed a retrospective review of 838 consecutive patients diagnosed with DVT between January 2013 and August 2014 in a single center. They used multivariable analysis to determine predictors of PE and hemodynamically significant PE.

Their results showed that patients who had undergone recent surgery were less likely to develop hemodynamically significant PE (13.3% vs. 27.2%; $P = .01$). In contrast, patients with proximal DVT were at higher risk for development of hemodynamically significant PE (80.7% vs. 64.2%; $P = .007$). They found no association between Caprini score and PE severity ($P = .17$) or the Caprini score and proximal DVT ($P = .89$).

"This study shows that the Caprini score does not correlate with the occurrence of PE or the severity of PE. On the other hand, a proximal location of DVT seems to have a high association with hemodynamically significant PE. Such patients may benefit from more aggressive anticoagulant therapy and work-up for PE," the researchers concluded.

The authors reported that they had no conflicts of interest.

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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, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month 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

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

Systemic and inhaled corticosteroid use may result in the following:

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

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

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

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

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

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

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
	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

IGRA preferred test for latent TB diagnosis

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – U.S.-based pulmonary and infectious disease specialists prefer interferon-gamma release assays (IGRA) over tuberculin skin tests (TST) for the diagnosis of latent TB infection, but may not fully understand how to use and interpret the test results, according to survey results presented at the CHEST annual meeting.

Adam G. Green, MD, conducted the research while he was a fellow in pulmonology/critical care at Montefiore Medical Center in New York. Dr. Green told attendees that about one-third of the world's population are infected with TB and about 15 million of those live in the United States. Two-thirds of U.S. cases are seen in foreign-born individuals and are clustered in four states—New, York, California, Florida, and Texas.

"Epidemiological models have indicated that in order to eliminate the threat of TB in the United States, it will require a strategy of targeting latent tuberculosis infection specifically among foreign-born individuals," he said during his presentation. "This highlights the need for us practitioners on the front line to have sound knowledge of identification, screening, and management of latent TB infection, especially given the multiple modalities for diagnosis."

Among 304 clinicians who responded to an invitation to an online questionnaire, 78% said they preferred to use IGRA over TST and 91% said they had a "good understanding" of how to use and interpret IGRA. However, when queried further on how to best use and interpret IGRAs according to current guidelines, their answers to 11 knowledge-based questions told a somewhat different story, said Dr. Green, who is an intensivist at Cooper University Health Care in Camden, N.J.

While 96% knew IGRAs are not helpful in monitoring response to TB treatment, 20% erroneously thought that a positive IGRA predicts latent TB infection reactivation in the future.

Most respondents correctly answered two "fundamental" questions on cross-reactivity of IGRAs with *Mycobacterium avium* complex and bacilli Calmette-Guérin (BCG) vaccination (84% and 96%, respectively). "While 80% sounds good, I think we're talking about ID and pulmonary docs at the best institutions across the United States, so I would have expected much higher," Dr. Green said.

Only one-third of respondents knew that the T-SPOT.TB test, an IGRA, had the highest sensitivity for identifying those with latent TB infection. And only about half were able to appropriately identify the need to initiate therapy for latent TB in a scenario in which the patient was at "high risk for latent tuberculosis with a positive tuberculin skin test and a negative interferon-gamma release assay."

Fellows comprised 42.5% of re-

Continued on following page

Outcomes better for patients with H1N1 vaccination

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Patients who received an influenza vaccination but still required hospitalization for H1N1 influenza had better outcomes, compared with unvaccinated patients, according to findings from a retrospective study.

In the hospital, vaccinated patients had significantly lower rates of acute kidney injury (6% vs. 35%; *P* = .038) and were more likely to be satisfactorily managed with noninvasive mechanical ventilation (41% vs. 6%; *P* = .004).


DR. CHANDAK

"Even though the vaccine is effective, it's not completely effective in preventing the illness," said Twinkle Chandak, MD, FCCP, a pulmonologist at the Berkshire Medical Center in Pittsfield, Mass., who presented the study at the CHEST annual meeting. The Centers for Disease Control and Prevention reported that 2015-2016 vaccination effectiveness was about 41%, she noted.

Dr. Chandak and her colleagues studied 72 cases of seasonal influenza requiring hospitalization from September 2015 to April 2016 at Berkshire Medical Center, a 300-bed teaching hospital in western Massachusetts. Based on rapid polymerase chain reaction testing, 51 of these patients were positive for H1N1, of which 38 had received a seasonal flu vaccine.

H1N1 patients who had received vaccination were significantly older (70.4 years vs. 59.6 years; *P* = .016) and were more often smokers (76% vs. 38%; *P* = .017), compared with patients who were unvaccinated.

The finding that the unvaccinated patients were younger and still had poorer outcomes "emphasizes the need for widespread vaccination," Dr. Chandak said.

There were several parameters that trended in favor of vaccination, but did not reach statistical significance due to the relatively small sample size, Dr. Chandak said. These included a trend toward more ICU admission in the unvaccinated, compared with vaccinated patients (21% and 12%, respectively; *P* = .699), a longer ICU stay (1.7 days and 0.2 days; *P* = .144), more multiorgan dysfunction syndrome (12% and 6%; *P* = .654), and more acute respiratory distress syndrome (6% and 0%; *P* = .547). Vasopressors were needed in a similar proportion of patients (12% of both groups).

During the 2009-2010 flu season, H1N1 was the cause of about 61 million cases of influenza in the United States, 274,000 hospitalizations, and 12,470 deaths, Dr. Chandak reported.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: "I never take the flu vaccine," my patient stated, following my suggestion that she be inoculated. "It makes me sick."

I reflected on the cases of influenza patients that I took care of the previous year in the ICU: the 50-year-old man with no comorbidities who died in respiratory failure; the 32-year-old pregnant woman who survived a 3-month hospitalization during which she was treated with ECMO and suffered irreversible kidney failure. "I take it every year," I told her.

While the influenza vaccine may not prevent all cases of influenza, those who develop influenza may have an attenuated illness. Data from Chandak and colleagues affirm improved outcomes in patients who receive the vaccine and still develop influenza.

Continued from previous page

spondents and the remainder were attendings of varying levels of seniority. About half of respondents were pulmonologists and the other half infectious disease specialists. The majority (91%) were practicing or training in university hospitals.

One major limitation of the study, said Dr. Green, is the low response rate. "I would have liked 3,000 responses," he said, rather than just over 300.

To disseminate the questionnaire, he contacted pulmonary and infectious disease academic program directors and coordinators and asked them to forward the survey invitation to their full-time faculty and fellows. Dr. Green also acknowledged that his project missed those physicians not working in academic centers.

"I would like to think that the reason people didn't do as well as I had hoped is because of the conflicting literature out there and using not necessarily the guidelines but rather their current knowledge on what was most recently published," said Dr. Green. "But maybe there is a true misunderstanding."

The authors reported there were no product or funding disclosures relevant to this study.

Abnormal potassium level: A red flag in ACS

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – A serum potassium level of at least 5.0 mmol/L or 3.5 mmol/L or less at admission for suspected acute coronary syndrome is a red flag for increased risk of in-hospital mortality and cardiac arrest, according to a Swedish study of nearly 33,000 consecutive patients.

That's true even if, as so often ultimately proves to be the case, the patient turns out not to have ACS, Jonas Faxén, MD, of the Karolinska Institute, Stockholm, reported at the annual congress of the European Society of Cardiology.

"This study highlights that, if you have a patient in the emergency department with a possible ACS and potassium imbalance, you should really be cautious," Dr. Faxén said.

He reported on 32,955 consecutive patients admitted to Stockholm County hospitals for suspected ACS during 2006-2011 and thereby enrolled in the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry.

Overall in-hospital mortality was 2.7%. In-hospital cardiac arrest occurred in 1.5% of patients. New-onset atrial fibrillation occurred in 2.4% of patients. These key outcomes were compared between the reference group – defined as patients with an admission serum potassium of 3.5 to less than 4.0 mmol/L – and patients with an admission serum potassium above or below those cutoffs.

In a multivariate logistic regression analysis adjusted for 24 potential confounders, including demographics, presentation characteristics, main diagnosis, comorbid conditions, medications on admission, and estimated glomerular filtration rate, patients with a serum potassium of 5.0 to less than 5.5 mmol/L were at 1.8-fold increased risk of in-hospital mortality. Those with a potassium of 5.5 mmol/L or greater were at 2.3-fold increased risk.

In contrast, a low rather than a high serum potassium was an independent risk factor for cardiac arrest. An admission potassium of 3.0 to less than 3.5 mmol/L carried a 1.8-fold increased risk of in-hospital cardiac arrest, while a potassium of less than 3.0 was associated with a 2.7-fold increased risk.


Bruce Jancin/Frontline Medical News

Dr. Jonas Faxén

A serum potassium below 3.0 mmol/L at admission also was associated with a 1.7-fold increased risk of new-onset atrial fibrillation.

Session cochair David W. Walker, MD, medical director of the East Sussex (England) Healthcare NHS Trust, observed, "When I was a junior doctor I was always taught that when patients came onto coronary care we had to get their potassium to 4.5-5.0 mmol/L. I think you might want to change that advice now."

The study was funded by the Swedish Heart and Lung Foundation and the Stockholm County Council.

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RELEASE THE POTENTIAL OF NUCALA

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

Indication

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

Important Safety Information

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

ADVERSE REACTIONS

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

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

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

Benefits of NUCALA:

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

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

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

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

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

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

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

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

Visit **NUCALAHCP.COM** to learn more

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

BRIEF SUMMARY

NUCALA®
(mepolizumab) for injection, for subcutaneous use

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

1 INDICATIONS AND USAGE

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

Limitations of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

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

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-term Safety

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

6.2 Immunogenicity

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

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

6.3 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Clinical Considerations

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

Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

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

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

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

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

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

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

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

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

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

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

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

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

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Cardiogenic shock boosts PAH readmissions 10-fold

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Cardiogenic shock, acute kidney injury, and chronic obstructive pulmonary disease were the top drivers of 30-day rehospitalizations in U.S. patients after an index hospitalization for pulmonary artery hypertension, based on an analysis of U.S. national data from 2013.

An episode of cardiogenic shock boosted 30-day rehospitalizations nearly 10-fold in recently discharged pulmonary artery hypertension (PAH) patients. A history of chronic obstructive pulmonary disease (COPD) linked with a threefold higher rehospitalization rate, and acute kidney injury linked with a doubled number of 30-day rehospitalizations, Kshitij Chatterjee, MD, said at the CHEST annual meeting.

"We were surprised" that acute disorders – cardiogenic shock and acute kidney injury – played such a key role in triggering readmissions, said Dr. Chatterjee, a hospitalist at the University of Arkansas for Medical Sciences in Little Rock. He contrasted the impact of these acute disorders on PAH with the main drivers of rehospitalization for other diseases, such as COPD and pneumonia, that more often link with chronic comorbidities.

The powerful impact of cardiogenic shock in particular suggests that interventions that improve patient compliance with stabilizing treatments following an index PAH hospitalization might be effective at preventing a patient's quick return to the hospital. Contacting PAH patients a week after their index hospitalization discharge to make sure they are compliant with their diuretic regimen, for example, might help prevent a decompensation that then leads to cardiogenic shock and a return trip to the hospital, Dr. Chatterjee suggested.

Follow-up of PAH patients after an index hospitalization "is probably the single most important thing, because it can help with compliance," he said in an interview.

The rehospitalizations he studied could be for any cause. His analysis showed that the most common cause of rehospitalization was heart failure, which caused 23% of the rehospitalizations, followed by pulmonary hypertension that caused 20%, and acute kidney injury, responsible for 11% of the 30-day rehospitalizations.

Dr. Chatterjee's study used data collected during 2013 in the National Readmissions Database, run by the federal Agency for Healthcare Quality and Research. During that period, 776 patients entered a U.S. hospital with a primary diagnosis of PAH. During the 30 days following discharge, 114 (15%) returned to the hospital. During the second hospitalization 8% died, and the median length of stay for those who remained alive was 7 days.

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Two NOACS linked to increase in GI bleeding risk

BY AMY KARON
Frontline Medical News

Compared with conventional anticoagulants, both dabigatran and rivaroxaban conferred small but statistically significant increases in the risk of major gastrointestinal bleeding in a systematic review and meta-analysis of randomized trials reported in Clinical Gastroenterology and Hepatology. (doi: 10.1016/j.cgh.2017.04.031)

But other novel oral anticoagulants (NOACs) showed no such effect compared with warfarin, aspirin, or placebo, reported Corey S. Miller, MD, of McGill University, Montreal, and his associates. "The

Continued on following page

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potentially increased risk of GI bleeding associated with dabigatran and rivaroxaban observed in some of our subgroup analyses merits further consideration," they wrote.

The NOACs (also known as non–vitamin K antagonist oral anticoagulants) help prevent stroke in patients with atrial fibrillation and prevent and treat venous thromboembolism. However, large AF trials have linked all except apixaban to an increased risk of major GI bleeding, compared with warfarin. Dabigatran currently is the only NOAC with an approved reversal agent, "making the question of GI bleeding risk even more consequential," the authors wrote.

They searched the MEDLINE, EMBASE, Cochrane, and ISI Web of Knowledge databases for reports of randomized trials of NOACs for approved indications published between 1980 and January 2016, which identified 43 trials of 166,289 patients. Most used warfarin as the comparator, but one study compared apixaban with aspirin and six studies compared apixaban, rivaroxaban, or dabigatran with placebo. Fifteen trials failed to specify bleeding sources and therefore could not be evaluated for the primary endpoint, the reviewers noted. In the remaining 28 trials, 1.5% of NOAC recipients developed major GI bleeding, compared with 1.3% of recipients of conventional anticoagulants (odds

Continued on following page

Intubation may increase cardiopulmonary risk

BY ANDREW D. BOWSER
Frontline Medical News

Prophylactic endotracheal intubation (PEI) prior to endoscopy for upper GI bleeding in critically ill adults may actually increase, rather than decrease, the risk of unplanned cardiopulmonary events, according to results of a retrospective cohort study.

The risk of patients developing pneumonia increased significantly, according to study author Umar Hayat, MD, Medicine Institute, Cleveland Clinic, and colleagues.

"The practice of PEI ... might be a factor that leads to this dreaded outcome [pneumonia] in patients presenting with upper GI bleeding, instead of preventing it," Dr. Hayat and colleagues wrote (Gastrointest Endosc. 2017;86:500-9. doi:10.1016/j.gie.2016.12.008).

The role of PEI in mitigating risk of cardiopulmonary adverse events remains controversial for patients presenting with upper GI bleeding, who can have mortality rates as high as 10% for nonvariceal bleeds and 20% for variceal causes, they said.

Data for 365 patients who had brisk upper GI bleeding were reviewed. The average patient age was 59 years and 64% were male; 144 (39.5%) underwent PEI prior to esophagogastroduodenoscopy (EGD).

The composite primary endpoint of the study, cardiopulmonary unplanned events, was defined as occurrence of pneumonia, pulmonary edema, acute respiratory distress syndrome, shock/hypotension, arrhythmia, myocardial infarction, or cardiac arrest within 48 hours of EGD. The final analysis included 200 intubated and nonintubated patients matched on a 1:1 basis using propensity score matching.

Post-EGD adverse outcomes were more common in patients who had undergone PEI prior to EGD (odds ratio, 3.8; 95% confidence interval, 1.4-10.2), published data show. The rate of unplanned cardiopulmonary events was 20% for intubated patients, compared with 6% for nonintubated patients (P = .008).

Continued from previous page

ratio, 0.98; 95% confidence interval, 0.80-1.21). Five trials of dabigatran showed a 2% risk of major GI bleeding, compared with 1.4% with conventional anticoagulation, a slight but significant increase (OR, 1.27; 95% CI, 1.04-1.55). Eight trials of rivaroxaban showed a similar trend (bleeding risk, 1.7% vs. 1.3%; OR, 1.40; 95% CI, 1.15-1.70). In contrast, subgroup analyses of apixaban and edoxaban found no difference in risk of major GI bleeding versus conventional treatment.

One author received research grants and speaker honoraria from Boehringer Ingelheim Canada, Bayer Canada, Daiichi Sankyo, Bristol-Myers Squibb, and Pfizer Canada; another author disclosed serving as a consultant to Pendopharm, Boston Scientific, and Cook.

Lung injury risk higher with apheresis blood products

BY ROXANNE NELSON
Frontline Medical News

SAN DIEGO – The method of manufacturing can markedly influence the interaction of products containing red blood cells and lung cells, according to research presented at the annual meeting of the American Association of Blood Banks.

Compared with other RBC products, those derived from apheresis significantly increased pulmonary cell interleukin (IL)–6 and IL-8 production, and this was further exacerbated by cell stretching. Conversely, red cell–filtered products appeared to be the least likely to cause cell injury.

"Several studies have shown that red blood cell transfusion is associated with acute lung injury, and transfusion induces leakage in ICU patients," said lead study author Mathijs Wirtz, MD, of the Academic Medical Center, Amsterdam.

ICU patients who did not receive any transfusions had significantly lower leakage than those who were transfused. "There also seems to be a synergy between transfusion and mechanical ventilation," Dr. Wirtz said.

Studies have also shown that there are differences in the prevalence of transfusion-related acute lung injury when comparing Europe to the United States. Storage and manufacturing methods do differ between Europe and the United States, Dr. Wirtz noted. "This led to our hypothesis that lung injury inflicted by red blood cell transfusion is influenced by manufacturing methods."

In this study, Dr. Wirtz and his colleagues investigated the response of pulmonary cells to the different methods of manufacturing RBC products. Using type A or B blood obtained from eight donors, a variety of RBC products were manufactured for the study, including whole-blood filtered, red-cell filtered, apheresis derived, and whole-blood derived.

For measuring thrombin generation and analyzing extracellular vesicles (EV), supernatants were prepared after 4-5 days of storage for fresh and 41-42 days for stored. The researchers selected A549 type II alveolar cells to seed onto flexible membranes, which were then incubated with RBC supernatant also stretched 25% using a cell stretcher.

After 24 hours, the production of IL-8 and IL-6 was measured.

Both fresh and stored supernatants that were derived from apheresis significantly increased the production of IL-6 and IL-8 in pulmonary cells, compared with nonincubated controls and most of the other RBC products. The production of IL-6 and IL-8 was exacerbated by cell stretching.

Average IL-6 production in nonstretched cells was 91 pg/mL for fresh and 87 pg/mL for expired (*P* less than .05 vs. control and other RBC products). For stretched cells, it was 130 pg/mL and 150 pg/mL (*P* less than .05 vs. control). For controls, mean nonstretched and stretched production was 21 pg/mL and 85 pg/mL.

Mean IL-8 production in nonstretched cells was 2,100 pg/mL for fresh and 1,900 pg/mL for stored (*P* less than .05 vs. control and other RBC products). For stretched cells, the means were 4,100 pg/mL for fresh and 5,200 pg/mL for stored (*P* less than .05 vs. control).

The average nonstretched and stretched control IL-8 production was 1,200 pg/mL for fresh and 4,300 pg/mL for stored.

Products derived from apheresis also demonstrated a significantly higher ability to generate thrombin, compared with other RBC products, and a significantly increased number of RBC-derived EVs, compared with filtered red cell and whole blood–derived products (*P* less than .05).

Lifesaving future seen for electronic cigarettes

BY RICHARD FRANKI
Frontline Medical News

A switch from cigarettes to e-cigarettes has the potential to prevent almost 90,000 premature deaths in the United States in the year 2026, according to a study examining e-cigarette substitution scenarios.

The investigators' "optimistic scenario" – in which new smokers use e-cigarettes instead of cigarettes, smoking prevalence falls to 5% over a 10-year period, and e-cigarettes have a 5% excess risk over regular cigarettes – projects 380,832 premature deaths from smoking in the year 2026. Under a "status quo scenario," which projected current cigarette initiation and cessation rates and did not include e-cigarettes or other tobacco products, there would be 470,743 deaths, reported David T. Levy, PhD, and his associates (Tob Control. 2017 Oct 2. doi: 10.1136/tobaccocontrol-2017-053759).

Their "pessimistic scenario," which would involve more young people starting to use both e-cigarettes and tobacco, smoking prevalence falling to just 10% over a 10-year period, and e-cigarettes having a 40% excess risk over regular cigarettes, resulted in 456,297 premature deaths in 2026, only 14,446 fewer than the status quo scenario, said Dr. Levy of Georgetown University in Washington and his associates.

Further projections suggest that the optimistic scenario could result in almost 6.6 million fewer premature deaths and 86.7 million years of life gained by the year 2100, compared with the status quo scenario, while the pessimistic scenario would prevent 1.6 million deaths and add an extra 20.8 million years of life, they noted.

Since "a strategy of replacing cigarette by e-cigarette use can yield substantial gains, even with conservative assumptions about related risks … an endgame scenario for cigarettes might well be within reach, if new technologies for delivering nicotine with substantially less harm, but sufficient satisfaction, are harnessed with sufficient passion and political will to aggressively phase out tobacco cigarettes," Dr. Levy and his associates wrote.

The study was funded by grants from the National Institute on Drug Abuse and the National Cancer Institute. One investigator received a research grant from Pfizer and served as an advisory board member to Johnson & Johnson, which manufactures smoking cessation medications. No other conflicts of interest were declared.

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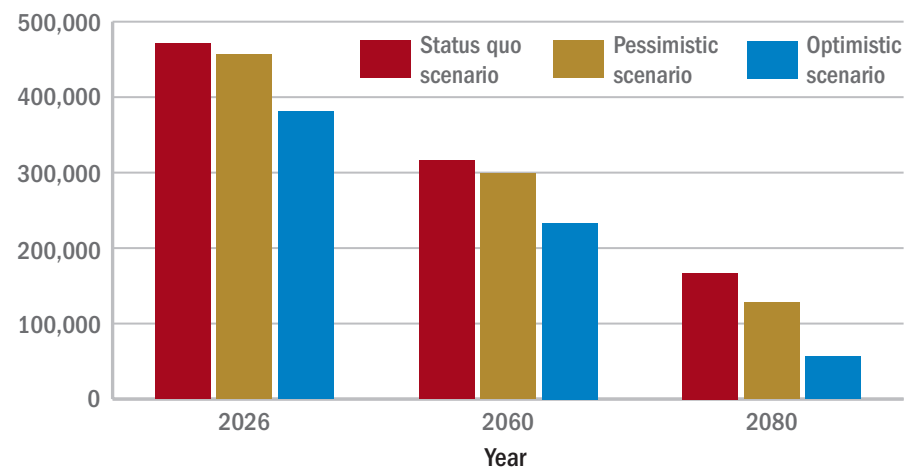
VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: This study seems to affirm the belief that e-cigarettes are a safer alternative to traditional cigarettes, and the thought "if patients are going to smoke, they are better than real cigarettes." While the available evidence mostly supports this, it must be recognized that there are significant assumptions being made regarding the relative safety of e-cigarettes – especially since there are no industry standards regarding their quality control or product contents. There exist significant conflicting data on both their safety and ability to serve as a cigarette alternative (for cessation or otherwise); and as with most things this complex, the truth probably is somewhere in the middle.

Premature deaths under e-cigarette substitution scenarios



Note: The scenarios were developed using data from the National Health Interview Survey and the American Cancer Society Cancer Prevention Studies.

Source: Tob Control. 2017 Oct 2. doi: 10.1136/tobaccocontrol-2017-053759

Remimazolam surpasses midazolam

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – An investigational sedative, remimazolam, that's similar to midazolam but with faster onset and offset, resulted in significantly better procedural success compared with midazolam in a multicenter, phase III trial with 431 patients.

The results also showed that remimazolam was as safe as midazolam (Versed), with a similar adverse event profile, said Gerard A. Silvestri, MD, FCCP, at the CHEST annual meeting.

Paion, the company developing remimazolam, plans to combine data from this bronchoscopy study with data collected from other procedural studies that included patients undergoing colonoscopy and upper gastrointestinal endoscopy, and seek U.S. Food and Drug Administration approval for the drug in 2018, according to a written statement.

The bronchoscopy trial enrolled patients at any of 15 U.S. centers with an American Society of Anesthesiologists (ASA) physical status classification of I-III and scheduled for diagnostic or therapeutic bronchoscopy. The enrolled patients averaged 62 years of age, and 38% were in ASA class III.

All patients received initial sedation treatment with fentanyl, followed by a three-to-one randomization to blinded remimazolam, blinded placebo that included midazolam rescue, or open-label midazolam. The study's primary efficacy endpoint was procedural success, defined as patients who underwent the complete procedure without need for an alternative sedative and without need for more than five doses

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP. comments: This medication may represent a valuable addition to our options for moderate sedation during procedures – in that its main benefit seems to be in its onset of sedation. It will be important to assess this study's outcome data once published – especially with regard to the driver of the differences seen between groups in the composite primary outcome (i.e., successfully completing a procedure would be the important primary endpoint to most, and we should be interested to see if it was the dosing/time-based outcomes that drove the primary outcome differences between the groups). Further, if there are significant cost differences between these two medications, this will certainly limit their incorporation into practice unless there are significant differences in patient-centered outcomes.

Mitchel L. Zoler/Frontline Medical News

Dr. Gerard A. Silvestri

Continued from previous page

of the patient's assigned medication within any 15-minute period during the procedure or need for more than three midazolam doses within any 12-minute period in the patients randomized to receive midazolam.

This primary endpoint occurred in 83% of 303 patients in the remimazolam arm, 5% of 59 patients in the placebo arm, and 34% of 69 patients in the midazolam arm, a statistically significant difference between the remimazolam patients and each of the comparator groups, reported Dr. Silvestri, a professor of medicine and a lung cancer pulmonologist at the Medical University of South Carolina in Charleston.

The results also demonstrated the faster onset and offset of remimazolam. Treatment achieved adequate sedation to start the procedure after a median of 5 minutes with remimazolam, a median of 15.5 minutes with midazolam, and a median of 17 minutes among patients in the placebo group. Once sedation finished, patients returned to being fully alert after a median of 6 minutes with

remimazolam, a median of 12 minutes with midazolam, and a median of 13.5 minutes for patients in the placebo arm.

"What's nice about remimazolam is that the adverse event profile is exactly the same as with placebo and midazolam, and you have a reversal agent," the same as what's used for midazolam, he said.

Midazolam is the current "workhorse" sedative, but "we can do better," commented Matthew B. Stanbrook, MD, FCCP, a pulmonologist at the University of Toronto. "There would be some benefit from a sedative with faster onset and offset," he said in an interview.

Dr. Silvestri suggested several additional studies he would like to see run on remimazolam to better understand its clinical performance and role. These include studying the drug in the elderly, patients with an ASA classification of IV, obese patients, and those on high narcotic doses. He also suggested comparing remimazolam directly with propofol, testing remimazolam as a stand-alone agent without fentanyl co-administration, and trying the drug during other pulmonary procedures such as pleural-catheter placement and other invasive procedures, and in ICU patients.

The trial was funded by Paion, the company developing remimazolam. Dr. Silvestri and Dr. Stanbrook had no relevant disclosures.

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Nebulized LABA safe for long-term use in COPD

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – No long-term safety signals were seen in a randomized trial that tested the formoterol fumarate inhalation solution (Perforomist, Mylan) against placebo in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Safety was confirmed despite patients being permitted to remain on other background treatment for COPD, including inhaled corticosteroids and anticholinergics, in this study presented at the CHEST annual meeting. An additional benefit of the therapy was that it significantly improved lung function from

baseline, according to some spirometry measures.

"These results are certainly reassuring from the safety perspective and confirm previously published shorter-term efficacy and safety studies with this medication," reported Nicola A. Hanania, MD, FCCP, from Baylor College of Medicine, Houston.

Formoterol significantly improved trough forced expiratory volume in 1 second, compared with placebo at 3 and 6 months of treatment, Dr. Hanania noted.

The Food and Drug Administration approved formoterol fumarate, a long-acting beta-2 agonist (LABA), as a nebulized maintenance treatment for bronchoconstriction in COPD. Because of a concern about long-term LABA safety in asthma patients, said Dr. Hanania, the FDA mandated this 1-year phase 4 study to evaluate the long-term safety of formoterol in patients with moderate to severe COPD.

This multicenter, double-blind, noninferiority study randomly assigned 1,071 patients with moderate

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to severe COPD (mean FEV_1, 44.4% of predicted value, at least one exacerbation in the past 12 months) to receive either nebulized formoterol 20 mcg/2 mL twice daily or matching placebo for up to 12 months. Subjects were permitted to remain on stable COPD therapy, including inhaled corticosteroids and anticholinergics but excluding long-acting beta-agonists.

"One thing we have to keep in mind is that formoterol is a full agonist, so there are dose-dependent adverse effects," said Nicola A. Hanania, MD.

Formoterol was noninferior to placebo for the primary safety endpoint, defined as a first occurrence of respiratory-related death, COPD-related emergency department visit, or COPD-related hospitalization, with an estimated hazard ratio of 0.965.

Formoterol significantly improved trough forced expiratory volume in 1 second (FEV_1), compared with placebo at 3 and 6 months of treatment, with (least squares) mean estimated differences of 42 mL (P = .007) and 41 mL (P = .025), respectively, but not at 9 or 12 months. Forced vital capacity was significantly improved with formoterol over placebo at all study visits (3, 6, 9, and 12 months), but improvements from baseline in inspiratory capacity did not significantly differ from placebo.

Mean age of study patients was 62.6 years and 48.5% were female. At baseline, about half of patients were still smokers, half were on inhaled corticosteroids, and about one-third were on concomitant long-acting muscarinic antagonists, mainly tiotropium, reported Dr. Hanania. The vast majority of patients had moderate or severe COPD, with less than 1% having very severe disease at baseline.

Debra L. Beck/Frontline Medical News

Dr. Nicola Hanania

In response to a question on dosing, Dr. Hanania told attendees, "One thing we have to keep in mind is that formoterol is a full agonist, so there are dose-dependent adverse effects. So, even though you get better lung function as you go up on the dose, there's no free lunch and always the potential for adverse effects."

The safety data was previously presented at the American Thoracic Society meeting in May 2017 (Hanania N et al. Am J Respir Crit Care Med. 2017;195 A5473 [abstract]), while the lung function data are new, said Dr. Hanania.

Dr. Hanania reported being an adviser for several pharmaceutical companies, including Mylan. Four of the six authors of the study's abstract are employees of Mylan.

Tezacaftor-ivacaftor safe, effective in Phe508del CFTR

BY ANDREW D. BOWSER
Frontline Medical News

The combination of ivacaftor and the investigational agent tezacaftor is effective and has a favorable safety profile in patients with cystic fibrosis homozygous for the Phe508del CFTR mutation, according to results of a 24-week randomized, placebo-controlled clinical trial.

Patients receiving the tezacaftor-ivacaftor combination experienced a mean increase in their percentage of predicted forced expiratory volume in 1 second of 3.4 percentage points, compared with a mean decrease of 0.6 percentage points in the control group, at the end of the trial (*P* less than .001). The pulmonary exacerbation rate was 35% lower in the tezacaftor-ivacaftor treatment arm than in the placebo arm (*P* = .005), data show. These results were recently published in the New England Journal of Medicine (2017 Nov 3. doi: 10.1056/NEJMoa1709846).

Most adverse events were mild to moderate, and serious adverse events occurred less frequently in the tezacaftor-ivacaftor treatment arm, compared with the placebo arm, reported Jennifer L. Taylor-Cousar, MD, of National Jewish Health, Denver, and her coinvestigators.

Tezacaftor-ivacaftor's improved safety profile as compared with currently available therapy, "in addition to its effect on multiple efficacy end points, supports its use in a broad range of patients with [CF]," noted the investigators.

Ivacaftor was the first approved modulator of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, and tezacaftor is an investigational CFTR corrector. Tezacaftor demonstrated efficacy in a previous phase 2 trial that included patients either homozygous for the Phe508del mutation or heterozygous for the Phe508del and G551D mutations, Dr. Taylor-Cousar and her coauthors said in their report.

The combination of ivacaftor and another CFTR corrector, lumacaftor, is already available to treat cystic fibrosis patients who are homozygous for the Phe508del CFTR mutation. However, not all patients can receive lumacaftor-ivacaftor because of its respiratory side effects, and lumacaftor is associated with "prohibitive drug-drug interactions" due to considerable cytochrome P-450-3A induction, according to the study authors.

"The improved safety profile of combination therapy with tezacaftor-ivacaftor, as compared with currently available therapy, in addition to its effect on multiple efficacy end points, supports its use in a broad range of patients with cystic fibrosis," wrote Dr. Taylor-Cousar and her colleagues.

The phase 3 trial included 509 cystic fibrosis patients at least 12 years of age who were homozygous for the CFTR Phe508del mutation. The mean percentage of predicted forced expiratory volume in 1 second of the patients was 60.0, at baseline.

All patients were randomized to combination therapy with tezacaftor 100 mg once daily and ivacaftor 150 mg twice daily, or matched placebo. A total of 475 patients completed the 24-week trial. The incidence of serious adverse events was just 12.4% of tezacaftor-ivacaftor–treated patients, compared with 18.2% in the placebo arm, and no serious adverse events led to treatment discontinuation.

"The rate of respiratory adverse events was not higher in the tezacaftor-ivacaftor group than in the placebo group, which shows that the safety profile for tezacaftor-ivacaftor is better than that reported for lumacaftor-ivacaftor," Dr. Taylor-Cousar and her colleagues wrote.

Treatments that modulate CFTR are promising, according to the authors, because they treat the underlying cause of cystic fibrosis.

Vertex Pharmaceuticals supported the study. Dr. Taylor-Cousar reported personal fees from Vertex Pharmaceuticals outside of the submitted work. Full disclosures for all authors were published on the New England Journal of Medicine website.

TAVR wallops SAVR in cost-effectiveness

BY BRUCE JANCIN
Frontline Medical News

DENVER – A formal cost-effectiveness analysis indicates that transcatheter aortic valve replacement (TAVR) is substantially more cost effective than surgical valve replacement in patients at intermediate surgical risk similar to those enrolled in the landmark PARTNER 2 trial. The analysis demonstrated that over a 1- and 2-year follow-up period, as well as with projected lifetime follow-up, TAVR entails both lower long-term costs and greater quality-adjusted life expectancy, David J. Cohen, MD, reported at the Transcatheter Cardiovascular Therapeutics annual educational meeting.

"These findings, taken together with the clinical data we now have, suggest that TAVR should be the preferred strategy for such patients, based on both clinical and economic considerations," said Dr. Cohen, director of cardiovascular research at Saint Luke's Mid America Heart Institute in Kansas City, Mo.

His two-part, patient-level economic analysis examined data from nearly 2,000 participants in the PARTNER 2A randomized trial comparing TAVR, using the Sapien XT valve, with surgical aortic valve replacement (SAVR), as well as the experience with the current-generation Sapien 3 TAVR valve in 1,077 intermediate–surgical risk TAVR patients in the S3i registry. The analysis utilized Medicare claims data on the costs of the index hospitalization and follow-up care.

In PARTNER 2A, the average total cost of the index hospitalization for valve replacement was $61,433 with TAVR. That was just $2,888 more than the SAVR hospitalization, despite the far higher acquisition cost of the Sapien 3 valve, which was roughly $32,500, compared with $5,000 for the surgical valve. Most of this additional cost of the TAVR valve was counterbalanced by TAVR's 2-hour shorter procedural duration, the 6.4-day average length of stay, compared with 10.9 days for SAVR, and the fact that TAVR patients spent only 2.4 days in intensive care while SAVR patients averaged 4.6 days, Dr. Cohen explained at the meeting sponsored by the Cardiovascular Research Foundation.

During 24 months of postdischarge follow-up in the PARTNER 2A trial, SAVR patients racked up an average of $9,303 more in costs than TAVR patients. This was mainly because of their much higher rates of rehospitalization and time spent in skilled nursing facilities and rehabilitation centers, mainly during months 2-6 post discharge. The result was that 2-year total costs including the index hospitalization averaged $107,716 per TAVR patient and $114,132 per SAVR patient.

"One of the really remarkable findings of this study was what happened during follow-up," the cardiologist observed.

Extrapolating to projected remaining lifetime years, TAVR using the Sapien XT valve resulted in a cost savings of $7,949 per patient and a 0.15-year increase in quality-adjusted life expectancy compared with SAVR.

But since the time of PARTNER 2A, the Sapien XT valve has been replaced by the updated Sapien 3 valve. The analysis of the S3i registry showed that the economic dominance of TAVR over SAVR was even greater owing to improved valve technology and contemporary care patterns. For this analysis, because there has been no randomized trial of TAVR with the Sapien 3 valve versus SAVR, patients in the SAVR arm of PARTNER 2A served as the comparison group.

The cost of the index hospitalization was more than $4,000 less with TAVR in the S3i registry than with SAVR. The total cost of TAVR through 1 year of follow-up averaged $80,977, which was $15,511 less than the $96,489 for SAVR. The cost post discharge out to 1 year was more than $11,000 less per TAVR patient, driven by sharply lower rates of both cardiovascular and noncardiovascular hospitalizations as well as a greater than 50% reduction in days spent in rehab centers and skilled nursing facilities, compared with SAVR patients.

Projected over estimated remaining years of life, TAVR with the Sapien 3 valve yielded a cost savings of $9,692 per patient compared with SAVR, as well as a 0.27-year gain in quality-adjusted life-years.

Eighty-eight percent of patients in the S3i registry received their Sapien 3 valve via a transfemoral approach. When Dr. Cohen and his coinvestigators compared their costs and clinical outcomes to the subset of PARTNER 2A TAVR patients who got the Sapien XT valve transfemorally, the outcomes were "virtually identical," he said.

The PARTNER 2A trial, the S3i registry, and the cost-effectiveness analysis were funded by Edwards Lifesciences. Dr. Cohen reported receiving research funding from and serving as a consultant to Edwards Lifesciences and other device companies.

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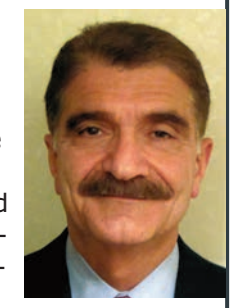
VIEW ON THE NEWS

Hossein Almassi, MD, FCCP, comments: The catheter valve technology has dramatically changed the treatment of aortic valve stenosis. Initially approved for the prohibitive and high-risk patients, it has become a common practice for the intermediate risk, and soon to be followed in the low risk patients. The long-term durability of the TAVR valves, however, remains unknown and, therefore, its wide application to the low risk patients group with an expected longer life expectancy should await more data from large-scale studies.



Robotic-assisted pulmonary lobectomy removes large tumors

BY LUCAS FRANKI
Frontline Medical News

FROM CHEST 2017 ▪ Robotic-assisted pulmonary lobectomy is a safe and effective way to remove large tumors in patients with non–small cell lung cancer (NSCLC), according to the abstract of a study from the CHEST annual meeting by Nirav Patel, MD, FCCP, of the Tampa Bay Sleep Center, and colleagues.

The study covers a retrospective analysis of 345 NSCLC patients with tumors who underwent robotic-assisted pulmonary lobectomy performed by one surgeon from September 2010 through August 2016. The participants were grouped into the following three cohorts: patients with tumors less than 5 cm in diameter, patients with tumors from 5 to 7 cm, and patients with tumors larger than 7 cm. The researchers excluded patients with pulmonary metastases or benign lesions from the study.

The 1- and 3-year survival rates for patients with tumors less than 5 cm were 91% and 84%; they were 86% and 75% in patients with tumors from 5 to 7 cm, and 76% and 47% in patients with tumors larger than 7 cm, respectively. A tumor size larger than 7 cm was significantly associated with both worse 1-year and 3-year survival, compared with patients with a tumor less than 5 cm ($P = .004$).

Patients with smaller tumors were more likely to have simple lobectomy or lobectomy plus wedge, while patients with larger tumors were more likely to require lobectomy with chest wall resection. Increased tumor size was also associated with increased intraoperative estimated blood loss, skin-to-skin operative time, hospital length of stay, and overall conversion to open lobectomy.

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VIEW ON THE NEWS

Hossein Almassi, MD, FCCP, comments: Robotic thoracic surgery has gained wide acceptance mostly as a result of a more favorable perioperative hospital course and patient comfort. This report outlines the outcomes of robotic lobectomy performed by one experienced surgeon. As stated by the presenting author during the presentation, standard mediastinal lymph node dissection was part of the procedure. Patient survival was dependent on the tumor size, i.e., the stage of the tumor. With advances in technology, robotic thoracic surgery would potentially be the standard surgical approach in the near future for the treatment of most thoracic pathologies.

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Cold stored platelets control bleeding after surgery

BY ROXANNE NELSON
Frontline Medical News

SAN DIEGO – Cold stored leukoreduced apheresis platelets in platelet additive solution were effective for controlling bleeding in a small study of patients undergoing complex cardiothoracic surgery, according to findings presented at the annual meeting of the American Association of Blood Banks.

The volume of postoperative bleeding was significantly lower among patients who received cold stored platelets compared with those who received standard room temperature storage platelets. Thromboembolic events did not differ between the two groups, nor did measures of coagulation at varying time points. Platelet counts and blood usage were also similar in the two groups. The study was small, however, and further studies are needed to confirm the findings.

"These patients are undergoing major surgery and are at high risk in every aspect," said Torunn Oveland Apelseth, MD, PhD, of the Laboratory of Clinical Biochemistry, Haukeland (Norway) University Hospital. "They are at high risk for bleeding, at high risk for thromboembolic events and high blood usage, and there is a need for optimized blood components."

There has been debate over the use of cold stored platelets, she noted. While storage at 4° C shortens platelet circulation time, some research shows that cold stored platelets have better hemostatic function.

In this study, one patient cohort was transfused with leukoreduced apheresis platelets stored at 4° C in platelet additive solution for up to 7 days under constant agitation, while the other group received platelets stored at standard room temperature. The study endpoints were comparisons between the two groups of postoperative bleeding, total blood usage, and laboratory measures of coagulation and blood cell counts within the first postoperative day. Thromboembolic events in the 28 days after surgery were also evaluated.

The study evaluated 17 patients who received cold stored platelets and 22 who received room temperature storage platelets. Patient demographics for the two groups were similar – as were their international normalized ratios, activated partial thromboplastin times, and fibrinogen levels – before surgery, immedi-

VIEW ON THE NEWS

Hossein Almassi, MD, FCCP, comments: This is a small study on the impact of cold stored platelets transfusion in reducing the postoperative chest tube drainage in cardiac surgical patients. It did not affect the platelet count or blood usage.

ately after heparin reversal, and the morning following the procedure.

Platelet counts and hemoglobin levels also did not significantly differ between groups.

As measured by chest drain output after chest closure, patients who received cold stored platelets had a significantly lower median amount of bleeding in the postoperative period compared with patients given room temperature storage platelets: 576 mL vs. 838 mL. Average chest drain output after chest closure was 594 mL in those who did not receive any transfusions.

"These patients are undergoing major surgery and are at high risk in every aspect," said Torunn Oveland Apelseth, MD, PhD.

Thromboembolic events occurred in 3 patients (18%) who received cold stored platelets and 7 (31%) of those given room temperature storage platelets. The difference was not statistically significant. In addition, blood usage – platelets, red blood cells, and solvent/detergent-treated pooled plasma – was similar for the two cohorts.

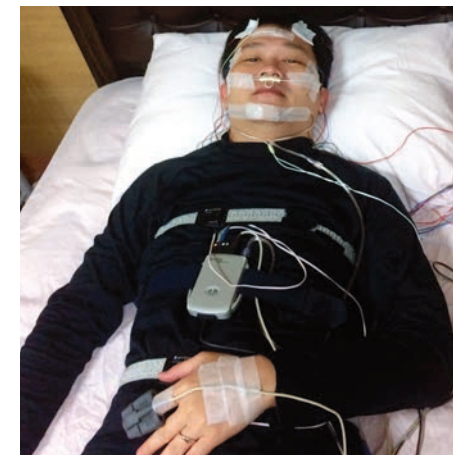
"There were also no differences in the number of thromboembolic episodes or length of stay in ICU," said Dr. Apelseth, who recommended larger studies to explore the use of cold stored platelet transfusion in the critical care setting.

OSA home testing less costly than PSG

BY SHANNON AYMES
Frontline Medical News

Home respiratory polygraphy had similar efficacy with substantially lower per-patient cost, compared with traditional polysomnography for diagnosing obstructive sleep apnea, a study showed.

Obstructive sleep apnea (OSA) is a common chronic disease associated with higher risk of cardiovascular disease and traffic accidents and a lower quality of life. Although expensive and time intensive, the polysomnography (PSG) has been the preferred test for diagnosing OSA. Home respiratory polygraphy (HRP) uses portable devices that are less complex than polysomnography and has been shown to have similar effectiveness in diagnosing OSA, compared with PSG, in patients with a high clinical suspicion of OSA. However, there is limited evidence for the cost effectiveness of HRP, compared with PSG (Am J Respir Crit Care Med. 2017 Nov 1;196[9]:1181-90).



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Jaime Corral-Peñafiel, MD, of San Pedro de Alcántara Hospital, Cáceres, Spain, and his colleagues sought to compare the long-term effectiveness of HRP to PSG in patients with an intermediate or high suspicion for sleep apnea.

The investigators conducted a multicenter, randomized controlled, noninferiority trial and cost-effectiveness analysis comparing PSG with HRP. Inclusion criteria included snoring or observed sleep apnea, Epworth Sleepiness Scale (ESS) of 10 or higher, and no suspicion of alternative causes for daytime sleepiness. Patients with a suspicion for OSA were randomized to polysomnography or respiratory polygraphy protocols. Both arms received counseling on proper sleep hygiene; counseling on weight loss, if overweight; and auto-CPAP titration if continuous positive airway pressure (CPAP) was clinically indicated.

Assessment of CPAP compliance or dietary and sleep hygiene compliance was assessed at months 1 and 3. ESS, quality of life measures, well-being measures, 24-hour blood pressure monitoring, auto accidents, and cardiovascular events were assessed at baseline and at month 6.

CPAP treatment was indicated in 68% of the PSG arm, compared with 53% of the HRP arm. After

Continued on following page

Aspirin responsiveness improved in some with obstructive sleep apnea

BY KATIE WAGNER LENNON
Frontline Medical News

FROM CHEST 2017 ▪ Obstructive sleep apnea patients with endothelial dysfunction gained aspirin responsiveness after using continuous positive airway pressure (CPAP) therapy, according to the findings of a small study by Lirim Krveshi, DO, of Danbury (Conn.) Hospital, and colleagues.

"Endothelial dysfunction is an important phenomenon implicated in cardiovascular morbidity in obstructive sleep apnea (OSA) patients. While it has been demonstrated that CPAP improves endothelial function, our understanding of the pathophysiologic links between CPAP therapy and cardiovascular outcomes remain limited," wrote Dr. Krveshi and colleagues, in the study's abstract from the CHEST annual meeting.

The researchers examined 18 patients' endothelial function before and after using CPAP therapy for a median of 37 days, along with the relationship between endothelial function and aspirin responsiveness in these same patients. All study participants had been recently diagnosed with moderate to severe OSA and underwent modified peripheral artery tonometry and platelet aggregometry before and after beginning CPAP therapy. Most of the patients (14) demonstrated aspirin resistance at baseline.


DR. KRVESHI

Endothelial dysfunction was defined as having a reactive hyperemia index (RHI) of less than or equal to 1.67, while aspirin resistance was defined as having a reading of at least 550 aspirin reaction units (ARU).

At baseline, the average RHI of patients was 1.79 (standard deviation = 0.3), with 8 of the patients having had endothelial dysfunction. Following CPAP use, patients' RHI increased by an average of 1.94 (SD = 0.36), and endothelial dysfunction was present in just 5 of the study participants.

Following CPAP use, patients' RHI increased by an average of 1.94 (SD = 0.36), and endothelial dysfunction was present in just 5 of the study participants.

After using CPAP, those patients with endothelial dysfunction at baseline were responsive to aspirin, with their average ARU reading at 520 following therapy. In contrast, those patients with normal endothelial function at baseline remained resistant to aspirin following CPAP use, based on mean ARU values before and after therapy.

The researchers received funding from the Arthur Kotch Foundation.

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Continued from previous page

intention-to-treat analysis, there was no statistically significant difference between the two groups for ESS improvement (HRP mean, –4.2, vs. PSG mean, –4.9; $P = .14$). The groups demonstrated similar results for quality of life, blood pressure, polysomnographic assessment at 6 months, CPAP compliance, and rates of cardiovascular events and accidents at follow-up.

The cost-effective analysis demonstrated respiratory polygraphy was less expensive, saving more than 400 euros/patient. "Because the effectiveness (ESS and QALYs [quality-adjusted life-years]) was similar between arms, the HRP protocol is preferable due to its lower cost," the authors wrote.

In all, 430 patients were randomized to HRP or PSG and consisted mostly of men (70.5%) with a mean body mass index of 30.7 kg/m^2. The groups had similar rates of alcohol consumption and hypertension.

Limitations of the study included unblinded randomization to the participants and researchers and the possibility of variability in therapeutic decisions. However, the authors noted that intraobserver variability was minimized by using the Spanish Sleep Network guidelines and centralized assessment.

"[The] HRP management protocol is not inferior to PSG and presents substantially lower costs. Therefore, PSG is not necessary for most patients with suspicion of OSA. This finding could change established clinical practice, with a clear economic benefit," the authors concluded.

Home respiratory polygraphy continues to impress

This study adds strong evidence to support the use of home respiratory polygraphy for the diagnosis of obstructive sleep apnea in patients without major comorbidities such as severe chronic restrictive or obstructive lung disease, heart failure or unstable cardiovascular disease, major psychiatric diagnoses, and neuromuscular conditions, noted Ching Li Chai-Coetzer, MBBS, PhD, and R. Doug McEvoy, MBBS, MD, in an accompanying editorial (Am J Respir Crit Care Med. 2017 Nov 1;196[9]:1096-8). However, lower-cost methods to diagnose OSA would still not address unmet needs such as the cost of continuous positive airway pressure and scarcity of sleep physicians to assess patients with OSA, and still may be too expensive for underresourced populations, they said.

Dr. Chai-Coetzer and Dr. McEvoy are affiliated with the Adelaide Institute for Sleep Health at Flinders University and the Sleep Health Service, Southern Adelaide Local Health Network, both in South Australia.

The study was supported by Sociedad Española de Neumología, Air Liquide (Spain), Asociacion de Neumologos del Sur, and Sociedad Extremeña de Neumología. The investigators report no disclosures.

Dr. Chai-Coetzer reported grants from National Health and Medical Research Council of Australia and nonfinancial support from Biotech Pharmaceuticals. Dr. McEvoy reported grants and nonfinancial support from Philips Respironics, nonfinancial support from ResMed, and grants from Fisher & Paykel.

VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: Home sleep apnea testing technology has expanded tremendously in the last decade given the need for expedient diagnosis of obstructive sleep apnea. Despite the American Academy of Sleep Medicine's guidelines for using unattended portable monitoring in the diagnosis of obstructive sleep apnea (OSA) in adults with intermediate to high clinical probability of OSA (Collop et al. J Clin Sleep Med 2007) and widespread usage of a multitude of home sleep testing technologies, questions about its effectiveness in comparison to polysomnography (PSG) and overall cost-benefit benefit remain. This study establishes that home respiratory polygraphy (HRP) was non-inferior to PSG for diagnosis and subsequent OSA treatment using 6-month quality of life and sleepiness measures, but HRP achieved this at substantially lower costs. This was despite higher continuous positive airway pressure prescription rates in the PSG arm as compared to the HRP arm (68% vs. 53%) that was attributed to Apnea-Hypopnea Index underestimations from HRP. While a slightly higher improvement in deep sleep in the PSG arm was seen at 6 months, a number of other key measures such as 24-hour ambulatory blood pressures did not show a difference. Besides demonstration of comparable CPAP usages in the PSG and HRP arms (5.3 hr/d vs. 5.1 hr/d), this study highlights the increasing reliance on quality of life and blood pressure measures as relevant endpoints in cost analyses assessing OSA diagnosis and care-process outcomes.

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

WARNINGS AND PRECAUTIONS

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

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

Eliquis®
(apixaban) tablets 5mg 2.5mg

ELIQUIS for initial DVT/PE treatment*—

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

To learn more about ELIQUIS, visit

hcp.eliquis.com

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

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

PREGNANCY CATEGORY B

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

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

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

Bristol-Myers Squibb Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

Reversal of Anticoagulant Effect

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

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

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

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

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

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

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

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

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

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

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

Other Adverse Reactions

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

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

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

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

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

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

* All bleeding criteria included surgical site bleeding.

† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

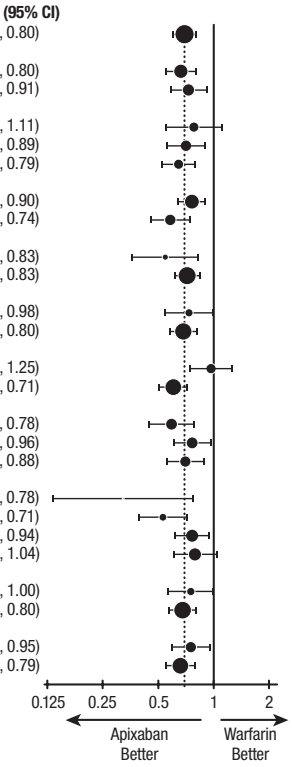
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

¶ CRNM = clinically relevant nonmajor.

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

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



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

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

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

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

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

Patients with End-Stage Renal Disease on Dialysis

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

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

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

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

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

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

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PULMONARY PERSPECTIVES®

The rise and fall of treatment trials in group 3 pulmonary hypertension: Where do we go from here?

BY CHRISTOPHER KING, MD, FCCP

Treatment of fibrotic interstitial lung disease (ILD) is often dissatisfying to clinicians and patients. Despite significant advances in the field, particularly the validation of the efficacy of the antifibrotic drugs nintedanib (Richeldi L, et al. *N Engl J Med.* 2014;370[22]:2071) and pirfenidone (King TE Jr, et al. *N Engl J Med.* 2014;370[(22]:2083) in slowing the progression of idiopathic pulmonary fibrosis (IPF), we are still left with a paucity of therapeutic options to modulate the course of disease and improve functional outcomes. Given the difficulties in addressing the progression of parenchymal fibrosis, the pulmonary community has looked for alternative ways to approach treatment of ILD. One potential therapeutic inroad that has garnered substantial interest is the treatment of concurrent pulmonary hypertension (PH) or group 3 PH (Seeger W, et al. *J Am Coll Cardiol.* 2013;62 (25 Suppl):D109).

Group 3 PH – The rationale to treat

Group 3 PH has an indisputable association with adverse outcomes, including decreased functional status, increased need for supplemental oxygen, and decreased survival (King CS, Nathan SD. *Pulmonary Hypertension and Interstitial Lung Disease*. Ed 2. Ch 4.2017;67-84). In fact, PH is such a powerful predictor of survival in fibrotic ILD, the International Society of Heart and Lung Transplant (ISHLT) guidelines on candidate selection for lung transplantation cite development of PH as an indication for transplant listing (Weill D, et al. *J Heart Lung Transplant.* 2015;34:1). When one considers the strong association between group 3 PH and adverse outcomes, the numerous pulmonary vasodilator agents available to treat pulmonary arterial hypertension (PAH), and the success achieved in treating PAH, it is easy to see why group 3 PH is such a tempting therapeutic target.

Previous studies of pulmonary vasodilator therapy for group 3 PH

Over 20 studies assessing the effectiveness of pulmonary vasodilator therapy in ILD have been published (King CS, Nathan SD. *Pulmonary Hypertension and Interstitial Lung Disease*. Ed 2. Ch 4. 2017;67) The majority was small and unblinded with inherent limitations. To date, no randomized controlled trial (RCT) of therapy for group 3 PH has demonstrated efficacy. Several studies amongst the RCTs deserve highlighting. The most encouraging RCT of therapy for group 3 PH was STEP-IPF. This study compared sildenafil with placebo in 180 patients with advanced IPF. Though the study failed to demonstrate a difference in the primary endpoint of ≥ 20% increase in 6-minute walk test (6MWT) distance, it did show improvement in several secondary endpoints, including arterial oxygen saturation and quality of life measures (Zisman DA, et al. *N Engl J Med.* 2010;363[7]:620).

The BUILD-3 study compared bosentan with placebo in 617 patients with IPF. Enrolled patients were not required to have PH. While bosentan was well tolerated, it failed to improve the primary endpoint of time to disease progression or death or secondary endpoints regarding quality of life or dyspnea (King TE Jr, et al. *Am J Respir Crit Care Med. 2011*; 184[1]:92). A smaller study comparing bosentan with placebo in 60 patients with fibrotic ILD with right-sided heart catheterization (RHC) confirmed PH failed to demonstrate any difference in pulmonary vascular hemodynamics, functional status, or symptoms (Corte TJ, et al. *Am J Respir Crit Care Med.* 2014;190[2]:208). Studies of the newer endothelin receptor antagonists, macitentan (Raghu, et al. *Eur Respir J.* 2013;42[6]:1622) and ambrisentan (Raghu, et al. *Ann Int Med.* 2013;158[9]:641), were conducted and failed to demonstrate improvements in outcomes, as well. Overall, the results of the available RCTs of pulmonary vasodilator therapy in group 3 PH have been disappointing, failing to conclusively improve the primary outcome in any of the studies performed.

Hot off the presses – RISE-IIP

The latest letdown in group 3 PH is "Riociguat for the Treatment of Pulmonary Hypertension in Idiopathic Interstitial Pneumonia (RISE-IIP). The results of the study were recently presented at the European Respiratory Society meeting in Milan, Italy, by my colleague from Inova Fairfax Hospital (Falls Church, VA), Dr. Steven Nathan. Riociguat is a soluble guanylate cyclase stimulator approved for use in PAH and chronic thromboembolic pulmonary hypertension. The rationale for the study was that riociguat would improve pulmonary hemodynamics leading to improved functional status. Additionally, several preclinical models have demonstrated antifibrotic effects of the drug (Geschka S, et al. *PLoS One.* 2011;6:e21853). Justification for the study was also bolstered by promising results from a pilot study conducted in 22 patients with RHC-confirmed PH with a mean pulmonary artery pressure (mPAP) > 30 and fibrotic lung disease. In this study, patients treated with riociguat had improved pulmonary vascular resistance, cardiac output, and 6MWT distance.

To be included in RISE-IIP, patients were required to have an idiopathic interstitial pneumonia, PH confirmed by RHC with a mPAP ≥ 25 mm Hg, World Health Organization Functional Class 2-4 symptoms, and a forced vital capacity (FVC) ≥ 45% predicted. Pertinent exclusion criteria included significant left-sided heart disease and extent of emphysema greater than fibrosis on HRCT. Patients with connective tissue disease, chronic hypersensitivity pneumonitis, occupational lung disease, and sarcoidosis were ineligible to participate. The placebo-controlled portion of the study lasted 26 weeks then crossed into an open label extension trial.

Dr. King is with Inova Fairfax Hospital, Falls Church, Virginia.

The study enrolled 147 total patients, with 73 receiving riociguat and 74 in the placebo arm. There was no significant improvement in the primary outcome of change in 6MWT distance or the secondary combined endpoint assessing clinical worsening. The study was terminated early for safety due to an increased number of deaths and adverse events in the treatment group. During the blinded phase of the study, eight deaths (11%) occurred in the riociguat arm as compared with three deaths (4%) in the placebo arm. Seventy patients entered the open label extension phase of the trial, and 9 of these patients died. Eight of these deaths occurred in the patients previously receiving placebo who were switched to riociguat. The authors of the study found no conclusive potential etiology to explain the increased mortality seen.

RISE'ing from the ashes – Where do we go from here?

So, what should we take away from the negative results of the RISE-IIP trial? Some may argue that treatment of group 3 PH is a flawed premise and should be abandoned. Perhaps development of group 3 PH is an adaptive response to worsening fibrotic lung disease, and treatment of the PH is unlikely to alter outcomes and introduces the possibility of harm through worsening hypoxemia due to increased ventilation/perfusion mismatch with nonselective pulmonary vasodilation. I suspect the truth is somewhat more nuanced. I believe there is a select population with severe or "out-of-proportion" PH that may still benefit from vasodilator therapy. Trials targeting patients with a higher mPAP or low cardiac index could test this hypothesis but will be difficult to enroll. Another possibility is that our mechanism of drug delivery in prior trials has been suboptimal. Inhaled pulmonary vasodilator therapy should minimize the risk of worsening ventilation/perfusion mismatch. An RCT assessing the response to inhaled treprostinil in group 3 PH (NCT02630316) is currently enrolling at 96 centers across the United States. Until data support-

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CRITICAL CARE COMMENTARY

Clostridium difficile in the ICU: A "fluid" issue

BY ADAM PETTIGREW, MD; JOHN F. TONEY, MD; AND SANDRA GOMPF, MD

In critically ill patients admitted to the ICU, diarrhea (defined as three or more watery loose stools within 24 hours) is a common problem. The etiologies of diarrhea are many, with infectious and non-infectious causes encountered.

Clostridium difficile infection (CDI) is the most common infectious cause of diarrhea in the hospital, including the ICU. The Centers for Disease Control and Prevention estimates the number of overall CDI cases to number about a half-million per year, of which 1 in 5 patients will have a recurrence, and 1 in 11 people aged ≥65 years will die within a month of CDI diagnosis. Age is a poor prognostic risk; greater than 80% of *C difficile* deaths occur in people 65 and older.

The increased use of electronic sepsis screening tools and aggressive antibiotic treatment, often done through protocols, has recently been identified as paradoxically increasing CDI occurrence (Hiensch R et al. *Am J Infect Control.* 2017;45[10]:1091). However, similar rapid identification and management of CDI can result in improved patient outcomes.

Issues with diagnosing CDI

Episodes of CDI can be rapid and severe, especially if due to hypertoxin producing–strains of *C difficile*, such as BI/NAP1/027, which produces significantly higher levels of Toxin A, Toxin B, and binary toxin CDT (Denève C, et al. *Int J*

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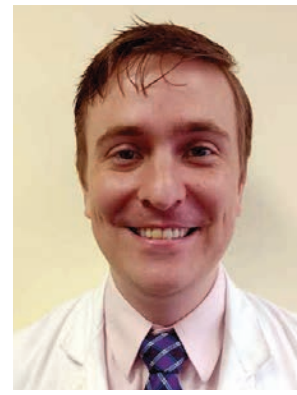
ing positive effects from treating group 3 PH emerge, I would recommend against off-label treatment and encourage referral to clinical trials. Given the potential for harm, riociguat should be avoided in group 3 PH. If off-label therapy is being entertained in a patient with severe PH that is out of proportion to the extent of fibrotic lung disease, it should be initiated cautiously at a center experienced in treating PH. Finally, clinicians should refer appropriate candidates with ILD and group 3 PH for lung transplantation evaluation.

The great inventor Thomas Edison is credited with saying "I have not failed. I've just found 10,000 ways that won't work." While disappointing, negative studies are to be expected as we search for improved therapies for our patients. It's essential that we reflect upon these studies, so we can improve future trial design.



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Antimicrob Agents. 2009;33:S24). Testing for CDI has been controversial; several methods have been employed to aid in the diagnosis of CDI. Currently, many institutions use either nucleic acid amplification tests (NAATs) for toxigenic *C difficile* or direct detection of the toxin produced by the bacteria. NAATs and past culture-based methods are more sensitive but less specific than toxin assays, whereas toxin assays are less sensitive but more specific than NAATs. However, detection of *C difficile* colonization due to high-sensitivity NAATs has caused a rise in the apparent rate of hospital-acquired CDI (Polage CR, et al. *JAMA Intern Med.* 2015;175[11]:4114).

To counter this, multi-step algorithmic approaches to CDI diagnosis have been recommended, including the use of glutamate dehydrogenase (GDH) antigen, toxin detection, and NAATs for toxin-producing *C difficile*. These multistep pathways attempt to minimize false-positive test results while affirming the presence or absence of true CDI (Fang F, et al. *J Clin Microbiol.* 2017; 55[3]:670).

However, controversy continues regarding which testing modalities are optimal, as some patients with positive toxin assays have asymptomatic colonization while some patients with negative toxin assays have CDI. The hope is that emerging, higher sensitivity toxin assays will decrease the number of CDI cases missed by negative toxin tests. Because *C difficile* toxins are labile at body temperature and susceptible to inactivation by digestive enzymes, stool samples must be expeditiously transported to the lab (time is of the essence), so as not to lose toxin or NAAT target detection. Repeat CDI testing for a "test for cure" is not recommended.

Management of CDI

The initial management of CDI has been discussed in many publications, including the current SHEA/IDSA Guidelines (Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31[5]:431).

Briefly, this involves stratifying CDI patients by clinical severity (mild, moderate, severe) and objective data (leukocytosis >15,000, septic shock, serum creatinine level > 1.5 times premorbid level) to guide initial antibiotic therapy. For mild/moderate first episode of CDI, oral or IV metronidazole is generally recommended; more severe disease is generally treated with oral vancomycin.

Complicated CDI in patients (hypotension/shock, ileus, toxic megacolon) requires aggressive management with both IV metronidazole and oral vancomycin (if ileus is present, consider vancomycin enemas). Additionally, fidaxomicin is available for oral CDI treatment and has been associated with decreased first-episode CDI recurrence.

The management of CDI recurrence commonly involves using oral vancomycin as a taper (or taper/pulse regimen) or using fidaxomicin. A recent publication (Sirbu et

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al. *Clin Infect Dis.* 2017;65[8]:1396) retrospectively compared vancomycin taper and pulse treatment strategies for 100 consecutive patients with CDI.

After taper, patents who received every other day (QOD) dosing had a cure rate of 61%, while those who received QOD dosing followed by every third day dosing achieved an 81% cure rate. A clinical trial comparing vancomycin standard therapy vs vancomycin taper with pulse vs fidaxomicin for first- and second-recurrence of CDI is underway.

Last year, the FDA approved bezlotoxumab, a monoclonal antibody that binds to *C difficile* toxin B. Bezlotoxumab treatment is indicated to reduce CDI recurrence in patients >18 years of age and is administered while CDI antibiotic therapy is ongoing.

When comparing 12-week efficacy using standard of care (SoC) CDI treatment vs SoC plus bezlotoxumab (SoC+Bmab), recurrence rates in SoC and SoC+Bmab were 27.6% vs1 7.4%, respectively, in one trial, and 25.7% vs 15.7% in another. While generally well-tolerated, bezlotoxumab is associated with increased risk for exacerbating heart failure. Data relating to the cost-effectiveness of bezlotoxumab are currently pending.

Fecal microbiota transplant (FMT)— duodenal or colonic instillation of donor fecal microbiota to "restore" normal flora— is an evolving CDI therapy with promising results but difficult administration. Although FMT has high published success rates, the FDA's policy of "enforcement discretion" permits practitioners to proceed with FMT only as an Investigational New Drug. This requires signed, informed consent to FMT as an investigational therapy with unknown long-term risks.

The FDA deemed these protections necessary as ongoing studies of the human microbiome have yet to define what constitutes "normal flora," and some investigators highlight the possibility of transmitting flora or gut factors associated with obesity, metabolic syndrome, or malignancy.

Experimental CDI preventive modalities include new antibiotics, monoclonal antibodies, probiotics, select other novel agents, and *C. difficile* vaccinations. These vaccines include recombinant fusion proteins and adjuvant toxoids, both of which have generally favorable tolerance profiles, as well as robust immune responses in clinical trial subjects. However, the efficacy of these vaccines at preventing clinical disease is still to be demonstrated.

Lastly, the ubiquitous use of proton pump inhibitors (PPI) in ICUs plays a role in promoting CDI incidence, severity, and recurrence. Accordingly, the pros and cons of PPI use must be weighed in each patient.

CDI prevention in the hospital environment

Hospital-acquired CDIs (HA-CDI) and nosocomial transmission clearly occur. A recent study of electronic health record data demonstrated that patients who passed through the hospital's emergency department CT scanner within 24 hours after a patient with *C difficile* were twice as likely to become infected (Murray SG, et al. *JAMA Internal Medicine.* published online October 23, 2017. doi:10.1001). Receipt of antibiotics by prior bed occupants was associated with increased risk for CDI in subsequent patients, implying that antibiotics can directly affect the risk for CDI in patients who do not themselves receive antibiotics. As such, aggressive environmental cleaning in conjunction with hospital antimicrobial stewardship efforts, such as appropriate use of antibiotics known to increase CDI occurrence, are required to minimize HA-CDI.

Contact precautions should be strictly enforced; wearing gloves and gowns is necessary for every encounter when treating patients with *C difficile*, even during short visits. Hand sanitizer does not kill *C difficile*, and although soap-and-water hand washing works better, it may be insufficient alone, reinforcing the importance of using gloves with all patient encounters.

The strain placed on ICUs by CDI has been increasing over the past several years. Physicians and hospitals are at risk for lower performance scores and reduced reimbursement due to CDI relapses. As such, burgeoning areas of debate and research include efforts to quickly and accurately diagnose CDI along with reducing recurrence rates. Yet, with all the capital investment, the most significant and cost-effective method to reduce CDI rates remains proper and frequent hand washing with soap and water. Prevention of disease remains the cornerstone to treatment.

NAMDRC Report

Pulmonary societies review legislative agenda

BY PHIL PORTE

Executive Director, NAMDRC

In mid-September, NAMDRC, along with the American Thoracic Society, the American Association for Respiratory Care, the COPD Foundation, the American Lung Association, and others met to discuss the components of a legislative agenda for the coming years. The primary purpose behind the meeting was the premise that IF the current Republican majority would shift in either the House or Senate after the 2018 election, the community should be prepared to move an already agreed upon legislative agenda. CHEST was involved in the preliminary discussions, as well as follow-up, but was not in attendance at the meeting due to a scheduling conflict. There was also tacit agreement that as these policies are fleshed out and crafted into specific legislative language, the community would re-evaluate the current political climate to determine the value of pushing an agreed upon agenda prior to the 2018 elections.

Various patient groups were also invited to participate, but scheduling conflicts precluded some societies from participating but signaled their desire to work with the broad pulmonary medicine community to pursue common goals.

Each society brought its legislative priorities to the table, and there was active discussion on issues ranging from funding for NIH/NHLBI, to CDC and its COPD Action Plan, to a range of Medicare-related issues.

NAMDRC brought three specific Medicare coverage and payment issues to the discussion: home mechanical ventilation, payment for high flow oxygen therapy, and site of service/Section 603 issues.

Home mechanical ventilation is admittedly a complex issue, but it is moving forward in at least two political directions. First, Senator Bill Cassidy (R-LA) and a physician by training, has signaled his desire

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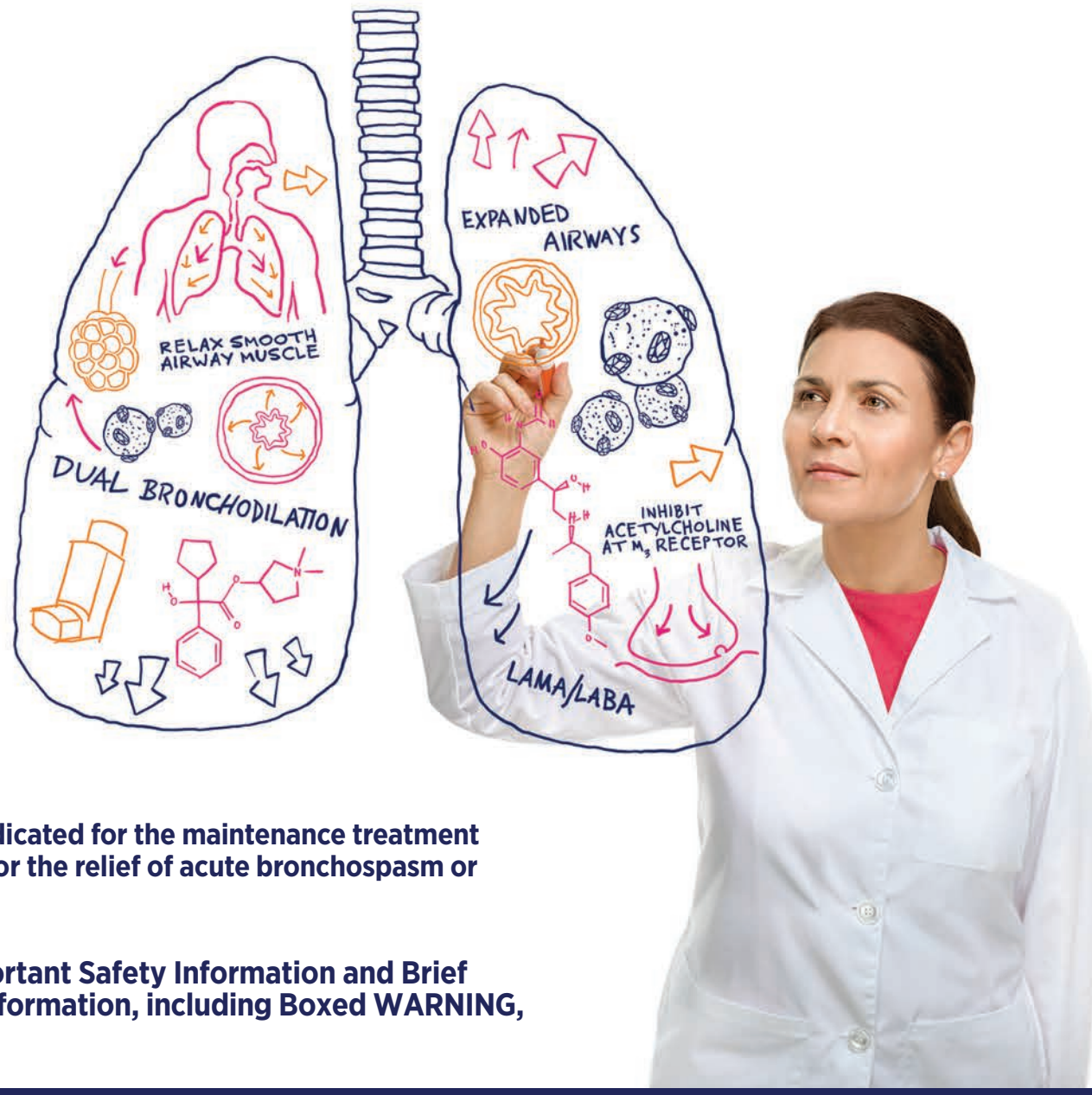
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



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, AZLP.

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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
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to move this issue forward, either legislatively or giving CMS one last chance to move forward through the regulatory structure. He agrees that a payment system that inhibits access to appropriate bi-level mechanical ventilators and encourages access to more complex life-sustaining ventilators, regardless of documented medical need, is appropriate. While CMS does have the authority to act, it has chosen to ignore repeated requests for action over the past 4 years.

Ironically, the House Energy and Commerce Committee, which shares jurisdiction on the House of Representatives with the Ways and Means Committee on Medicare issues, has sent a request to the Congressional Budget Office to provide a cost estimate (a "score" in Washington vernacular) of likely savings from a legislative solution to this matter. In the current political climate, a legislative proposal that actually saves $$$ is politically attractive, and we are working both the regulatory and legislative pathway to seek a workable solution.

On the oxygen therapy issue, there is growing evidence that, for a small group of Medicare beneficiaries who need high flow oxygen therapy as their disease progresses (pulmonary fibrosis, end-stage COPD, etc), there are no oxygen systems readily available to meet that need outside the home. At home, numerous concentrators can meet that need, but outside the home, the ideal solution, liquid systems, is not readily available because of the payment system tied to competitive bidding. CMS payment data indicate that a very low percentage of oxygen users need more than 4 liters per minute, and current law would make a payment adjustment unique to certain patients a very difficult hurdle, particularly in the era of competitive bidding, a legislative change is the best solution facing the community. The challenge is to craft legislative language that addresses the need but would preclude abuse by suppliers who might jump at the chance for higher payment for liquid, well above current payment levels. And because liquid systems fit into a "delivery model" business plan, contrary to portable oxygen concentrators and transfill systems, the solution is not as easy as a payment bump to make provision of liquid systems more attractive.

Site of service regulations are hitting pulmonary rehabilitation particularly hard, and CMS concedes that the only solution is a legislative one. Under current policy, a pulmonary rehab program that is located off campus but needs to expand or move from its current location (losing a lease, for example), if the expanded program is NOT within 250 yards of the main hospital campus, the program is then reimbursed at the physician fee schedule rate, a rate cut of approximately 50%. Needless to say, hospitals are not pursuing that approach. Likewise, a hospital that chooses to open a NEW program is also constrained, needing to locate within 250 yards of the main campus or face the dramatic cut in payment.

As these issues evolve and the political climate perhaps opens unique opportunities, we can expect the broad pulmonary community to pursue these and other issues.

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FRONTLINE MEDICAL COMMUNICATIONS

This month in *CHEST*

Editor's picks

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

ORIGINAL RESEARCH

Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results From an NTM Info and Research Patient Survey and the Bronchiectasis and NTM Research Registry.
By Dr. E. Henkle, et al.

Totally Implantable Intravenous Treprostinil Therapy in Pulmonary Hypertension: Assessment of the Implantation Procedure.
By Dr. A. Lautenbach, et al.

COMMENTARY

Crotalaria (Monocrotaline) Pulmonary Hypertension: The Fiftieth Anniversary.
By Dr. J. Kay.

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

2 Lin, P., et al., "Comparison of Percutaneous Ultrasound-Accelerated Thrombolysis versus Catheter-Directed Thrombolysis in Patients with Acute Massive Pulmonary Embolism." *Vascular*, Vol. 17, Suppl. 3, 2009, S137-S147.

3 Nykamp M., et al. "Safety and efficacy of ultrasound-accelerated catheter-directed lytic therapy in acute pulmonary embolism with and without hemodynamic instability." *J Vascular Surgery: Venous and Lymphatic Disorders* 2015; 3(5): 251-7.

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

5 Acute efficacy pending long-term data availability for OPTALYSE PE.

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