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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Courtesy Dr. Jonathan Corren

It took longer for those treated with tezepelumab to have a first exacerbation, noted Dr. Corren and colleagues.

Tezepelumab reduces exacerbations in asthma

BY BIANCA NOGRADY
Frontline Medical News

Patients whose asthma remains uncontrolled despite treatment may benefit from a new monoclonal antibody that targets an inflammatory cytokine known to be promoted in asthmatic airways, according to data presented at the annual congress of the European Respiratory Society.

Writing in the Sept. 7 issue of the New England Journal of Medicine, researchers reported on a phase 2, randomized placebo-controlled trial of three dosing regimens of subcutaneous tezepelumab, which targets the epithelial cell–derived cytokine thymic stromal lymphopoietin (TSLP). The trial involved 584 patients with uncontrolled asthma, despite treatment with long-acting beta-agonists and medium to high doses of inhaled glucocorticoids.

The investigators found that exacerbation rates were significantly lower for all three doses of tezepelumab, compared with placebo, with an overall 34% reduction in the risk of exacerbation with tezepelumab (N Engl J Med. 2017;377:936-46).

At 70 mg every 4 weeks, exacerbation rates were 61% lower than in the placebo group; at 210 mg every 4 weeks, they were 71% lower; and at 280 mg every 2 weeks, they were 66% lower

TIME TO FIRST EXACERBATION UPPED // *continued on page 4*

Statins linked to lower death rates in COPD

BY AMY KARON
Frontline Medical News

FROM *CHEST* ▪ Receiving a statin prescription within a year after diagnosis of chronic obstructive pulmonary disease was associated with a 21% decrease in the subsequent risk of all-cause mortality and a 45% drop in risk of pulmonary mortality, according to the results of a large retrospective administrative database study.

The findings belie those of the recent Simvastatin in the Prevention of COPD Exacerbation (STATCOPE) trial, in which daily simvastatin (40 mg) did not affect exacerbation rates or time to first exacerbation in high-risk COPD patients, wrote Larry D. Lynd, PhD, a professor at the at the University of British Columbia, Vancouver, and his associates. Their study was observational, but the association between statin use and decreased mortality "persisted across several measures of statin exposure," they wrote. "Our findings, in conjunction with previously reported evidence, suggest that there may be a specific subtype of COPD patients that may benefit from statin use." The study appears in the September issue of CHEST (2017;152;486-93).

COPD affects about 12% of adults aged 30

MOST RECEIVED ATORVASTATIN // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST

An interview with the incoming CHEST President

Page 59

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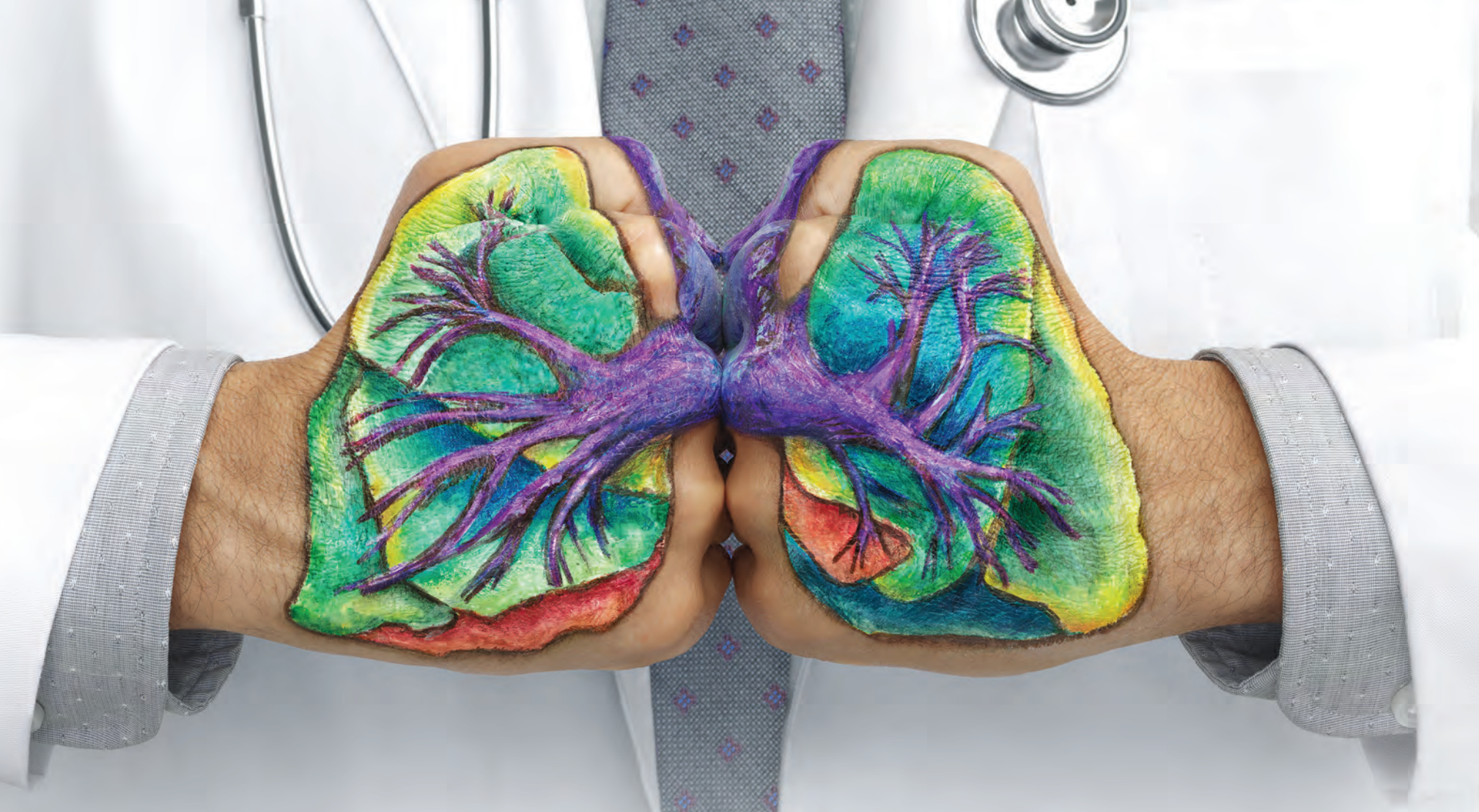

Indication

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

Select Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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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]

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(pirfenidone) tablets 267 mg 801 mg

"The observed improvements in disease control in patients who received tezepelumab highlight the potential pathogenic role of TSLP across different asthma phenotypes," said Dr. Jonathan Corren.

Time to first exacerbation upped // *continued from page 1*

(*P* was less than .001 in comparisons between each group and the placebo).

The overall annualized exacerbation rates by week 52 were 0.26 for the 70-mg group, 0.19 for the 210-mg group, and 0.22 for the 280-mg group, compared with 0.67 in the placebo group, regardless of a patient's baseline eosinophil count. Patients treated with tezepelumab had a longer time to first asthma exacerbation. They also experienced a significantly higher change from baseline in their pre-bronchodilator forced expiratory volume in 1 second at week 52, when compared with patients on the placebo.

"The observed improvements in disease control in patients who received tezepelumab highlight the potential pathogenic role of TSLP across different asthma phenotypes,"

reported Jonathan Corren, MD, of the University of California, Los Angeles, and his coauthors. "... Although TSLP is central to the regulation of type 2 immunity, many cell types that are activated by or respond to TSLP, such as mast cells, basophils, natural killer T cells, innate lymphoid cells, and neutrophils, may play a role in inflammation in asthma beyond type 2 inflammation."

The incidences of adverse events and serious adverse events were similar across all groups in the study. Three serious adverse events – pneumonia and stroke in the same patient and one case of Guillain-Barré syndrome – in patients taking tezepelumab, were deemed to be related to the treatment.

Tezepelumab 'most promising' asthma biologic to date

Tezepelumab is the first biologic that has a substantial positive effect on two important markers of the inflammation of asthma – namely, blood eosinophil counts and the fraction of exhaled nitric oxide, noted Elisabeth H. Bel, MD, PhD, in an editorial accompanying the New England Journal of Medicine's publication of this study (*2017;377:989-91*). It appears to be the broadest and most promising biologic for the treatment of persistent uncontrolled asthma to date, said Dr. Bel, of the department of respiratory medicine, Academic Medical Center, the University of Amsterdam.

The observation that tezepelumab reduces the level of both inflammatory markers shows that it hits a more upstream target and that it blocks at least two relevant inflammatory pathways in asthma, she noted. This is likely to be clinically relevant, since simultaneously increased exhaled nitric oxide levels and blood eosinophil counts are related to increased morbidity due to asthma.

Tezepelumab is the first biologic that has a substantial positive effect on two important markers of the inflammation of asthma, noted Elisabeth H. Bel, MD, PhD.

The study was supported by tezepelumab manufacturers MedImmune (a member of the AstraZeneca group) and Amgen. Six of the seven authors are employees of MedImmune or Amgen. One author declared support and honoraria from several pharmaceutical companies, one declared a related patent, and five also had stock options in either MedImmune or Amgen.

Dr. Bel declared consultancies and grants from pharmaceutical companies including AstraZeneca.

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: The impact of chronic respiratory disease on patients can be burdensome. Therapies seek to reduce this disease's impact on patients' lives.

The disease burden takes a particularly heavy toll when the response to therapies is less than optimal. Quality of life and health pay the price. The authors of this phase 2 trial advance another possible therapy which may hold promise for patients severely affected by persistent, treatment-resistant asthma.

Most received atorvastatin // *continued from page 1*

years and older worldwide and is associated with increased risk of progressive cardiovascular disease and cardiovascular mortality. "Localized chronic inflammation of the airways has long been observed in COPD patients, but there is a growing understanding of systemic inflammation in a subset of patients," the researchers noted. For example, studies have linked chronic low-level systemic inflammation or elevated C-reactive protein levels with increased risks of severe airway obstruction, other pulmonary outcomes, and adverse cardiovascular events. Such findings prompted experts to suggest that COPD progression results from systemic inflammation, not a "spill over" of pulmonary inflammation, and that statins might help slow or block this process. Although STATCOPE did not support this idea, several prior observational studies did. Inflammation-inhibiting therapy also reduced cardiovascular events and lung cancer in the recent CANTOS trial, which this issue covers on page 7.

"Localized chronic inflammation of the airways has long been observed in COPD patients, but there is a growing understanding of systemic inflammation in a subset of patients."

To further explore the question, the researchers analyzed linked health databases from nearly 40,000 patients aged 50 years and older who had received at least three prescriptions for an anticholinergic or a short-acting beta agonist in 12 months some time between 1998 and 2007. The first prescription was considered the date of COPD "diagnosis." The average age of the patients was 71 years; 55% were female.

A total of 7,775 patients (19.6%) who met this definition of incident COPD were prescribed a statin at least once during the subsequent year. These patients had a significantly reduced risk of subsequent all-cause mortality in univariate and multivariate analyses, with hazard ratios of 0.79 (95% confidence intervals, 0.68-0.91; *P* less than .002). Statins also showed a protective effect against pulmonary mortality, with univariate and multivariate hazard ratios of 0.52 (*P* = .01) and 0.55 (*P* = .03), respectively.

The protective effect of statins held up when the investigators narrowed the exposure period to 6 months after COPD diagnosis and when they expanded it to 18 months. Exposure to statins for 80% of the 1-year window after COPD diagnosis – a proxy for statin adherence – also led to a reduced risk of all-cause mortality, but the 95% confidence interval for the hazard ratio did not reach statistical significance (0.71-1.01; *P* = .06).

DR. LYND

The most common prescription was for atorvastatin (49%), usually for 90 days (23%), 100 days (20%), or 30 days (15%), the researchers said. While the "possibility of the 'healthy user' or the 'healthy adherer' cannot be ignored," they adjusted for other prescriptions, comorbidities, and income level, which should have helped eliminate this effect, they added. However, they lacked data on smoking and lung function assessments, both of which are "important confounders and contributors to mortality," they acknowledged.

Despite [its] limitations, the study results are intriguing and in line with findings from other retrospective cohorts, noted Or Kalchiem-Dekel, MD, and Robert M. Reed, MD, in an editorial published in CHEST (2017;152:456-7. doi: 10.1016/j.chest.2017.04.156).

How then can we reconcile the apparent benefits observed in retrospective studies with the lack of clinical effect seen in prospective trials, particularly the in the

Continued on following page

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: The interplay of multiple chronic diseases contributing to a patient's medical history is a complex one. As the provider seeks to treat the whole patient, improvements in common endpoints may occur. The observations of the authors of this study are interesting. Further study could help better understand the effects of statins in COPD patients.

IN THIS ISSUE

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

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CANTOS sings of new strategy for reducing CV events

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Inhibiting the interleukin-1 beta innate immunity pathway with canakinumab reduced recurrent cardiovascular events and lung cancer in the groundbreaking phase 3 CANTOS trial, Paul M. Ridker, MD, reported at the annual congress of the European Society of Cardiology.

"These data provide the first proof that inflammation inhibition in the absence of lipid lowering can improve atherogenic outcomes and potentially alter progression of some fatal cancers," declared Dr. Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital, Boston, and professor of medicine at Harvard Medical School.

"Just like we've learned that lower LDL is better, I think we're now learning that lower inflammation is better," he said.

CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) was a randomized, double-blind, placebo-controlled trial involving 10,061 patients in 39 countries, all of whom had a previous MI and a chronically high level of systemic inflammation as reflected in a median baseline high-sensitivity C-reactive protein (CRP) level of 4.1 mg/L. Ninety-one percent of participants were on statin therapy, with a median LDL cholesterol of 82 mg/dL when randomized to subcutaneous canakinumab at 50, 150, or 300 mg or to placebo once every 3 months.

Canakinumab is a fully human monoclonal antibody targeting IL-1B, a key player in systemic inflammation. The cytokine is activated by the nucleotide-binding oligomerization domain-like receptor protein 3

Continued on following page

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STATCOPE study? Could it be that both negative and positive studies are "correct"? Prospective studies have thus far not been adequately powered for mortality as an endpoint, said the editorialists, who are both at the pulmonary and critical care medicine division, University of Maryland, Baltimore.

This most recent study reinforces the idea that statins may play a beneficial role in COPD, but it isn't clear which patients to target for therapy. It is unlikely that the findings will reverse recent recommendations by the American College of Chest Physicians and Canadian Thoracic Society against the use of statins for the purpose of prevention of COPD exacerbations, but the suggestion of survival advantage related to statins certainly may breathe new life into an enthusiasm greatly tempered by STATCOPE, they said.

Canadian Institutes of Health Research supported the study. One coinvestigator disclosed consulting relationships with Teva, Pfizer, and Novartis; the others had no conflicts of interest. Neither editorialist had conflicts of interest.

Increase in sepsis incidence stable from 2009 to 2014

BY RICHARD FRANKI
Frontline Medical News

The trend for sepsis incidence from 2009 to 2014, "calculated relative to the observed 2014 rates," was a stable increase of 0.6% per year using the more accurate of two forms of analysis, investigators reported.

The incidence of sepsis was an adjusted 5.9% among hospitalized adults in 2014, with in-hospital mortality of 15%, according to a retrospective cohort study published online Sept. 13 in JAMA.

"Most studies [of sepsis incidence] have used claims data, but increasing clinical awareness, changes in diagnosis and coding practices, and variable definitions have led to uncertainty about the accuracy of reported trends," wrote Chanu Rhee, MD, of Harvard Medical School, Boston, and his associates (JAMA. 2017 Sep 13. doi: 10.1001/jama.2017.13836).

They used claims-based estimates using ICD-9-CM codes and clinical data from electronic health records (EHRs) to analyze data for more than 2.9 million adults admitted to 409 U.S. academic, community, and federal acute-care hospitals in 2014. The claims-based explicit-codes approach used discharge diagnoses of severe sepsis (995.92) or septic shock (785.52), while the EHR-based, clinical-criteria method included blood cultures, antibiotics, and concurrent organ dysfunction with or without the criterion of a lactate level of 2.0 mmol/L or greater.

The explicit-codes approach produced an increase of 10.3% per year in sepsis incidence from 2009 to 2014, compared with 0.6% per year for the clinical-criteria approach, while in-hospital mortality declined by 7% a year using explicit codes and 3.3% using clinical criteria, Dr. Rhee and his associates reported.

"EHR-based criteria were more sensitive than explicit sepsis codes on medical record review, with comparable [positive predictive value]; EHR-based criteria had similar sensitivity to implicit or explicit codes combined but higher [positive predictive value]," they said. The estimates provided by Dr. Rhee and his associates lead to "a clearer understanding of trends in the incidence and mortality of sepsis in the United States but also a better understanding of the challenges in improving ICD coding to accurately document the global burden of sepsis," Kristina E. Rudd, MD, of the University of Washington, Seattle, and her associates said in an editorial (JAMA. 2017 Sep 13. doi: 10.1001/jama.2017.13697).

The Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, National Institutes of Health, Department of Veterans Affairs, National Institutes of Health Clinical Center, and National Institute of Allergy and Infectious Diseases funded the study. Three authors received personal fees from private companies or served on advisory boards or as consultants.

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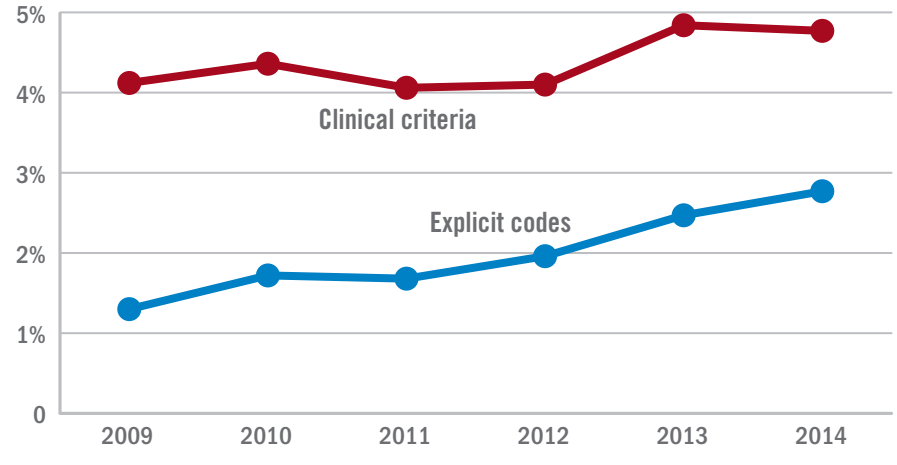
Unadjusted sepsis incidence, 2009-2014



Notes: Based on data for adults admitted to 409 academic, community, and federal hospitals. Rates for 2009-2013 calculated relative to observed 2014 rates.

Source: JAMA 2017 Sep 13. doi: 10.1001/jama.2017.13836

Continued from previous page

(NLRP3) inflammasome, a part of the innate immune system. Canakinumab is approved as Ilaris for treatment of several uncommon rheumatologic diseases, including cryopryin-associated periodic syndrome and systemic juvenile idiopathic arthritis.

At a median follow-up of 3.7 years, the incidence of the primary composite efficacy endpoint of nonfatal MI, nonfatal stroke, or cardiovascular death was 4.5 events per 100 person-years in the control group, significantly higher than the 3.86 and 3.9 events per 100 person-years in patients on canakinumab at 150 and 300 mg, respectively.

Since event rates were virtually identical in the 150- and 300-mg study arms, Dr. Ridker combined those two patient groups in his analysis. They showed a 15% reduction in the risk of the primary efficacy endpoint, compared with placebo-treated controls, along with a 39% reduction from baseline in CRP. They also were 30% less likely to undergo percutaneous coronary intervention or coronary artery bypass graft during follow-up.

"That's quite important, because that's a progression-of-atherosclerosis endpoint and also obviously a cost and financial endpoint," he observed.

A key finding in CANTOS was that patients with a reduction in CRP at or exceeding the median decrease just 3 months into the study – that is, after a single injection – had a 27% reduction in major vascular events during follow-up. Patients with a lesser reduction in CRP at that point did not experience a significant reduction in the primary endpoint, compared with placebo.

"The clinician in me would say we probably ought to give a single dose of the drug, see what happens, and if you get a large inflammation reduction we could perhaps consider treating that patient, but if you did not get a large reduction perhaps this is not a therapy for that patient. Why not avoid the toxicity in people who aren't going to respond?" Dr. Ridker said.

Side effects related to canakinumab consisted of mild leukopenia and a small but statistically significant increase in fatal infections, which he called "not surprising."

"It's in the same range as one gets in treating rheumatoid arthritis with a biologic drug, which rheumatologists are very comfortable doing.

Dr. Paul M. Ridker

You would imagine that, if this does become a treatment, physicians will get much better at bringing patients in early when they have signs and symptoms of infection," the cardiologist continued.

Patients on canakinumab showed significant reductions in incident rheumatoid arthritis, gout, and osteoarthritis. The drug had no kidney or liver adverse events.

Cancer was a prespecified secondary outcome in CANTOS. The investigators saw the trial as an opportunity to test a longstanding hypothesis that inhibiting IL-1B would have a positive impact on lung cancer in particular.

"Smoking, exposure to diesel fuel, inhalation of asbestos or other silicates – these cause inflammation which activates the NLRP3 inflammasome, but in the pulmonary system rather than the arteries," explained Dr. Ridker, who reported serving as a consultant to Novartis.

An entry requirement in CANTOS was that patients needed to be free of known cancer. During study follow-up, 129 patients were diagnosed with lung cancer. The risk was reduced in dose-dependent fashion with canakinumab: by 39% relative to placebo in the 150-mg group and by 67% in the 300-mg group. Lung cancer mortality was reduced by 77% in the canakinumab 300-mg group.

"I don't think this is about oncogenesis per se. I think the tumors are already there, but they don't progress because we've altered the tumor's inflammatory microenvironment," he continued.

Simultaneous with Dr. Ridker's presentation in Barcelona, both the atherosclerotic disease findings (N Engl J Med. 2017 Aug 27. doi: 10.1056/NEJMoa1707914) and the cancer findings (Lancet. 2017 Aug 27. doi: 10.1016/S0140-6736(17)32247-X) were published.

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Bedside imaging finds best PEEP settings

BY MICHELE G. SULLIVAN
Frontline Medical News

A noninvasive bedside imaging technique can individually calibrate positive end-expiratory pressure settings in patients on extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS), a study showed.

The step-down PEEP (positive end-expiratory pressure) trial could not identify a single PEEP setting that optimally balanced lung overdistension and lung collapse for all 15 patients. But, electrical impedance tomography (EIT) allowed investigators to individually titrate PEEP settings for each patient, Guillaume Franchineau, MD, wrote (Am J Respir Crit Care Med. 2017;196[4]:447-57. doi: 10.1164/rccm.201605-1055OC).

"We found that EIT could provide individual, noninvasive, real-time, radiation-free lung imaging with reliable global and regional dynamic analyses of the lungs on ECMO," wrote Dr. Franchineau of the Pierre and Marie Curie University, Paris. "Using EIT allowed monitoring of the PEEP effect that prevented excessive lung collapse or overdistension. ... The large variability of EIT-based best compromise PEEP settings … reinforces the notion of an individually tailored approach to mechanical ventilation. Because of the wide diversity of respiratory-system mechanical properties among patients, bedside tools for monitoring mechanical ventilation on ECMO are crucial to achieve this goal."

The 4-month study involved 15 patients (aged, 18-79 years) who were in acute respiratory distress syndrome for a variety of reasons, including influenza (7 patients), pneumonia (3), leukemia (2), and 1 case each of *Pneumocystis*, antisynthetase syndrome, and trauma. All patients were receiving ECMO with a constant driving pressure of 14 cm H_2O. After verifying that the inspiratory flow was 0 at the end of inspiration, PEEP was increased to 20 cm H_2O (PEEP 20) with a peak inspiratory pressure of 34 cm H_2O. $PEEP_{20}$ was held for 20 minutes and then lowered by 5-cm H_2O decrements with the potential of reaching $PEEP_0$.

The EIT device, consisting of a silicone belt with 16 surface electrodes, was placed around the thorax aligning with the sixth intercostal parasternal space and connected to a monitor. By measuring conductivity and impeditivity in the underlying tissues, the device generates a low-resolution, two-dimensional image. The image was sufficient to show lung distension and collapse as the PEEP settings changed. Investigators looked for the best compromise between overdistension and collapsed zones, which they defined as the lowest pressure able to limit EIT-assessed collapse to no more than 15% with the least overdistension.

There was no one-size-fits-all PEEP setting, the authors found. The setting that minimized both overdistension and collapse was $PEEP_{15}$ in seven patients, $PEEP_{10}$ in six patients, and $PEEP_5$ in two patients.

At each patient's optimal PEEP setting, the median tidal volume was similar: 3.8 mL/kg ideal body weight for $PEEP_{15}$, 3.9 mL/kg ideal body weight for $PEEP_{10}$, and 4.3 mL/kg ideal body weight for $PEEP_5$.

Respiratory system compliance was also similar among the groups, at 20 mL/cm H_2O, 18 mL/cm H_2O, and 21 mL/cm H_2O, respectively. However, arterial partial pressure of oxygen decreased as the PEEP setting decreased, dropping from 148 mm Hg to 128 mm Hg to 100 mm Hg, respectively. Conversely, arterial partial pressure of CO_2 increased (32-41 mm Hg).

EIT also allowed clinicians to pinpoint areas of distension or collapse. As PEEP decreased, there was steady ventilation loss in the medial-dorsal and dorsal regions, which shifted to the medial-ventral and ventral regions.

"Most end-expiratory lung impedances were located in medial-dorsal and medial-ventral regions, whereas the dorsal region constantly contributed less than 10% of total end-expiratory lung impedance," the authors noted.

"The broad variability of EIT-based best compromise PEEPs in these patients with severe ARDS reinforces the need to provide ventilation settings individually tailored to the regional ARDS-lesion distribution," they concluded. "To achieve that goal, EIT seems to be an interesting bedside noninvasive tool to provide real-time monitoring of the PEEP effect and ventilation distribution on ECMO."

Positive PEEP trial, but questions remain

This first study to examine EIT in patients under extracorporeal membrane oxygenation shows important clinical potential, but also raises important questions, Claude Guerin, MD, wrote in an accompanying editorial. (Am J Respir Crit Care Med. doi: 10.1164/rccm.201701-0167ed).

The ability to titrate PEEP settings to a patient's individual needs could substantially reduce the risk of lung derecruitment or damage by overdistension.

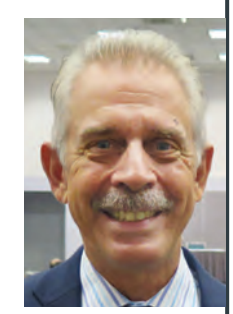
The current study, however, has limitations that must be addressed in the next phase of research, before this technique can be adopted into clinical practice, noted Dr. Guerin, a pulmonologist at the Hospital de la Croix Rousse, Lyon, France. The 5-cm H_20 PEEP steps may be too large to detect relevant changes, he said.

In several other studies, PEEP was reduced more gradually in 2- to 3-cm H_2O increments. "Surprisingly, PEEP was reduced to 0 cm H_2O in this study, with this step main-

Continued on following page

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: We have learned that patients with ARDS should be treated with mechanical ventilation in a fashion that minimizes driving pressure and optimizes PEEP. The use of electrical impedence tomography to noninvasively inform clinicians about optimal PEEP in ARDS patients receiving extracorporeal membrane oxygenation is therefore intriguing. Conclusions are limited by the small size of this study. Further work will be needed to learn if these measurements will be generally applicable.



Doubts about pediatric CAP diagnostic practices

BY THOMAS R. COLLINS
Frontline Medical News

New studies raise doubts on the reliability of physical exam findings in suspected pediatric community-acquired pneumonia cases and on the value of blood cultures in hospitalized pediatric CAP cases.

In one study, 128 cases of suspected CAP in children aged 3 months to 18 years presenting to an ED from July 2013 to May 2016 underwent paired assessments within 20 minutes of each other. Only 3 of 19 exam findings used to diagnose CAP – wheezing, retractions, and respiratory rate – had acceptable levels of inter-rater reliability, with the lower end of the 95% confidential interval at a Fleiss' kappa value of 0.4 or higher.

Eight exam findings – capillary

Continued on following page

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tained for 20 minutes, raising the risk of derecruitment and further stretching once higher PEEP levels were resumed."

The investigators did not perform any recruitment maneuvers before proceeding with PEEP adjustment. This is contrary to what has been done in prior animal and human studies.

The computation of driving pressure was done without taking total PEEP into account. "As total PEEP is frequently greater than PEEP in patients with [acute respiratory distress syndrome], driving pressure can be overestimated with the common computation."

The optimal PEEP that the investigators aimed for was determined retrospectively from an offline analysis of the data; this technique would not be suitable for bedside management. "When 'optimal' PEEP was defined from [EIT criteria], from a higher Pa_{O2} [arterial partial pressure of oxygen] or from a higher compliance of the respiratory system during the decremental PEEP trial, these three criteria were observed together in only four patients with [acute respiratory distress syndrome]."

The study was done only once and cannot comply with the need for regular PEEP-level assessments over time, as could be done with some other strategies.

"Further studies should also consider taking into account the role of chest wall mechanics," Dr. Guerin said.

Nevertheless, he concluded, EIT-based PEEP titration for each individual patient represents a prospective tool for assisting with the treatment of acute respiratory distress syndrome, and should be fully investigated in a large, prospective trial.

Dr. Franchineau reported receiving speakers fees from Mapquet. Dr. Guerin had no relevant financial disclosures.

msullivan@frontlinemedcom.com
On Twitter @alz_gal

CDC/Amanda Mills

Continued from previous page

refill time, cough, rhonchi, head bobbing, behavior, grunting, general appearance, and decreased breath sounds – had poor to fair reliability, with a kappa of 0-0.4, the investigators found. These results came from an ongoing prospective cohort study of children with suspected CAP called Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine, or CARPE DIEM.

"The reliability of these findings must be considered in the clinical management and research of children with CAP," said lead author Todd Florin, MD, associate research director in emergency medicine at Cincinnati Children's Hospital Med-

ical Center and his associate. (Pediatrics. 2017;140[3]:e20170310)

In a retrospective cohort analysis, researchers found that just 2.5% of 2,568 hospitalized children with CAP who had a blood culture performed actually grew a pathogen. And of the detected pathogens, 82% were susceptible to penicillin. *Streptococcus pneumoniae* accounted for 78% of all the pathogens that were found; it was detected in only 2% of all children who had blood cultures taken.

Just 11 children – or 0.43% of the children with a blood culture performed – had growth of a pathogen that was not treatable with penicillin, said lead author Mark Neuman, MD, director of research at Boston Children's Hospital and his associates (Pediatrics. 2017;140[3]:e20171013).

The analysis was drawn from a cohort of 7,509 children hospitalized from 2007 to 2011, with children with complex chronic conditions excluded. Data for the analysis came from the Pediatric Health Information System Plus database, in which administrative, billing, laboratory, and radiographic information is stored from six tertiary children's hospitals.

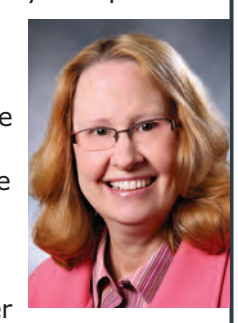
The investigators said that one challenge is that when blood cultures are drawn early in the course of evaluation and treatment, the severity of the child's CAP might not be apparent, which makes it difficult to know which children would benefit from a blood culture.

The routine performance of blood cultures in these children may not be indicated," Dr. Neuman and his associates said. "Researchers in future studies should seek to identify the clinical characteristics of children in whom obtaining blood cultures would lead to changes in clinical management, especially when identifying those patients at risk for CAP caused by organisms not susceptible to guideline-recommended, narrow-spectrum antibiotics."

Both studies were funded by the National Institutes of Health. For the physician exam study, additional funding was provided by individual grants from the Gerber Foundation, the National Center for Research Resources and the National Center for Advancing Translational Sciences, the National Institute for Allergy and Infectious Diseases and the National Institutes of Health, and a Trustee Award from Cincinnati Children's Hospital Medical Center. For the blood cultures study, individual researchers received funding from the National Institute of Allergy and Infectious Diseases and the Agency for Healthcare Research and Quality. For the physician exam study, no financial disclosures were reported. For the blood cultures study, Anne Blaschke, MD, PhD, reported receiving research funding from and other financial relationships with BioFire Diagnostics.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This study is important, because it included a large number of children. We have known for a long time that blood cultures are typically not helpful in older infants and children with CAP. The study also reminds me when educating residents and medical students that physical exam won't necessarily distinguish between bacterial vs viral pneumonias.



Can we stop worrying about the age of blood?

BY CHRISTOPHER L. CARROLL, MD, MS, FCCP

Blood transfusions are common in critically ill patients; two in five adults admitted to an ICU receive at least one transfusion during their hospitalization (Corwin HL, et al. *Crit Care Med.* 2004;32[1]:39). Recently, there has been growing concern about the potential dangers involved with prolonged blood storage. Several provocative observational and retrospective studies found that prolonged storage time (ie, the age of the blood being transfused) negatively affects clinical outcomes (Wang D, et al. *Transfusion.* 2012;52[6]:1184). But now, some newly published trials on blood transfusion practice, including one published in late September 2017 (Cooper DJ, et al. *N Engl J Med.* Published online, September 27, 2017) seem to debunk much of this literature. Was all of the concern about age of blood overblown?

The appeal of "fresh" blood is intuitive. As consumers, we're conditioned that the fresher the better. Fresh food tastes best. Carbonated beverages go "flat" over time. The newest iPhone® device is superior to your old one. So, of course, it follows that fresh blood is also better for your health than older blood.

But, in order to have a viable transfusion service, blood has to be stored. Blood is a scarce resource, and blood banks need to keep an adequate supply on hand for expected clinical necessities, as well as for emergencies. Donors can't be on standby, waiting in the hospital to provide immediate whole blood transfusion. Also, blood needs to be tested for infections and for potential interactions with the patient, and whole blood must be broken down into individual components for transfusion. All of this requires time and storage.

According to the US FDA, blood can safely be stored for up to 42 days, requiring that there be less than 1% hemolysis at the end of storage, and that more than 75% of the red blood cells remain in circulation 24 hours after the transfusion. But some have suggested that these specifications aren't comprehensive enough, citing studies that have linked prolonged storage to the development of "red blood storage lesion." Red blood storage lesion has been theorized to have a variety of effects, including altered immunologic response and defective oxygen carrying capacity (Spinella PC, et al. *Transfusion.* 2011;51[4]:894). But do these changes have clinical implications?

In a randomized study of 100 critically ill adults supported by mechanical ventilation, 50 were randomized to receive "fresh" blood (median storage age 4 days, interquartile range 3-5 days) and 50 were randomized to receive "standard" blood (median storage age 26.5 days, interquartile range 21-36 days) (Kor DJ, et al. *Am J Respir Crit Care Med.* 2012;185[8]:842). The primary outcome was gas exchange, as prolonged storage of red blood cells could potentially lead to an increased inflammatory response in patients. However, the authors found no difference in gas exchange between the two groups, and there were no differences in immunologic function or coagulation status.

The ABLE (Age of Blood Evaluation) trial was a randomized, blinded trial of transfusion practices in critically ill patients (Lacroix J, et al. *N Engl J Med.* 2015;372:1410). In 64 centers in Canada and Europe, 2,430 critically ill adults were randomized to receive either "fresh" blood (mean storage age 6.1 ± 4.9 days) or "standard" blood (mean storage age 22.0 ± 8.4 days). The primary outcome was 90-day mortality, with a power of 90% to detect a 5% change in mortality between the two groups. The investigators found no statistically significant difference in 90-day mortality between the "fresh" and "standard" groups (37% vs 35.3%; hazard ratio 1.1; 95% CI 0.9 – 1.2). Additionally, there were no differences in secondary outcomes, including multiorgan system dysfunction, duration of supportive care, or development of nosocomial infections.

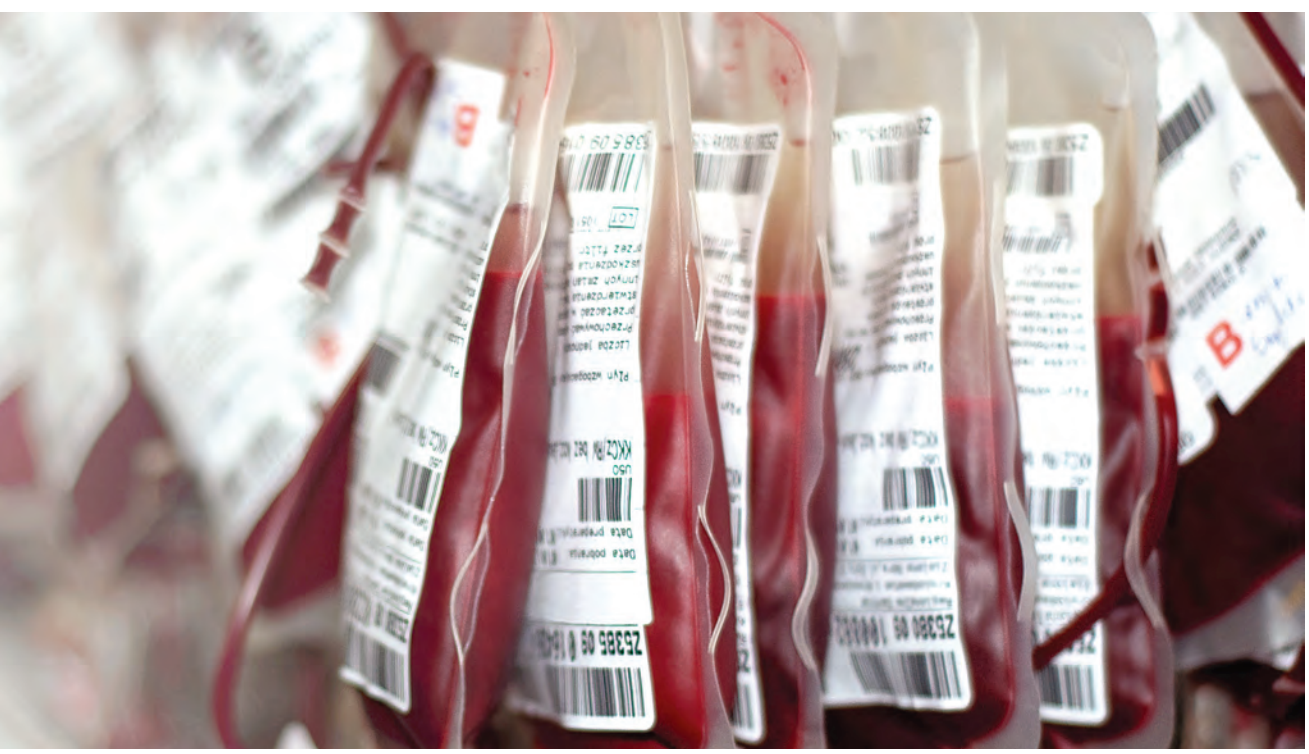
Dr. Carroll is Professor of Pediatrics, University of Connecticut, Division of Critical Care, Connecticut Children's Medical Center, Hartford, Connecticut.

The INFORM (Informing Fresh versus Old Red Cell Management) trial was a randomized study of patients hospitalized in six centers in Canada, Australia, Israel, and the United States (Heddle NM, et al. *N Engl J Med.* 2016;375[2]:1937). A total of 24,736 patients received transfusions with either "fresh" blood (median storage age 11 days) or "standard" blood (median storage age 23 days). The primary outcome was in-hospital death, with a 90% power to detect a 15% lower relative risk. When comparing the 8,215 patients who received "fresh" blood and the 16,521 patients who received "standard" blood, the authors found no difference in mortality between the two groups (9.1% vs 8.8%; odds ratio 1.04; 95% CI 0.95 to 1.14). Furthermore, there were no differences in outcomes in the high-risk subgroups that included patients with cancer, patients in the ICU, and patients undergoing cardiovascular surgery.

A meta-analysis examined 12 trials of patients who received "fresh" blood compared with those who received "older" or "standard" blood (Alexander PE, et al. *Blood.* 2016;127[4]:400); 5,229 patients were included in these trials, in which "fresh" blood was defined as blood stored for 3 to 10 days and "older" blood was stored for longer durations. There was no difference in mortality between the two groups (relative risk 1.04; 95% CI 0.94 - 1.14), and no difference in adverse events (relative risk 1.02; 95% CI 0.91 - 1.14). However, perhaps surprisingly, "fresh" blood was associated with an increased risk of nosocomial infections (relative risk 1.09; 95% CI 1.00 - 1.18).

And finally, in the recently published TRANSFUSE trial (Cooper DJ, et al. *N Engl J Med.* Published online, September 27, 2017), 4,994 critically ill adults were randomized by 59 centers in five countries to receive transfusions stored for a short-term (median storage of 11 days) or long-term (median 21 days). Similar to the other three randomized trials, there was no difference in mortality between the two groups at both 90 and 180 days.

So, can we stop worrying about the age of the blood that we are about to transfuse? Probably. Taken together, these studies suggest that differences in the duration of red blood cell storage allowed within current US FDA standards aren't clinically relevant, even in critically ill patients. At least, for now, the current practices for age of blood and duration of storage appear unrelated to adverse clinical outcomes.



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Transient tachypnea ups bronchiolitis risk

BY BRUCE JANCIN
Frontline Medical News

MADRID – A new Finnish study raises a provocative question: Is transient tachypnea of the newborn really transient?

Transient tachypnea of the newborn (TTN) has traditionally been viewed as a benign, self-limited condition involving 1-3 days of respiratory distress. But data from Finland's comprehensive national health registries indicate that TTN in term babies is associated with significantly increased risk of subsequent bronchiolitis during infancy, Otto Helve, MD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

Data from Finland's comprehensive national health registries indicate that transient tachypnea of the newborn in term babies is associated with significantly increased risk of subsequent bronchiolitis during infancy.

"This association suggests similar pathogenic mechanisms in transient tachypnea of the newborn and bronchiolitis. We suggest that an intrinsic defect in sodium ion–driven pulmonary fluid transport may predispose to clinically significant bronchiolitis during the first year of life," said Dr. Helve, a pediatrician at the National Institute for Health and Welfare, Helsinki, and the University of Helsinki.

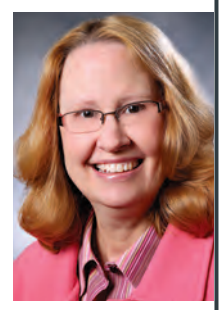
Of more than 1 million term babies born in Finland during 1996-2015, 17,569 were diagnosed with TTN. During the same period, 40,338 infants were hospitalized with a diagnosis of bronchiolitis attributable to respiratory syncytial virus infection.

In a multivariate analysis adjusted for birth year, gender, delivery method, gestational age, and parity, TTN was independently associated with a 1.2-fold increased risk of bronchiolitis during the first year of life.

Dr. Helve reported having no financial conflicts of interest regarding his study.

bjancin@frontlinemedcom.com

VIEW ON THE NEWS



Susan Millard, MD, FCCP, comments: In the old days, transient tachypnea of the newborn (TTN) was a diagnosis that didn't get much press. Now we know that children with primary ciliary dyskinesia have an increased incidence of TTN at birth and this registry reports a risk for future bronchiolitis. We clearly need to learn more about this neonatal respiratory disease!

Thirdhand smoke shaping up as potential hazard

BY BRUCE JANCIN
Frontline Medical News

DENVER – Thirdhand smoke – the persistent residue that collects on indoor surfaces where people have smoked – is "clearly" a potentially hazardous exposure, John M. Rogers, PhD, said at the annual meeting of the Teratology Society.

Everyone knows about the hazards of secondhand smoke, which have led to widespread bans on smoking in public spaces. Still, the Centers for Disease Control and Prevention estimates that 58 million nonsmokers in the United States are exposed to secondhand smoke on a regular basis. And where there is secondhand smoke, there is typically exposure to thirdhand smoke as well.

The odiferous thirdhand smoke residue, composed of tobacco-smoke toxins and known cancer-causing agents, adheres to house dust, furniture, carpets, walls, window glass, and other surfaces.

"If you walk into a hotel room you were told is a nonsmoking room and you take one breath and you know it's not nonsmoking, that's thirdhand smoke. Thirdhand smoke is all over the place where smokers have been," explained Dr. Rogers, director of the toxicity assessment division at the Environmental Protection Agency in Research Triangle Park, N.C.

Tobacco smoke contains thousands of chemicals. Among those known to be harmful developmentally are nicotine, tobacco-specific nitrosamines, lead, cadmium, and various reactive molecules. The odiferous thirdhand smoke residue, composed of tobacco-smoke toxins and known cancer-causing agents, adheres to house dust, furniture, carpets, walls, window glass, and other surfaces. It's difficult to remove. Unlike with secondhand smoke, ventilation won't do the job.

The main potential health risk is to young children, who ingest thirdhand smoke by the hand-to-mouth route and skin contact.

Thirdhand smoke is a much newer concept than secondhand smoke and has not yet actually been shown to pose a significant health risk. The term "thirdhand smoke" is still unfamiliar to many physicians and the general public. But that is likely to change.

Thirdhand smoke has become an area of intensive research interest, with California leading the way. The Tobacco-Related Disease Research Program, a state agency funded by a tax on the sale of tobacco products, has created a research consortium on thirdhand smoke, with studies underway investigating thirdhand smoke's precise chemical composition,

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E-cigarettes most popular among youngest adults

BY RICHARD FRANKI
Frontline Medical News

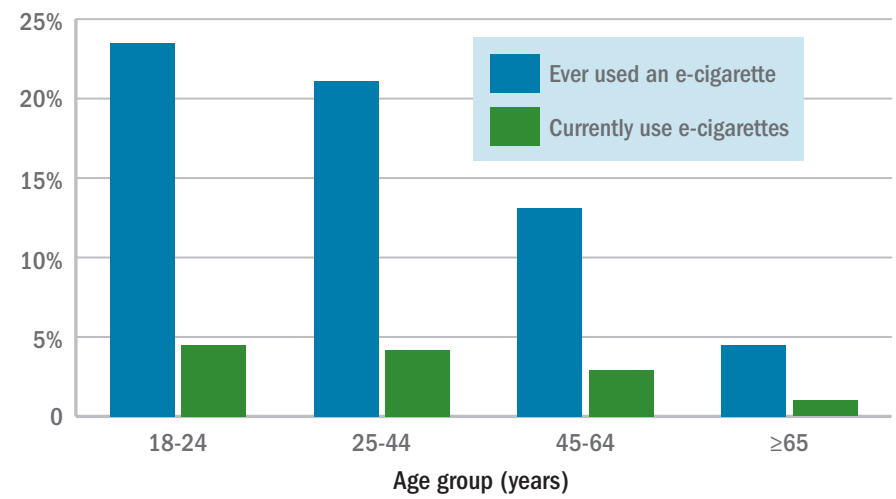
Over 15% of adults have used electronic cigarettes at some time, and about 3% reported current use when they were surveyed in 2016, according to the Centers for Disease Control and Prevention.

When those numbers are broken down by age group, the youngest adults are the most likely e-cigarette users: 23.5% of those aged 18-24 years had ever vaped and 4.5% were currently vaping either every day or on some days, the CDC reported (MMWR. 2017;66[33]:892).

For adults aged 25-44 years, ever use of e-cigarettes was 21.1% and current use was 4.2%, with adults aged 45-64 years at 13.1% and 2.9% and those aged 65 years and older checking in at 4.5% ever use and 1% current use, based on estimates derived from National Health Interview Survey data.

rfranki@frontlinemedcom.com

Prevalence of e-cigarette use among adults by age, 2016



Note: Based on data from the National Health Interview Survey.
Source: MMWR. 2017;66(33):892

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cytotoxicity, genotoxicity, and true impact on public health (www.trdrp.org).

Concern regarding thirdhand smoke's potential public health impact ramped up in response to a study in which investigators at the University of York (England) measured levels of various tobacco-specific nitrosamines, *N*-nitrosamines, and nicotine in house dust samples from the homes of smokers. The researchers estimated that years of early-life exposure to these compounds at the levels they detected could result in one excess case of cancer per 1,000 exposed individuals (Environ Int. 2014 Oct;71:139-47).

In addition to his update on thirdhand smoke, Dr. Rogers also touched on other recent tobacco-related developments, including a determination by the Food and Drug Administration that there has been no decline in tobacco use in the last 5 years in adolescents and young adults. While cigarette smoking by young people decreased, this was offset by a large increase in the use of electronic cigarettes and a smaller rise in the use of hookah tobacco. Indeed, e-cigarette use is now about double that of cigarettes among youth.

Also of concern is evidence of a striking socioeconomic disparity in smoking prevalence: Low-education, low-income Americans have far higher tobacco use rates.

"That's pretty alarming," he said. "I think a lot of people in this audience probably don't see a lot of smoking these days, but it's still around."

Dr. Rogers drew attention to updated evidence reviews on the reproductive and developmental effects of smoking contained in the U.S. Surgeon General's voluminous 2014 report on the health consequences of smoking. The report concluded that there is now sufficient evidence to infer a causal relationship between maternal smoking in pregnancy, ectopic pregnancy, and orofacial clefts. The available evidence is "suggestive but not sufficient" to infer causality between maternal smoking in pregnancy and atrial septal defects, clubfoot, gastroschisis, and attention-deficit/hyperactivity disorder and other disruptive behavior disorders.

Dr. Rogers reported having no financial disclosures related to his presentation, which he noted did not necessarily reflect the views and policies of the EPA.

bjancin@frontlinemedcom.com

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Also of concern is evidence of a striking socioeconomic disparity in smoking prevalence: Low-education, low-income Americans have far higher tobacco use rates.

Respiratory infections linked to celiac disease

BY LORI LAUBACH
Frontline Medical News

The frequency of respiratory infections in the first 2 years of life could distinguish children who will develop celiac disease (CD) from those who will not in those with a family history of CD, according to Renata Auricchio, MD, University of Naples (Italy) Federico II, and her associates.

In a prospective cohort study, 373 newborns from families with at least one relative with CD were recruited. The cumulative incidence of new cases of CD was 6% at 3 years and 13.5% at 5 years of age, the researchers noted. In the first year when no child produced anti–tissue transglutaminase (anti-tTG) antibodies, respiratory infections (upper and lower tract) were more common among the

case patients than among the controls (58% vs. 40%). During the second year, respiratory infections were again more frequent among the case patients than among controls (52% vs. 32%). And in the third year of life when most of the case patients were diagnosed with CD, no clinical event was more frequent in the case patients than in the control group.

In a multivariate analysis, the researchers found that only respiratory infections in the second year of life were associated with a twofold increase in the risk of developing CD (odds ratio, 2.25; $P = .04$). The second variable was respiratory infections in the first year of life, which had a score of 1.58. Results from the stepwise discriminant analysis suggested respiratory infections in the first and second years of life significantly contributed to the index of discrimination between the case patients and the controls.

"In this study, we report that early infections significantly contribute to the risk of developing CD," Dr. Auricchio and her associates concluded. "It is possible that the exposure to early infection stimulates a genetically predisposed immune profile, which contributes to the switch from tolerance to intolerance to gluten, which is a common food antigen."

Read the full study in Pediatrics (doi: 10.1542/peds.2016-4102).

llaubach@frontlinemedcom.com

Hospital-led interventions cut hospitalizations

BY BIANCA NOGRADY
Frontline Medical News

Hospital-driven interventions designed to improve management of asthma in children achieved significant reductions in monthly asthma-related hospitalizations and emergency department visits, according to a paper published online Sept. 18 in JAMA Pediatrics.

Long-term management of pediatric asthma is challenging, and around 40% of children and adolescents hospitalized with the disease tend to be rehospitalized or revisit the emergency department within 12 months, according to Carolyn M. Kercsmar, MD, of Children's Hospital Medical Center in Cincinnati, and her coauthors.

"Traditional care models do not adequately address underlying risk factors, propagating disparities

and costly health care use," they wrote (JAMA Pediatrics. 2017, Sep 18. doi: 10.1001/jamapediatrics.2017.2600).

This study, initiated by Cincinnati Children's Hospital Medical Center, involved a range of interventions implemented with inpatients and outpatients and through the community setting, targeting the region's more than 36,000 children and adolescents with asthma, approximately 13,000 of whom were Medicaid insured.

These included a program that gave all patients a 30-day supply of medications, an asthma action plan, and standardized inhaler training; an asthma-specific history and physical examination form prompting assessment of chronic asthma control, severity, and triggers; a home health pathway of up to five in-home nurse visits; and care coordinators who applied interventions such as a risk assessment, education, medication home delivery, collaboration with a Medicaid managed care practitioner, and improved access to community resources.

Over the 5-year study, researchers saw a 41.8% relative reduction in asthma-related hospitalizations – from 8.1 to 4.7 per 10,000 Medicaid patients per month. Asthma-related visits to the ED decreased by 42.4%, from 21.5 to 12.4 per 10,000 Medicaid patients per month, and the percentage of

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patients rehospitalized or who returned to the ED for asthma within 30 days declined from 12% to 7%, "within 3 years of implementation of the inpatient care interventions," the researchers noted.

There was also a significant increase in the percentage of patients discharged with a 30-day supply of inhaled controller medications, from 50% in May 2008 to 90% in May 2010, and the percentage of patients discharged with a short course of oral corticosteroids increased from 0% to 70% by March 2011.

Outpatient processes ensured that Asthma Control Test scores were collected and that patients were provided with asthma action plans. This was associated with an increase in the percentage of patients with well-controlled asthma from 48% to 54%.

"Implementation of an integrated, multilevel approach focused on enhancing availability and accessibility of treatments, removing barriers to adherence, mitigating risks related to adverse exposures, and augmenting self-management and collaborative relationships between the family and the health care system was associated with improved asthma outcomes," the authors wrote.

Noting that previous research has found 38%-70% of patients do not get their prescribed medications at hospital discharge, the authors said they believed giving a 30-day supply of all daily asthma medications at discharge was a key part of their success.

The study was supported by the Cincinnati Children's Hospital Medical Center and one author received a grant from the National Institutes of Health. One author declared compensation for a committee role on a study of asthma treatments in children. No other conflicts of interest were declared.

VIEW ON THE NEWS

Biopsychosocial model can improve pediatric asthma outcomes

Of importance, any future efforts to replicate this work in a patient-centered way should include consideration of how information on asthma management is communicated to and understood by patients. Standard tools such as asthma action plans often contain language and other information that is inaccessible to populations with low health literacy levels.

After years of elevated morbidity, the work of Kercsmar et al. is a demonstration of how interdisciplinary care focused within a biopsychosocial model can improve outcomes for vulnerable children. Future efforts to replicate these results in other communities should continue to emphasize this patient-centered, biopsychosocial philosophy, with heightened attention to the challenges that remain for children and families.

Sean M. Frey, MD, and Jill S. Halterman, MD, MPH, are in the department of pediatrics at the University of Rochester (N.Y.) School of Medicine and Dentistry. These comments are taken from an accompanying editorial (JAMA Pediatrics. 2017, Sep 18. doi: 10.1001/jamapediatrics.2017.2609). No conflicts of interest were declared.

FDA approves new therapy for COPD

Three COPD treatments are now available in one inhaler.

BY LUCAS FRANKI
Frontline Medical News

The Food and Drug Administration has approved Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol), a triple-therapy inhaler for the treatment of chronic obstructive pulmonary disease (COPD) in adult patients, according to a press release from GlaxoSmithKline and Innoviva.

Trelegy Ellipta combines an inhaled corticosteroid, a long-acting muscarinic antagonist, and a long-acting beta$_2$-adrenergic agonist into an inhaler meant for once-daily use in people with COPD. Chronic bronchitis and/or emphysema patients are also indicated for treatment. The FDA-approved dosage is 100 mcg of fluticasone furoate, 62.5 mcg of umeclidinium, and 25 mcg of vilanterol.

The most common adverse events associated with Trelegy Ellipta include headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, and gastroenteritis, and the inhaler is contraindicated for people with "severe hypersensitivity to milk proteins." Trelegy Ellipta is not indicated for people with asthma or acute bronchospasm.

"This approval represents a significant therapeutic convenience for those appropriate patients already on Breo Ellipta, that require additional bronchodilation or for those patients already on a combination of Breo Ellipta and Incruse Ellipta," Mike Aguiar, CEO of Innoviva said in the press release.

In results supporting the FDA approval, the IMPACT study, a 52-week phase 3 clinical trial including 10,355 COPD patients sponsored by GSK, found that patients receiving Trelegy Ellipta experienced a 25% reduction in moderate to severe exacerbations compared to patients receiving Anoro Ellipta, and a 15% reduction in moderate to severe exacerbations, compared with patients receiving Relvar/Breo Ellipta. Change from baseline FEV_1, change from baseline scores on the St George's Respiratory Questionnaire, and time to first moderate/severe COPD exacerbation also were improved in the Trelegy Ellipta study group compared to the others.

"This is the first study to report a comparison of a single inhaler triple therapy with two dual therapies, providing much needed clinical evidence about the ability of a single inhaler triple therapy to reduce exacerbations," Patrick Vallance, president of R&D at GSK, noted in a press release announcing the results of the IMPACT study.

lfranki@frontlinemedcom.com

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: For our Global Initiative for Chronic Obstructive Lung Disease 3 and 4 patients who have had hospitalizations, the prescription of multiple classes of inhaled medication is common. These patients are often receiving other medications, with complicated regimens. A patient's medication list can become the time-schedule-map that consumes much of the day. This has significant impact on the patient's life, finances, and the likelihood of compliance with medications. For those on triple therapy, the approval of this triple-therapy combination inhaler may offer hope for increased compliance with therapy.

Vaccine reduced risk for flu visits by 42%

BY MARY ANN MOON
Frontline Medical News

Last year's influenza vaccination reduced the overall risk for flu-related medical visits by 42%, according to the Centers for Disease Control and Prevention.

In an article summarizing influenza activity in the United States during October 2016–May 2017, investigators said that most of the viral strains antigenically characterized at the CDC "were similar to the reference viruses representing the recommended components for the 2016-2017 vaccine."

In addition, none of the thousands of samples tested showed resistance to the antivirals oseltamivir, zanamivir, and peramivir, said epidemiologist Lenee Blanton, MD, and her associates in the influenza division, National Center for Immunization and Respiratory Diseases in Atlanta.

The 2017-2018 influenza vaccine has been updated to include an additional influenza A (H1N1) component. This change was recommended by the Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee, based on data from global influenza virologic and epidemiologic surveillance, genetic and antigenic characterization, human serology studies, antiviral susceptibility, and the availability of candidate influenza viruses (MMWR. 2017;66[25]:668-76).

Preliminary data show that, during the 2016-2017 flu season, there were 18,184 laboratory-confirmed, flu-related hospitalizations, for an overall incidence of 65 per 100,000 population, more than double that for the 2015-2017 season (31/100,000). Broken down by age groups, the rates per 100,000 population in this past season were 44 at ages 0-4 years, 17 at ages 5-17 years, 20 at ages 18-49 years, and 65 at ages 50-64 years, compared with 291 at ages 65 years and older. Finalized estimates of the number of influenza illnesses, medical visits, and hospitalizations averted by vaccination during the 2016-2017 season will be published in December, the investigators said.

Small study: Patients prefer microneedle flu vaccine

BY ELI ZIMMERMAN
Frontline Medical News

Influenza vaccinations given through a microneedle patch (MNP) received higher patient approval compared with traditional inoculation methods, according to a small study funded by the National Institutes of Health.

In a phase 1, randomized, placebo-controlled study, 100 patients between the ages of 18 and 49 years were split into four groups: one given the patch by a health care worker, one instructed to apply the patch at home, one given a vaccine through a traditional intramuscular injection, and one given a placebo.

Of those who took the patch, 70% (33 of 47) preferred the patch to intramuscular injection (The Lancet. 2017 Jun 27. doi: 10.1016/S0140-6736[17]30575-5).

All nonplacebo groups were given Fluvirin, the 2014-2015 licensed trivalent inactivated influenza vaccine, according to the researchers.

Protection against the virus 6 months after vaccination was similar across all groups other than the placebo group: 20-24 (83%-100%) of 24 participants given the patch by a health care worker, 18-24 (75%-100%) of 24 in the group of patients who gave themselves the patch, and 20-25 (80%-100%) of 25 in the injection group having achieved seroprotection against the three influenza strains 6 months after vaccination.

When measuring reactogenicity, the investigators did find more patients (41 of 50) reported cases of pruritis in the microneedle group than in the injection group (4 of 25). However, these cases were mostly mild, while the injection group reported more grade 2 and grade 3 reactions, with grade 4 being the most severe.

There may also be potential for use among pediatric patients, who may be resistant to vaccinations because of the injection method, the researchers noted.

Some of the researchers are employees of Micron Biomedical, a company that manufactures microneedle products, and are listed as inventors on the licensed patents of these products. The investigators reported no other relevant financial disclosures.

ezimmerman@frontlinemedcom.com
On Twitter@eaztweets

No increased mortality with readmission declines

BY SHARON WORCESTER
Frontline Medical News

Concerns that efforts to reduce 30-day hospital readmission rates under the Affordable Care Act's Hospital Readmission Reduction Program might lead to unintended increases in mortality rates appear to be unfounded, according to a review of more than 6.7 million hospitalizations for heart failure, acute myocardial infarction, or pneumonia between 2008 and 2014.

In fact, reductions in 30-day readmission rates among Medicare fee-for-service beneficiaries are weakly but significantly correlated with reductions in hospital 30-day mortality rates after discharge, according to Kumar Dharmarajan, MD, of Yale New Haven (Conn.) Health, and colleagues (JAMA. 2017 Jul 18;318[3]:270-8. doi: 10.1001/jama.2017.8444).

During the study period, a total of 2.96 million hospitalizations for heart failure, 1.2 million for acute MI, and 2.5 million for pneumonia were identified at 5,106 (heart failure), 4,772 (MI), and 5,057

VIEW ON THE NEWS

Time to reexamine, reengineer HRRP?

The findings by Dharmarajan and colleagues are "certainly good news," Karen E. Joynt Maddox, MD, wrote in an editorial.

The study provides support for strategies that hospitals are using to reduce readmissions, and also underscores the importance of evaluating unintended consequences of policy changes such as the Affordable Care Act's Hospital Readmissions Reduction Program (HRRP), she said (JAMA. 2017 Jul 18;318[3]:243-4).

The study did not address the possibility that attention to reducing readmissions has taken priority over reducing mortality, which could have the unintended consequence of slowing improvements in mortality, she noted, suggesting that for this and other reasons it may be "time to reexamine and reengineer the HRRP to avoid unintended consequences and to ensure that its incentives are fully aligned with the ultimate goal of improving the health outcomes of patients.

"Only with full knowledge of the advantages and disadvantages of a particular policy decision can policy makers and advocates work to craft statutes and rules that maximize benefits while minimizing harms," she wrote.

Dr. Joynt Maddox is with Brigham and Women's Hospital, Boston. She is supported by a grant from the National Heart, Lung, and Blood Institute.

(pneumonia) short-term acute care hospitals, respectively. In January 2008, the mean hospital 30-day risk-adjusted readmission rates (RARRs) and risk-adjusted mortality rates (RAMRs) after discharge were 24.6% and 8.4% for heart failure, 19.3% and 7.6% for acute MI, and 18.3% and 8.5% for pneumonia, respectively, the investigators said.

From 2008 to 2014, the RARRs declined in aggregate across hospitals (–0.053% for heart failure, –0.044% for acute MI, and –0.033% for pneumonia).

"In contrast, monthly aggregate trends across hospitals in 30-day risk-adjusted mortality rates after discharge varied by admitting condition" the investigators said.

For heart failure, acute MI, and pneumonia, there was an increase of 0.008%, a decrease of 0.003%, and an increase of 0.001%, respectively, they said.

The authors work under contract with the Centers for Medicare & Medicaid Services to develop and maintain performance measures. Dr. Dharmarajan reported serving as a consultant and scientific advisory board member for Clover Health at the time this research was performed. He is supported by grants from the National Institute on Aging and the American Federation for Aging Research, and the Yale Claude D. Pepper Older Americans Independence Center.

sworcester@frontlinemedcom.com

FDA tries to curtail abuse of 'orphan drug' program

BY SARAH JANE TRIBBLE, KAISER HEALTH NEWS

The Food and Drug Administration is changing the way it approves orphan drugs after revelations that drugmakers may be abusing a law intended to help patients with rare diseases.

In a blog post Sept. 12, FDA Commissioner Scott Gottlieb, MD, said he wants to ensure financial incentives are granted "in a way that's consistent with the manner Congress intended" when the Orphan Drug Act was passed in 1983. That legislation gave drugmakers a package of incentives, including tax credits, user-fee waivers, and 7 years of market exclusivity if they developed medicines for rare diseases.

A Kaiser Health News investigation published in January 2017

found many drugs that now have orphan status aren't entirely new. Of about 450 drugs that have won orphan approval since 1983, more than 70 were drugs first approved by the FDA for mass-market use. Those include rosuvastatin (Crestor), aripiprazole (Abilify), and adalimumab (Humira), the world's best-selling drug.

Dr. Gottlieb announced plans to close a loophole that allows manufacturers to skip pediatric testing requirements when developing a common-disease drug for orphan use in children. He also signaled that bigger changes are being considered, announcing a public meeting to explore issues raised by scientific advances, such as the increase in precision medicine and biologics.

"We need to make sure our policies take notice of all of these new challenges and opportunities," he wrote. Dr. Gottlieb, through his agency, declined multiple requests for interviews.

Over the years, drugmakers have fueled a boom in orphan drugs, which often carry six-figure price tags. Nearly half of the new drugs approved by the FDA are now for rare diseases – even though many of them also treat and are marketed for common diseases.

Dr. Gottlieb became commissioner in May, a few months after three key Republican senators called for a federal investigation into potential abuses of the Orphan Drug Act, and the Government Accountability Office agreed to investigate.

The GAO has yet to begin its investigation, saying it doesn't expect to start work until late this year, when staff is available. Regardless, in late June, Dr. Gottlieb announced what would be the first in a series of updates that shift the way the FDA handles orphan drugs.

Those include:

- Eliminating a backlog in drug applications for orphan designation or status. Getting a designation is a critical first step if a company wants to win orphan incentives once the drug is approved for treatment use. And, much like the rise in approvals, the requests by companies to get drugs designated with orphan status has also skyrocketed. Dr. Gottlieb said in June that he wanted to get rid of the backlog; his blog post noted the effort was complete. About half of the 200 applications from drugmakers won orphan status.
- Mandating that drugmakers prove their medicine is clinically superior before getting the market exclusivity that comes with orphan drug status. The agency had lost a lawsuit in which a company said it was owed the exclusivity period regardless of whether its medicine was better. And two more lawsuits had been filed by Eagle Pharmaceuticals and United Therapeutics. The FDA Reauthorization Act, which passed in August, made it law that a drug has to be clinically superior to get the incentives.
- Closing the loophole for pediatric orphan drugs by requiring all drugs approved for common adult diseases, like inflammatory bowel disease, undergo pediatric testing when getting approval as a pediatric orphan drug. Pediatric testing is not required for orphan drugs, and Congress recently mandated that orphan drugs for cancer be tested for children. Still, the American Academy of Pediatrics celebrated the proposed change but warned it was only a first step. Bridgette Jones, MD, chair of American Academy of Pediatrics Committee on Drugs,

Continued on following page

Medicare payments may be lower than promised

BY GREGORY TWACHTMAN
Frontline Medical News

Physicians will likely see a 0.31% uptick in their Medicare payments in 2018 and not the 0.5% promised in the Medicare Access and CHIP Reauthorization Act.

Officials at the Centers for Medicare & Medicaid Services were not able to find adequate funding in so-called misvalued codes to support the larger increase, as required by law, according to the proposed Medicare physician fee schedule for 2018.

CMS also failed to hit its misvalued code target in 2016, resulting in a 0.18% across-the-board reduction to the physician fee schedule in 2017 instead of the statutorily promised 0.5% increase.

Other provisions in the proposed Medicare physician fee schedule may be more palatable than the petite pay raise.

The proposal would roll back data reporting requirements of the Physician Quality Reporting System (PQRS), to better align them with the new Quality Payment Program (QPP), and will waive half of penalties assessed for not meeting PQRS requirements in 2016.

"We are proposing these changes based on stakeholder feedback and to better align with the MIPS [Merit-Based Incentive Payment System track of the QPP] data submission requirements for the quality performance category," according to a CMS fact sheet on the proposed fee schedule.

"This will allow some physicians who attempted to report for the 2016 performance period to avoid penalties and better align PQRS with MIPS as physicians transition to QPP," officials from the American College of Physicians said in a statement.

Other physician organizations said they believed the proposal did not go far enough.

"While the reductions in penalties represent a move in the right direction, the [American College of Rheumatology] believes CMS should establish a value modifier adjustment of zero for 2018," ACR officials said in a statement. "This would align with the agency's policy to 'zero out' the impact of the resource use component of the Merit-based Incentive Payment System in 2019, the successor to the value modifier program. This provides additional time to continue refining the cost measures and gives physicians more time to understand the program."

'While the reductions in penalties represent a move in the right direction, the [American College of Rheumatology] believes CMS should establish a value modifier adjustment of zero for 2018.'

The proposed fee schedule also would delay implementation of the appropriate use criteria (AUC) for imaging services, a program that would deny payments for imaging services unless the ordering physician consulted the appropriate use criteria.

The American Medical Association "appreciates CMS' decision to postpone the implementation of this requirement until 2019 and to make the first year an opportunity for testing and education where consultation would not be required as a condition of payment for imaging services," according to a statement.

"We also applaud the proposed delay in implementing AUC for diagnostic imaging studies," ACR said in its statement. "We will be gauging the readiness of our members to use clinical support systems. ... We support simplifying and phasing-in the program requirements. The ACR also strongly supports larger exemptions to the program," such as physicians in small groups and rural and underserved areas.

The proposed fee schedule also seeks feedback from physicians and organizations on how Medicare Part B pays for biosimilars. Under the 2016 fee schedule, the average sales prices (ASPs) for all biosimilar products assigned to the same reference product are included in the same CPT code, meaning the ASPs for all biosimilars of a common reference product are used to determine a single reimbursement rate.

That CMS is looking deeper at this is being seen as a plus.

Biosimilars "tied to the same reference product may not share all indications with one another or the reference product [and] a blended payment model may cause significant confusion in a multitiered biosimilars market that may include both interchangeable and noninterchangeable products," the Biosimilars Forum said in a statement. The current situation "may lead to decreased physician confidence in how they are reimbursed and also dramatically reduce the investment in the development of biosimilars and thereby limit treatment options available to patients."

Both the Biosimilars Forum and the ACR support unique codes for each biosimilar.

"Physicians can better track and monitor their effectiveness and ensure adequate pharmacovigilance in the area of biosimilars" by employing unique codes, according to ACR officials.

The fee schedule proposal also would expand the Medicare Diabetes Prevention Program (DPP), currently a demonstration project, taking it nationwide in 2018. The proposal outlines the payment structure and supplier enrollment requirements and compliance standards, as well as beneficiary engagement incentives.

Physicians would be paid based on performance goals being met by patients, including meeting certain numbers of service and maintenance sessions with the program as well as achieving specific weight-loss goals. For beneficiaries who are able to lose at least 5% of body weight, physicians could receive up to $810. If that weight-loss goal is not achieved, the most a physician could receive is $125, according to a CMS fact sheet. Currently, DPP can only be employed via office visit; however, the proposal would allow virtual make-up sessions.

"The new proposal provides more flexibility to DPP providers in supporting patient engagement and attendance and by making performance-based payments available if patients meet weight-loss targets over longer periods of time," according to the AMA.

The fee schedule also proposes more telemedicine coverage, specifically for counseling to discuss the need for lung cancer screening, including eligibility determination and shared decision making, as well psychotherapy for crisis, with codes for the first 60 minutes of intervention and a separate code for each additional 30 minutes. Four add-on codes have been proposed to supplement existing codes that cover interactive complexity, chronic care management services, and health risk assessment.

For clinicians providing behavioral health services, CMS is proposing an increased payment for providing face-to-face office-based services that better reflects overhead expenses.

Comments on the fee schedule update were due Sept. 11. The final rule is expected in early November.

gtwachtman@frontlinemedcom.com

Continued from previous page

said Sept. 12 that orphan drugs are "still mostly exempt from pediatric study requirements … children deserve access to safe, effective medications."

Martin Makary, MD, who wrote a critical 2015 paper on orphan approvals, said the changes at the agency indicate that Dr. Gottlieb seems "concerned about all the right things. The government does a lot of lip service in general. This is not lip service."

The restructuring has been swift in some ways.

Sandra Heibel, PhD, a senior consultant at Haffner Associates, a firm that helps companies submit orphan drug applications, noted that the approval process for designations definitely sped up over the summer, and "we are absolutely getting responses from the FDA back in 90 days. That has come through."

Other changes to the agency, though, will evolve slowly. For example, the orphan drug office has begun reaching across the FDA's divisions for help in reviewing drugs. In May, the FDA's orphan reviews began to work with the office of pediatric therapeutics to review pediatric applications – ideally increasing the expertise applied when considering a company's request for orphan drug use in children.

In an interview, FDA confirmed that Dr. Gottlieb's orphan modernization plan is part of a larger effort to increase competition and decrease drug prices. One focus is on targeted drugs – especially those that affect rare diseases or diseases for which there is no effective therapy, the agency said.

"Such drugs present some of the biggest opportunities in medicine to treat and cure debilitating and very costly diseases," the agency stated.

Kaiser Health News is a national health policy news service that is part of the nonpartisan Henry J. Kaiser Family Foundation.

Hurricane Harvey tests hospital teams' mettle

BY ELI ZIMMERMAN
Frontline Medical News

As Houston-area citizens evacuated or hunkered down at home in anticipation of Hurricane Harvey, doctors like Mary L. Brandt, MD, packed a bag and headed to work.

"I came in on Saturday morning [Aug. 23] – I was on call – and so I packed a big suitcase and a big bag of food because I anticipated I would be here until Thursday," Dr. Brandt said in an interview, "So I became part of the 'ride-out crew.' "

Hospitals were hit hard by Hurricane Harvey, and many struggled against the effects of the Category 4 storm, which made landfall then stalled over Texas for almost a week, pummeling the area.

Preparations began well before the hurricane arrived. As weather experts and government officials warned of the storm's imminent arrival, Houston's Texas Children's Hospital wasted no time making necessary plans in addition to the safeguards their facilities already had in place, Dr. Brandt said.

"We all know this [flooding] could happen, so all the facilities in the medical center have flood gates, and generators are out of the basement so that there is not any risk of losing all electricity, but then the issue becomes the staff," Dr. Brandt said. "They can't get to and from the facility, and that's particularly true if they live in the periphery of Houston, which is common."

The situation was the same for many area hospitals. Just 2 miles away from Texas Children's Hospital, SreyRam Kuy, MD, associate chief of staff at the Michael E. DeBakey VA Medical Center, and her colleagues prepared to run the hospital with a skeleton crew.

"We were preparing when it was still a tropical storm, and we talked to the staff ahead of time to let them know this would be a marathon, not a sprint," Dr. Kuy said in an interview. "We had people staying in the hospital ahead of time because we were worried that when the hurricane hit, we would not be able to have people return."

But when Harvey made landfall with Category 4 intensity, many medical facilities were caught by surprise.

"We didn't know how bad it would be, I honestly don't think anyone in the city or the state had any idea of how tremendous the impact would be, particularly with the flooding," Dr. Kuy said. "We had staff going 5, 6 days here at the hospital, working continuously, sleeping on the floor, and because of that, we were able to perform multiple emergency surgeries during the disaster, including laparoscopic treatment of ruptured appendicitis and replacement of an infected aortic graft, which required massive transfusion." The VA hospital broke from its core mission of caring for veterans, treating "homeless folks and nonveterans who were brought here by the Coast Guard, or the ambulances, or by air."

At Texas Children's Hospital, Dr.

Continued on page 34

For appropriate patients with DVT/PE

Choose ELIQUIS from the **START**

DVT: deep vein thrombosis; PE: pulmonary embolism.

INDICATIONS

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

Eliquis®
(apixaban) tablets 5mg 2.5mg

ELIQUIS for initial DVT/PE treatment*—

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

To learn more about ELIQUIS, visit

hcp.eliquis.com

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

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

PREGNANCY CATEGORY B

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

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

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

Bristol-Myers Squibb Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

Reversal of Anticoagulant Effect

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

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

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

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

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

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

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

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

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

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

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

Other Adverse Reactions

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

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

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

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

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

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

* All bleeding criteria included surgical site bleeding.

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

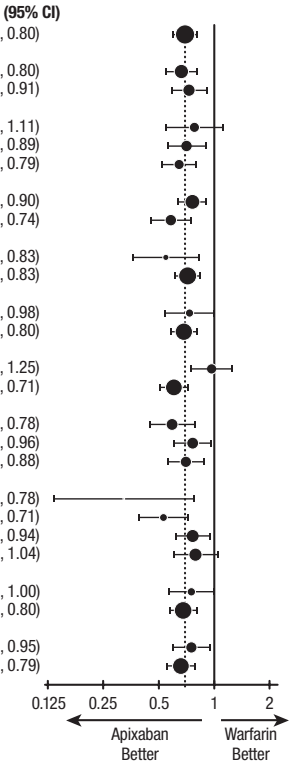
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

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

¶ CRNM = clinically relevant nonmajor.

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

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



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

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

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

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

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

Patients with End-Stage Renal Disease on Dialysis

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

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

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

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

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

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

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The National Guard Malcolm McClendon/Texas Military

Continued from page 29

Brandt and her colleagues were dealing with similar situations, staying on their feet and moving quickly as rescued patients arrived by air.

"We were near the area that was flooding really terribly, and so the Coast Guard had been coming in and bringing kids," Dr. Brandt said. "Sometimes, we knew what was coming and sometimes we didn't. It was pretty much controlled chaos."

Staff shared responsibilities, often taking on tasks far outside their usual roles.

"We didn't have enough people working the cafeteria, and so, at one point, I put on my hair net, grabbed a ladle, and served in the lunch line," Dr. Kuy said.

Throughout the storm and flooding, medical professionals fought through exhaustion and depleting supplies, all with little or no knowledge of how their own homes and families were faring.

"We had people here for so long, and they had no idea what was happening in their own homes," Dr. Kuy said. "They were watching on the news, seeing the reports and watching their own neighborhoods flooded."

Dr. Brandt and her colleagues would watch as reports came in of what was happening beyond the hospital walls.

"We have some meeting areas, we would watch the weather together and that goes from the janitors to the head of the hospital who was in the hospital with us," she said.

Despite the chaos outside, morale did not waiver for either Dr. Kuy's or Dr. Brandt's crew.

"I remember walking throughout the hospital, doing my rounds, checking up on the units. I went to talk with some of the staff nurses, and what struck me was as I walk in I see these big smiles on their faces; I absolutely did not expect that," Dr. Kuy said. "They had been in the hospital for 5 days; they were exhausted. It just makes me so proud to serve along these kinds of people."

As travel became possible, Dr. Kuy and other area physicians – as well as volunteers from across the country – began to shift their focus to evacuation shelters, treating ambulatory patients there.

"The response has been phenomenal," said Dr. Kuy. "I met an ER doctor from North Carolina who came to volunteer, we have FEMA [Federal Emergency Management Agency] doctors from all across the state, and then of course, all the people from the different VA [hospitals]."

Pediatricians have sent their support as well, offering time and supplies to help take care of the patients at Texas Children's Hospital, Dr. Brandt said.

At presstime, volunteers were still needed. The Texas Department of State Health Services opened a web portal for volunteer opportunities, and lifted restriction on out-of-state doctors from practicing medicine without state registration.

While there is still much that needs to be done to recover, those on the ground said that they feel an overwhelming feeling of community as people face what will inevitably be a tough road ahead.

"Houston has a reputation and a culture of helping neighbors and it has been astounding to watch what's happening," said Dr. Brandt. "No matter how tired people are or how stressful any cases are, everyone's morale stays high."

ezimmerman@frontlinemedcom.com
On Twitter @eaztweets

Health IT: Cybercrime risks are real

BY ELI ZIMMERMAN
Frontline Medical News

Thinkstock compilation

Aging equipment, valuable data, and an improperly trained workforce make health care IT extraordinarily vulnerable to external malfeasance, as demonstrated by the WannaCry virus episode that occurred this spring in the United Kingdom.

Computer hackers used a weakness in the operating system employed by the U.K. National Health Service, allowing the WannaCry virus to spread quickly across connected systems. The ransomware attack locked clinicians out of patient records and diagnostic machines that were connected, bringing patient care to a near standstill.

The attack lasted 3 days until Marcus Hutchins, a 22-year-old security researcher, stumbled onto a way to slow the spread of the virus enough to manage it, but not before nearly 60 million attacks had been conducted, Salim Neino, CEO of Kryptos Logic, testified June 15 at a joint hearing of two subcommittees of the House Science, Space & Technology Committee. Mr. Hutchins is employed by Kryptos Logic.

U.S. officials are keenly aware that a similar attack could happen here. In June, the federally sponsored Health Care Industry Cybersecurity Task Force issued a report on their year-long look at the state of the health care IT in this country. The task force was mandated by the Cybersecurity Act of 2015 and formed in March 2016.

"The health care system cannot deliver effective and safe care without deeper digital connectivity. If the health care system is connected, but insecure, this connectivity could betray patient safety, subjecting them to unnecessary risk," according to the task force report. "Data collected for the good of patients and used to develop new treatments can be used for nefarious purposes such as fraud, identity theft, supply chain disruptions, the theft of research and development, and stock manipulation. Most importantly, cybersecurity attacks disrupt patient care."

Specifically, the task force made the following recommendations:

- Define and streamline leadership, governance, and expectations for health care industry cybersecurity.
- Increase the security and resilience of medical devices and health IT.
- Develop the health care workforce capacity necessary to prioritize and ensure cybersecurity awareness and technical capabilities.
- Increase health care industry readiness through improved cybersecurity awareness and education.
- Identify mechanisms to protect research and development efforts and intellectual property from attacks or exposure.
- Improve information sharing of industry threats, weaknesses, and mitigations.

Health care cybercrime is a significant problem in the United States. In 2016, 328 U.S. health care firms reported data breaches, up from 268 in 2015, with a total of 16.6 million Americans affected, according to a report conducted by Bitglass, a security software company. In February 2016, a hospital in California was forced to pay about $17,000 in Bitcoin, an electronic currency that is known to be favored by cybercriminals, to access electronic health records that were held in a similar manner to last month's attack on the NHS.

For physicians, this may seem like someone else's problem; however, unsafe day-to-day interactions with connected devices and patient EHRs were among the task force's primary concerns.

For many, creating a safe password or not giving out critical information may seem like common sense, but many physicians are not able or willing to take the time to make sure they are interacting with systems safely, or they are overconfident in their security system, according to task force member Mark Jarrett, MD, senior vice president and chief quality officer at Northwell Health in New York.

"Most physicians now will try to access medical records of their patients who have been in the hospital because that's good care," Dr. Jarrett said in an interview.

But they have to recognize that "they cannot give these passwords to other people and they need to make these passwords complex," noted Dr. Jarrett.

"Phishing" is another concern. In a phishing scam, cybercriminals will pose as a fraudulent institution or individual in order to trick a target into downloading a virus, sending additional valuable information, or even paying money directly to the criminals.

"Physicians checking their emails need to be aware of possible phishing episodes, because they could be infected, and then there is the possibility that infection could be introduced into the system, Dr. Jarrett said.

"I think the disconnect is [that physicians] are not used to [cybersecurity]. It's not part of their daily life and they also, up until recently, thought 'it's never going to happen to me.'"

ezimmerman@frontlinemedcom.com
On Twitter @eaztweets

VIEW ON THE NEWS

WannaCry provides wake-up call

When computer hackers took control of the United Kingdom's National Health Service using a virus known as WannaCry, doctors and nurses were left helpless, blocked from the files they would need to treat their patients until they paid to get those files back.

Doctors were forced to revert to older methods, slowing everything to a snail's pace.

The media coverage of the event was dramatic, but there is no doubt the effects made it justifiably so.

NHS hospitals had not achieved their goal of being paperless; had they been, the service would have been completely unable to stop the attack. It was not just software that was affected but medical devices as well. Physicians were unable to perform x-rays, and some hospitals found that the refrigerators used to store blood products were shut down.

While the NHS was particularly vulnerable to the WannaCry because of budget cuts, this cybercrime could have happened to any hospital, and its lessons are applicable for all.

Doctors do understand the value of patients records, but they seem to be unaware of the physical harm that could befall patients from a cyberattack.

This attack needs to serve as a wake-up call for health care professionals who are not invested in their facilities' cybersecurity practices.

Underfunding left NHS hospitals terribly exposed and, if physicians continue to be complacent with how to handle this issue, the results are sure to be more severe.

Rachel Clarke, MD, is at Oxford (England) University Hospitals NHS Foundation Trust, and Taryn Youngstein, MD, is at Imperial College Healthcare NHS Trust, London. They reported having no relevant financial conflicts of interest. Their remarks were make in a perspective published in the New England Journal of Medicine (doi: 10.1056/NEJMp1706754).

Take a different path

*INDICATIONS

- Adempas (riociguat) tablets is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.†

  Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

† Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.
- Patients with Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Adempas—the first and only approved treatment for both PAH (WHO Group 1) and CTEPH (WHO Group 4)* adult patients

Adempas has proven efficacy, as demonstrated by the following measures:

- Exercise capacity, as measured by 6MWD in PAH and CTEPH
- WHO Functional Class in PAH and CTEPH
- Hemodynamics: PVR and NT-proBNP in PAH and CTEPH
- Delayed time to clinical worsening in PAH†

Learn more or contact a representative at adempas-us.com

FOR PAH. FOR CTEPH.

Adempas®

riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

WARNINGS AND PRECAUTIONS (continued)

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

WARNINGS AND PRECAUTIONS (continued)

Pulmonary Veno-Occlusive Disease. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%). Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the brief summary of the full Prescribing Information, including Boxed Warning, on the following pages.

Bayer
100 Bayer Boulevard, Whippany, NJ 07981 USA

PP-400-US-3547 May 2017

ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer Adempas to a pregnant female because it may cause fetal harm *[see Contraindications (4.1), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Dosage and Administration (2.3), Warnings and Precautions (5.1, 5.2),and Use in Specific Populations (8.6)]*.**
- **For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program *[see Warnings and Precautions (5.1, 5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class *[see Clinical Studies (14.1)]*.

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) *[see Clinical Studies (14.2)]*.

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated *[see Dosage and Administration (2.6), Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.

4.4 Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP)

Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program *[see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)]*.

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program *[see Warnings and Precautions (5.1)]*.

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Bleeding *[see Warnings and Precautions (5.4)]*

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years *[see Clinical Studies (14.1, 14.2)]*.

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypo-tension *[see Contraindications (4.2) and Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil *[see Dosage and Administration (2.6)]*. Clinical experience with co-administration of Adempas and other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50% to 60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat *[see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered *[see Clinical Pharmacology (12.3)]*.

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Boxed Warning and Contraindications (4.1)]*.

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas *[see Clinical Pharmacology (12.3)]*.

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus *[see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)]*.

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling *[see Boxed Warning]*.

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

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

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program *[see Warnings and Precautions (5.2)]*. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Instruct patients to report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines *[see Adverse Reactions (6.1)]*. Advise patients to be aware of how they react to Adempas before driving or operating machinery, and if needed, consult their physician. Patients should consult their physicians if dizziness gets worse with Adempas.

Manufactured for:

Bayer HealthCare

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

Revised: 1/2017

6710504BS

New data update guidance on nonstatin LDL lowering

BY SHARON WORCESTER
Frontline Medical News

The American College of Cardiology Task Force on Expert Consensus Decision Pathways has released a "focused update" for the 2016 ACC Expert Consensus Decision Pathway (ECDP) on the role of nonstatin therapies for LDL cholesterol lowering in the management of atherosclerotic cardiovascular disease (ASCVD) risk.

The update was deemed by the ECDP writing committee to be desirable given the additional evidence and perspectives that have emerged since the publication of the 2016 version, particularly with respect to the efficacy and safety of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors for the secondary prevention of ASCVD, as well as the best use of ezetimibe in addition to statin therapy after acute coronary syndrome.

'This ECDP addresses current gaps in care for LDL-C lowering to reduce ASCVD risk.'

DR. LLOYD-JONES

"This ECDP addresses current gaps in care for LDL-C lowering to reduce ASCVD risk and provides recommendations that build on the evidence base established by the 2013 [American College of Cardiology/American Heart Association] cholesterol guideline," explained the committee, which was chaired by Donald M. Lloyd-Jones, MD, of Northwestern University, Chicago (J Am Coll Cardiol. 2017. doi: 10.1016/j.jacc.2017.07.745)

The ECDP algorithms endorse the four evidence-based statin benefit groups identified in the 2013 guidelines (adults aged 21 and older with clinical ASCVD, adults aged 21 and older with LDL-C of 190 mg/dL or greater, adults aged 40-75 years without ASCVD but with diabetes and with LDL-C of 70-189 mg/dL, and adults aged 40-75 without ASCVD or diabetes but with LDL-C of 70-189 mg/dL and an estimated 10-year risk for ASCVD of 7.5% or greater) and assume that the patient is currently taking or has attempted to take a statin, they noted.

Among the changes in the 2017 focused update are:

- Consideration of new randomized clinical trial data for the PCSK9 inhibitors evolocumab and bococizumab. Namely, they included results from the cardiovascular outcomes trials FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and SPIRE-1 and SPIRE-2 (Studies of PCSK9 Inhibition and the Reduction of Vascular Events), which were published in early 2017.
- An adjustment in the ECDP algorithms with respect to thresholds for consideration of net ASCVD risk reduction. The 2016 ECDP thresholds for risk-reduction

benefit were percent reduction in LDL-C with consideration of absolute LDL-C level in patients with clinical ASCVD, baseline LDL-C of 190 mg/dL or greater, and primary prevention. In patients with diabetes with or without clinical ASCVD, clinicians were allowed to consider absolute LDL-C and/or non-HDL-cholesterol levels. In the 2017 ECDP update, the thresholds are percent reduction in LDL-C with consideration of absolute LDL-C or non-HDL-C levels for patients in each of the four statin benefit groups. This change was based on the inclusion criteria of the FOURIER trial, the ongoing ODYSSEY Outcomes trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), and the SPIRE-2 trial, all of which included non-HDL-C thresholds. "In alignment with these inclusion criteria, the 2017 Focused Update includes both LDL-C and non-HDL-C thresholds for evaluation of net ASCVD risk-reduction benefit when considering the addition of nonstatin therapies for patients in each of the four statin benefit groups" the update explained.

- An expansion of the threshold for consideration of net ASCVD risk-reduction benefit from a reduction of LDL C of at least 50%, as well as consideration of LDL-C

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less than 70 mg/dL or non-HDL-C less than 100 mg/dL for all patients (that is, both those with and those without comorbidities) who have clinical ASCVD and baseline LDL-C of 70-189 mg/dL. The 2016 ECDP had different thresholds for those with versus those without comorbidities. This change was based on findings from the FOURIER trial and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)."Based on consideration of all available evidence, the consensus of the writing committee members is that lower LDL-C levels are safe and optimal in patients with clinical ASCVD due to [their] increased risk of recurrent events," they said.

- An expanded recommendation on the use of ezetimibe and PCSK9 inhibition. The 2016 ECDP stated that, "if a decision is made to proceed with the addition of nonstatin therapy to maximally tolerated statin therapy, it is reasonable to consider the addition of ezetimibe as the initial agent and a PCSK9 inhibitor as the second agent." However, based on the FOURIER findings, the ongoing ODYSSEY Outcomes trial, and IMPROVE-IT, the 2017 Focused Update states that, if such a decision is made in patients with clinical ASCVD with comorbidities and baseline

LDL-C of 70-189 mg/dL, it is reasonable to weigh the addition of either ezetimibe or a PCSK9 inhibitor in light of "considerations of the additional percent LDL-C reduction desired, patient preferences, costs, route of administration, and other factors." The update also spells out considerations that may favor the initial choice of ezetimibe versus a PCSK9 inhibitor (such as requiring less than 25% additional lowering of LDL-C, an age of over 75 years, cost, and other patient factors and preferences).

- Additional factors, based on the FOURIER trial results and inclusion criteria, that may be considered for the identification of higher-risk patients with clinical ASCVD. The 2016 ECDP included on this list diabetes, a recent ASCVD event, an ASCVD event while already taking a statin, poorly controlled other major ASCVD risk factors, elevated lipoprotein, chronic kidney disease, symptomatic heart failure, maintenance hemodialysis, and baseline LDL-C of at least 190 mg/dL not due to secondary causes. The 2017 update added being 65 years or older, prior MI or non-hemorrhagic stroke, current daily cigarette smoking, symptomatic peripheral artery disease with prior MI or stroke, history of non-MI related coronary revascularization, residual coronary artery disease with at least 40% stenosis in at least two large vessels, HDL-C less than 40 mg/dL for men and less than 50 mg/dL for women, high-sensitivity C-reactive protein greater than 2 mg/L, and metabolic syndrome.

The content of the full ECDP has been changed in accordance with these updates and now includes more extensive and detailed guidance for decision making – both in the text and in treatment algorithms.

'The 2017 Focused Update includes both LDL-C and non-HDL-C thresholds for evaluation of net ASCVD risk-reduction benefit when considering the addition of nonstatin therapies for patients in each of the four statin benefit groups.'

Aspects that remain unchanged include the decision pathways and algorithms for the use of ezetimibe or PCSK9 inhibitors in primary prevention patients with LDL-C less than 190 mg/dL or in those without ASCVD and LDL-C of 190 mg/dL or greater unattributable to secondary causes.

In addition to other changes made for the purpose of clarification and consistency, recommendations regarding bile acid–sequestrant use were downgraded; these are now only recommended as optional secondary agents for consideration in patients who cannot tolerate ezetimibe.

"[These] recommendations attempt to provide practical guidance for clinicians and patients regarding the use of nonstatin therapies to further reduce ASCVD risk in situations not covered by the guideline until such time as the scientific evidence base expands and cardiovascular outcomes trials are completed with new agents for ASCVD risk reduction," the committee concluded.

Dr. Lloyd-Jones reported having no disclosures.

sworcester@frontlinemedcom.com

Rivaroxaban plus aspirin cut cardiovascular events in stable patients

BY MITCHEL L. ZOLER
Frontline Medical News

BARCELONA – Combined treatment with a very low dosage of the anticoagulant rivaroxaban plus low-dose aspirin produced significant cuts in major adverse coronary, cerebral, and peripheral artery disease events with just a modest rise in major bleeding events in patients with stable disease in the COMPASS pivotal, randomized trial with more than 27,000 patients.

The benefits from the rivaroxaban plus aspirin regimen included a statistically significant 24% relative risk reduction in the study's primary, combined endpoint, and a significant 18% relative risk reduction in all-cause death, compared with a standard regimen of aspirin only, John W. Eikelboom, MD, said at the annual congress of the European Society of Cardiology. In addition, analysis of the net clinical benefit from treatment that took into account both the major adverse cardiovascular events prevented and major bleeding events induced, showed that the rivaroxaban-plus-aspirin regimen cut these by a statistically significant 20%, compared with aspirin alone.

Other notable benefits documented by the findings included a statistically significant 42% relative risk reduction for stroke and a statistically significant 46% relative risk reduction in the incidence of major adverse limb events among the roughly one-quarter of enrolled patients who entered the study with evidence of peripheral artery disease.

These risk reductions are similar in magnitude to the secondary-prevention benefits produced by controlling hypertension or dyslipidemia, noted Dr. Eikelboom, a researcher at McMaster University in Hamilton, Ont. "In the future, rivaroxaban will take its place among the other foundational treatments for long-term, secondary prevention," he predicted in a video interview, available on CHEST Physician's web site at http://www.mdedge.com/chestphysician/article/145492/cad-atherosclerosis/video-rivaroxaban-plus-aspirin-cut-cardiovascular.

The COMPASS trial produced "unambiguous results that should change guidelines and the management of stable coronary artery disease," commented Eugene Braunwald, MD, designated discussant for Dr. Eikelboom's report. The results are "an important step for thrombocardiology," said Dr. Braunwald, professor of medicine at Harvard Medical School in Boston.

Concurrently with Dr. Eikelboom's report the results appeared in an article published online (N Engl J Med. 2017 Aug 27. doi: 10.1056/NEJMoa1709118). This publication also include an editorial by Dr. Braunwald (N Engl J Med. 2017 Aug 27. doi: 10.1056/NEJMe1710241).

The Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS) trial enrolled 27,395 patients with stable coronary, carotid, or peripheral artery disease, or a combination of two or more of these, at 602 centers in 33 countries. About 90% of enrolled patients had coronary artery disease and 27% had peripheral artery disease. The enrolled patients averaged 68 year old and were an average of 7 years removed from their index arterial event. Randomization assigned patients to receive 2.5 mg rivaroxaban (Xarelto) twice daily plus 100 mg aspirin daily, 5 mg rivaroxaban twice daily, or 100 mg aspirin once daily. The trial stopped early, after an average follow-up of 23 months, because of the overwhelming benefit seen for the rivaroxaban plus aspirin combination. The rivarox-

Continued on page 46

Mitchel L. Zoler/Frontline Medical News

Dr. John W. Eikelboom

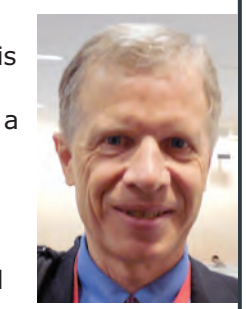
VIEW ON THE NEWS

Low-dose rivaroxaban benefits despite increased bleeding

The key message from COMPASS was that, although adding a very low dosage of rivaroxaban to aspirin in patients with stable coronary or peripheral artery disease resulted in a clear increase in major bleeding events, patients received an overall net beneficial effect from the combined regimen. The finding that clinches the net benefit from the rivaroxaban plus aspirin combination, compared with aspirin alone, was that the combined regimen produced a statistically significant relative risk reduction of 18% for all-cause mortality. This finding reinforces the idea that the primary outcome was beneficial despite an increase in major bleeding events.

The finding that rivaroxaban plus aspirin produced benefit with a modest increase in bleeding risk in patients with peripheral artery disease (PAD) is especially important because PAD is really difficult to treat. Very few interventions have previously been proven to have a beneficial effect for patients with PAD. It's very important to find an intervention that can reduce critical limb ischemia events in addition to reducing coronary events, stroke, and overall mortality.

The very low dosage of rivaroxaban used in COMPASS, 2.5 mg twice daily, seems to be a very important part of the study's design. This dosage appeared to hit the sweet spot of being large enough to reduce events but with a gentle enough anticoagulation effect to avoid a significant increase in fatal, intracerebral, or critical organ bleeds. However, the patients enrolled in COMPASS, like most patients who enter trials, were generally at a lower risk for bleeding complications than we usually see in routine practice in patients with stable coronary or peripheral artery disease. Presuming that the Food and Drug Administration will soon approve the 2.5-mg formulation of rivaroxaban used in COMPASS, clinicians will need to be careful using this regimen on patients at increased risk for bleeding, such as frail or elderly patients with a history of bleeding events or taking other treatments that could increase bleeding risk, such as nonsteroidal anti-inflammatory drugs. In general, clinicians are wary of using treatments that increase bleeding risk, and so they may hesitate to use this combination of rivaroxaban plus aspirin in patients with a high bleeding risk.



The success of the approach used in COMPASS became possible with the introduction of the new oral anticoagulant drugs. Now that this class of agents has been available for a few years, clinicians have grown increasingly comfortable with them, compared with warfarin. When the new oral anticoagulants first came out, many considered them similar to warfarin. Today, there is a better appreciation that these drugs are distinct from warfarin by really causing fewer bleeding complications.

Christopher B. Granger, MD, is a cardiologist and professor of medicine at Duke University in Durham, N.C. He has been a consultant to and has received research support from Bayer and from other drugs companies that market new oral anticoagulants. He made these comments in an interview.

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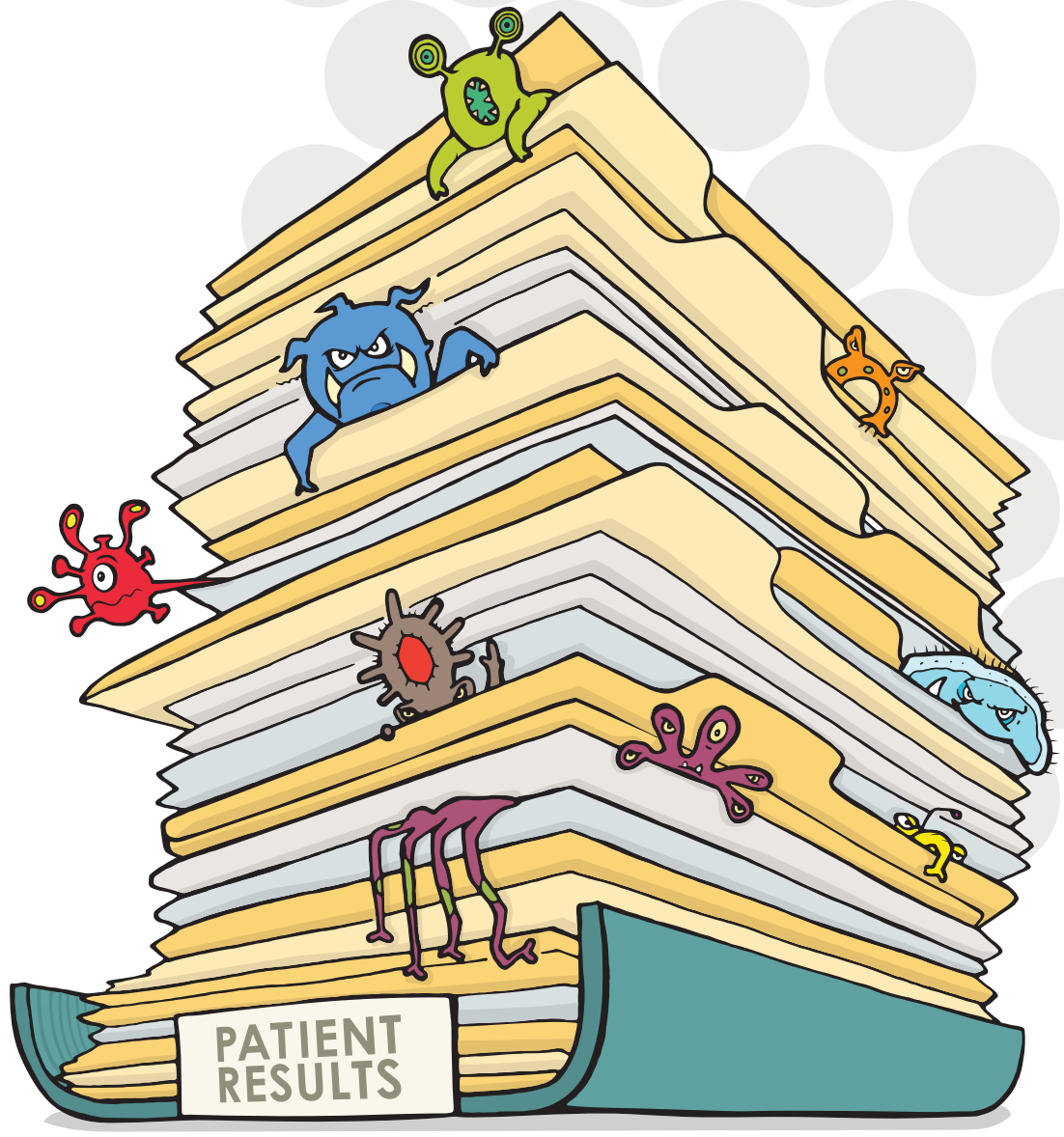

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Continued from page 44

aban-monotherapy arm failed to show any statistically significant benefits, compared with the aspirin-monotherapy control group.

The study's primary endpoint – the combined rate of cardiovascular disease death, nonfatal stroke, and nonfatal MI – occurred in 4.1% of patients in the rivaroxaban-plus-aspirin group and in 5.4% of patients on aspirin alone. The rate of major bleeding events was 3.1% among patients on rivaroxaban plus aspirin and 1.9% in those who received aspirin only, a 51% relative increase among patients on the dual regimen, but the results showed no statistically significant increase in the rates of fatal bleeds, intracerebral bleeds, or bleeding in other critical organs.

Sonia Anand, MD, a colleague of Dr. Eikelboom's at McMaster, presented a separate set of analyses that focused on the 7,470 enrolled patients who had been diagnosed at enrollment with peripheral artery disease. In this subgroup, the rivaroxaban-plus-aspirin regimen produced a statistically significant 28% relative risk reduction in the rate of the primary endpoint, compared with the aspirin control group. The dual regimen also produced a statistically significant 46% relative risk reduction in major adverse limb events and a significant 70% relative reduction in the incidence of major lower-extremity amputations, reported Dr. Anand, professor of medicine and director of the vascular medicine clinic at McMaster.

Dr. Sonia Anand

Dr. Eugene Braunwald

The COMPASS findings follow a 2012 published report from the ATLAS ACS 2-TIMI 51 trial showing that treatment with the same low-dose rivaroxaban regimen plus aspirin and a thienopyridine (clopidogrel or ticlopidine) reduced the same combined triple endpoint by a statistically significant 16%, compared with aspirin and a thienopyridine alone, in patients with a recent acute coronary syndrome event (N Engl J Med. 2012 Jan 5;366[1]:9-19). Despite this evidence, the Food and Drug Administration never approved the 2.5-mg formulation of rivaroxaban, nor did it approve marketing of rivaroxaban for this acute coronary syndrome population. This decision may have been driven in part by a problem with incomplete follow-up of several of the enrolled patients.

The COMPASS results were "very consistent" with the ATLAS ACS 2-TIMI 51 results. noted Dr. Eikelboom. "I think it's time to look at these two trials in combination," he suggested. Availability of the 2.5-mg rivaroxaban formulation used in both trials would allow "a treatment strategy that could start early after an acute coronary syndrome event and then extend long term," he said.

COMPASS was sponsored by Bayer, which markets rivaroxaban (Xarelto). Dr. Eikelboom has received research support from Bayer and also from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, Janssen, Pfizer, Portola, and Sanofi. Dr. Anand has received speaking honoraria from several drug compnies. Dr. Braunwald had no relevant financial disclosures.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

Idarucizumab reversed dabigatran completely, rapidly

BY AMY KARON
Frontline Medical News

One IV 5-g dose of idarucizumab completely, rapidly, and safely reversed the anticoagulant effect of dabigatran, according to final results for 503 patients in the multicenter, prospective, open-label, uncontrolled RE-VERSE AD study.

Uncontrolled bleeding stopped a median of 2.5 hours after 134 patients received idarucizumab. In a separate group of 202 patients, 197 were able to undergo urgent procedures after a median of 1.6 hours, Charles V. Pollack Jr., MD, and his associates reported at the International Society on Thrombosis and Haemostasis congress. The report was simultaneously published in the New England Journal of Medicine.

The study uncovered no serious safety signals, and rates of thrombosis were 4.8% and 6.8% at 30 and 90 days, respectively, which resembled other reports of these patient populations (N Engl J Med. 2017 Jul 11. doi: 10.1056/NEJMoa1707278).

Idarucizumab was specifically developed to reverse the anticoagulant effect of dabigatran. Many countries have already licensed the humanized monoclonal antibody fragment based on interim results for the first 90 patients enrolled in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study (NCT02104947), noted Dr. Pollack, of Thomas Jefferson University, Philadelphia.

Uncontrolled bleeding stopped a median of 2.5 hours after 134 patients received idarucizumab.

DR. POLLACK

The final RE-VERSE AD cohort included 301 patients with uncontrolled gastrointestinal, intracranial, or trauma-related bleeding and 202 patients who needed urgent procedures. Participants from both groups typically were white, in their late 70s (age range, 21-96 years), and receiving 110 mg (75-150 mg) dabigatran twice daily. The primary endpoint was maximum percentage reversal within 4 hours after patients received idarucizumab, based on diluted thrombin time and ecarin clotting time.

The median maximum percentage reversal of dabigatran was 100% (95% confidence interval, 100%-100%) in more than 98% of patients, and the effect usually lasted 24 hours. Among patients who underwent procedures, intraprocedural hemostasis was considered normal in 93% of cases, mildly abnormal in 5% of cases, and moderately abnormal in 2% of cases, the researchers noted. Seven patients received another dose of idarucizumab after developing recurrent or postoperative bleeding.

A total of 24 patients had an adjudicated thrombotic event within 30 days after receiving idarucizumab. These events included pulmonary embolism, systemic embolism, ischemic stroke, deep vein thrombosis, and myocardial infarction. The fact that many patients did not restart anticoagulation could have contributed to these thrombotic events, the researchers asserted. They noted that idarucizumab had no procoagulant activity in studies of animals and healthy human volunteers.

About 19% of patients in both groups died within 90 days. "Patients enrolled in this study were elderly, had numerous coexisting conditions, and presented with serious index events, such as intracranial hemorrhage, multiple trauma, sepsis, acute abdomen, or open fracture," the investigators wrote. "Most of the deaths that occurred within 5 days after enrollment appeared to be related to the severity of the index event or to coexisting conditions, such as respiratory failure or multiple organ failure, whereas deaths that occurred after 30 days were more likely to be independent events or related to coexisting conditions."

Boehringer Ingelheim Pharmaceuticals provided funding. Dr. Pollack disclosed grant support from Boehringer Ingelheim during the course of the study and ties to Daiichi Sankyo, Portola, CSL Behring, Bristol-Myers Squibb/Pfizer, Janssen Pharma, and AstraZeneca. Eighteen coinvestigators also disclosed ties to Boehringer Ingelheim and a number of other pharmaceutical companies. Two coinvestigators had no relevant financial disclosures.

Bad news keeps piling up for Absorb coronary scaffold

BY BRUCE JANCIN
Frontline Medical News

PARIS – Device thrombosis occurred nearly four times more frequently in recipients of the Absorb everolimus-eluting bioresorbable vascular scaffold than with the Xience everolimus-eluting metallic stent during 2 years of prospective follow-up in the randomized AIDA trial.

AIDA (the Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial) was the first randomized trial designed to compare the Absorb scaffold to a drug-eluting metallic stent in a broad patient population reflecting routine real-world clinical practice. The disturbing AIDA finding follows upon earlier serious concerns raised regarding an increased risk of scaffold thrombosis – and the particularly worrisome complication of late thrombosis – in the ABSORB Japan and ABSORB II trials, Joanna J. Wykrzykowska, MD, reported at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

Importantly, the AIDA investigators could not identify any predictors of increased device thrombosis risk in Absorb recipients other than the device itself. Neither age, presenting symptoms, lesion characteristics, vessel size, cardiovascular risk factors, nor residual percentage stenosis defined a subgroup of scaffold recipients at particularly increased risk for this complication, said Dr. Wykrzykowska of the University of Amsterdam.

The device was approved by the Food and Drug Administration in July 2016. In March 2017 the agency issued a safety alert regarding the Absorb scaffold after release of the 2-year data from the 2,008-patient ABSORB III trial showing a significantly higher rate of target-lesion failure than with the Xience stent. Both devices are marketed by Abbott Vascular.

AIDA was a single-blind multicenter Dutch trial that randomized 1,845 patients undergoing PCI, 55% of whom presented with acute cor-

Continued on page 52

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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New-onset AF after AVR did not affect long-term survival

BY MARK S. LESNEY
Frontline Medical News

New-onset atrial fibrillation after aortic valve replacement was not an independent risk factor for decreased long-term survival, according to the results of a single-center, retrospective study reported by Ben M. Swinkels, MD, of St. Antonius Hospital, Nieuwegein, and his colleagues in the Netherlands.

Key to this success, however, is restoring normal sinus rhythm before hospital discharge, they said.

In this retrospective, longitudinal cohort study, 569 consecutive patients with no history of AF who underwent AVR with or without concomitant coronary artery bypass grafting during 1990-1993 were followed for a mean of 17.8 years (J Thorac Cardiovasc Surg. 2017;154:492-8).

Thirty-day and long-term survival rates were determined in the 241 patients (42%) with and the 328 patients (58%) without new-onset postoperative atrial fibrillation (POAF), which was defined as electrocardiographically documented AF lasting for at least several hours, and occurring after AVR while the patient was still admitted. Standard therapy to prevent new-onset POAF was the use of sotalol in patients who were not on beta-blocker therapy, and continuation of beta-blocker therapy for those who were already on it.

There were no significant differences between the two groups in demographic characteristics. There were also no significant differences between the two groups in operative characteristics, postoperative in-hospital adverse events, and postoperative hospital lengths of stay until discharge home, except for mechanical ventilation time, which was significantly longer in the patients with new-onset POAF ($P = .011$).

Thirty-day mortality was 1.2% in the patients with POAF, and 2.7% in those without, a nonsignificant difference. There was no statistically significant difference between the two survival curves. The Kaplan-Meier overall cumulative survival rates at 15 years of follow-up in the patients with new-onset POAF vs. those without were not statistically different (41.5% vs. 41.3%, respectively).

In addition, the 18-year probability of long-term first adverse events, including recurrent AF, transient ischemic attack, ischemic or hemorrhagic stroke, peripheral venous thromboembolism, or major or minor bleeding was not significantly different between the two groups.

"New-onset POAF after AVR does not affect long-term survival when treatment is aimed to restore sinus rhythm before the patient is discharged home. Future studies with a prospective, randomized design should be done to confirm this finding in patients undergoing different kinds of cardiac surgery," the researchers concluded.

The study was funded by the authors' home institution; the authors reported they had nothing to disclose.

mlesney@frontlinemedcom.com

VIEW ON THE NEWS

Results contradict previous studies, but can still reassure

The incidence of atrial fibrillation after valve surgery has been described to be as high as 50%, Manuel J. Antunes, MD, said in an editorial commentary. "The adverse effect on long-term survival may not be related to the short-lived new-onset AF but rather to the underlying pathology associated to the arrhythmia, especially pathology that affects the myocardium, principally in atherosclerotic coronary artery disease," he wrote. "It is not survival alone, however, that should be cause for concern; AF, even in episodes of limited duration, may result in transient ischemic attacks, ischemic, or hemorrhagic strokes, and peripheral thromboembolism, which is why affected patients should immediately be anticoagulated." This study, however, is at odds with previously published studies, with opposite conclusions, according to Dr. Antunes. Swinkels and his colleagues suggest that one of the reasons for the discrepancy was the homogeneous character of their series, which consisted almost entirely of patients who had isolated AVR. Dr. Antunes also adds that another important aspect to consider is that the antiarrhythmic drugs used prophylactically or therapeutically for this patient cohort (treated during 1990-1993) are no longer used or have been replaced by new and more efficacious pharmacologic agents.

"This contribution from Swinkels and colleagues reassures us that new-onset AF, common after heart surgery, may have no significant impact on early and late survival if sinus rhythm is effectively and permanently restored early after the onset of the arrhythmia and before the patient's discharge from the hospital."

Manuel J. Antunes, MD, of the University Hospital and Faculty of Medicine, Coimbra, Portugal, made these remarks in an invited editorial (J Thorac Cardiovasc Surg. 2017;154:490-1). He reported having nothing to disclose.

Continued from page 47

onary syndrome, and 26% of whom had ST-elevation MI. The primary endpoint was target vessel failure, a composite of cardiac death, target vessel MI, or target-vessel revascularization. The 2-year cumulative rate did not differ significantly between the two study arms: 11.7% in the scaffold group and 10.7% in the metallic stent recipients.

However, definite or probable device thrombosis occurred in 3.5% of the scaffold group compared with 0.9% of metallic stent recipients, for a highly significant 3.9-fold increased risk. This was associated with a significantly increased 2-year cumulative risk of MI: 5.5% versus 3.2%.

On the basis of this unsettling finding, coupled with the fact that ABSORB II investigators did not find any instance of very late scaffold thrombosis among 63 patients who remained on dual-antiplatelet therapy (DAPT) continuously for up to 3 years, Dr. Wykrzykowska and her coinvestigators have informed AIDA participants of their treatment assignment. They have also recommended that the Absorb recipients go on extended DAPT, even though there is no high-grade evidence as yet that this will prevent late scaffold thrombosis or that the drug-induced increased bleeding risk of prolonged DAPT might cancel or perhaps even outweigh the potential protection against device thrombosis.

Dr. Joanna J. Wykrzykowska

On top of all this, implantation of the scaffold entails a longer procedure time and a greater volume of contrast material.

Discussant Mahmoud Hashemian, MD, observed that, while bioresorbable vascular scaffolds are "physiologically ideal" because – unlike metallic stents – theoretically they leave no permanent implant to impede vasomotion and serve as a nidus for neoatherosclerosis, to date they have shown no real-world benefits over current-generation drug-eluting metallic stents, but only disadvantages.

"This doesn't mean we have to feel hopeless. I'm not hopeless at all," said Dr. Hashemian, an interventional cardiologist at Day General Hospital in Tehran. "I'm sure this [bioresorbable scaffolds] will be the future of our stents. But it needs more work. The company tells me they are going to launch a newer one, maybe next year, with thinner struts and more expandability."

Asked about the likely mechanism of prolonged thrombosis risk with Absorb, Dr. Wykrzykowska was quick to say no one really knows at this point.

"Technique [predilation at a 1:1 balloon-to-artery ratio with an appropriately sized balloon] can obviously improve things in the short term for early events, but I don't think we understand the biology of late events. We don't understand the interaction between the device and the vessel. It's extremely complex," she said.

AIDA was funded by an unrestricted educational grant from Abbott Vascular. Dr. Wykrzykowska reported receiving consulting and lecture fees from the company.

bjancin@frontlinemedcom.com

Preventive upstream therapy curbs atrial fib progression

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Aggressive treatment of known risk factors for atrial fibrillation resulted in improved 1-year maintenance of sinus rhythm in patients with recent-onset atrial fibrillation and heart failure in the randomized multicenter RACE 3 trial, Isabelle C. van Gelder, MD, reported at the annual congress of the European Society of Cardiology.

"We now screen for AF, making it possible to catch patients early. That's what we've learned from this trial: If we start treating patients after their first episode of AF and aggressively reduce risk factors for AF, it may help the sinus rhythm. I think that's an important message: Do not wait too long; start treatment early," said Dr. van Gelder, professor of cardiology at the University of Groningen (the Netherlands).

She calls the interventional strategy tested in RACE 3 "risk factor-driven upstream therapy." The four-pronged strategy consisted of statin therapy, a mineralcorticoid receptor antagonist, an ACE inhibitor and/or an angiotensin receptor blocker, and a 9- to 11-week supervised cardiac rehabilitation program emphasizing lifestyle modification through physical training and dietary changes supported by professional counseling to promote adherence.

RACE 3 (Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure 3) was a multicenter, randomized, nonblinded clinical trial including 245 patients with, on average, a 3-month history of AF, a 2-month history of persistent AF, and a 2-month history of mild to moderate heart failure, either with preserved or reduced ejection fraction. All participants received guideline-directed rhythm control and heart failure therapies. In addition, half of participants were randomized to the upstream intervention. Three weeks after enrollment, all patients underwent electrical cardioversion.

The primary outcome was maintenance of sinus rhythm at 1 year as determined by 7-day Holter monitoring analyzed in blinded fashion at a central laboratory. The rate was 75% in the upstream intervention group, significantly better than the 63% in controls. This represented a 76% greater likelihood of sinus rhythm at 1 year in the upstream intervention group. They also showed significant reductions in systolic and diastolic blood pressure, *N*-terminal pro-brain natriuretic peptide, and LDL cholesterol, compared with controls. However, at 1 year, the two groups didn't differ significantly in body mass index or left atrial volume.

The lack of impact on left atrial volume was disappointing, Dr. van Gelder said.

The RACE 3 trial was supported by the Netherlands Heart Foundation and the Netherlands Heart Institute. Dr. van Gelder reported having no relevant financial interests.

bjancin@frontlinemedcom.com

Cancer screening in elderly: When to just say no

BY BRUCE JANCIN
Frontline Medical News

ESTES PARK, COLO. – A simple walking speed measurement over a 20-foot distance is an invaluable guide to physiologic age as part of individualized decision making about when to stop cancer screening in elderly patients, according to Jeff Wallace, MD, professor of geriatric medicine at the University of Colorado at Denver.

"If you have one measurement to assess 'am I aging well?' it's your gait speed. A lot of us in geriatrics are advocating evaluation of gait speed in all patients as a fifth vital sign. It's probably more useful than blood pressure in some of the older adults coming into our clinics," he said at a conference on internal medicine sponsored by the University of Colorado.

Dr. Wallace also gave a shout-out to the ePrognosis cancer-screening decision tool, available free at www.eprognosis.org, as an aid in shared decision-making conversations regarding when to stop cancer screening. This tool, developed by researchers at the University of California, San Francisco, allows physicians to plug key individual patient characteristics into its model, including comorbid conditions, functional status, and body mass index, and then spits out data-driven estimated benefits and harms a patient can expect from advanced-age screening for colon or breast cancer.

Of course, guidelines as to when to stop screening for various cancers are available from the U.S. Preventive Services Task Force, the American Cancer Society, and specialty societies. However, it's important that nongeriatricians understand the serious limitations of those guidelines.

"We're not guidelines followers in the geriatrics world because the guidelines don't apply to most of our patients," he explained. "We hate guidelines in geriatrics because few studies – and no lung cancer or breast cancer trials – enroll patients over age 75 with comorbid conditions.

Continued on following page

DR. WALLACE

Continued from previous page

Also, most of these guidelines do not incorporate patient preferences, which probably should be a primary goal. So we're left extrapolating."

Regrettably, though, "it turns out most Americans are drinking the Kool-Aid when it comes to patient preferences. It's amazing how much cancer screening is going on in this country. We're doing a lot more than we should," said Dr. Wallace.

He highlighted a University of North Carolina study of more than 27,000 participants aged 65 years or older in the population-based National Health Interview Survey. Among those deemed at very high risk of mortality within 9 years, 55% of men had recently undergone prostate cancer screening, and 53% of women had recently had a mammogram. Up to 56% of women who underwent a hysterectomy for benign reasons had a Pap test within the previous 3 years. Moreover, more than one-third of women with less than a 5-year life expectancy had a recent mammogram (JAMA Intern Med. 2014 Oct;174[10]:1558-65).

All of that is clearly overscreening. Experts unanimously agree that, if someone is not going to live for 10 years, the person is not likely to benefit from cancer screening. The one exception is lung cancer screening of high-risk patients, where there are data to show that annual low-dose CT screening is beneficial

in those with even a 5-year life expectancy.

As part of the Choosing Wisely program, the American Geriatric Society has advocated that physicians "don't recommend screening for breast, colorectal, prostate, or lung cancer without considering life expectancy and the risks of testing, overdiagnosis, and overtreatment."

That's where gait speed and ePrognosis come in handy in discussions with patients regarding what they can realistically expect from cancer screening at an advanced age.

The importance of gait speed was highlighted in a pooled analysis of nine cohort studies totaling more than 34,000 community-dwelling adults aged 65 years and older with 6-21 years of follow-up. Investigators at the University of Pittsburgh identified a strong relationship between gait speed and survival. Every 0.1-m/sec made a significant difference (JAMA. 2011 Jan 5;305[1]:50-8).

A gait speed evaluation is simple: The patient is asked to walk 20 feet at a normal speed, not racing. For men age 75, the Pittsburgh investigators found, gait speed predicted 10-year survival across a range of 19%-87%. The median speed was 0.8 m/sec, or about 1.8 mph, so a middle-of-the-pack walker ought to stop all cancer screening by age 75. A fast-walking older man won't reach a 10-year remaining life

Continued on following page

the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

Hypercorticism and Adrenal Suppression

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

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

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

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

Continued from previous page

expectancy until he's in his early to mid-80s; a slow walker reaches that life expectancy as early as his late 60s, depending upon just how slow he walks. A woman at age 80 with an average gait speed has roughly 10 years of remaining life, factoring in plus or minus 5 years from that landmark depending upon whether she is a faster- or slower-than-average walker, Dr. Wallace explained.

The U.S. Preventive Services Task Force currently recommends colon cancer screening routinely for 50- to 75-year-olds, declaring in accord with other groups that this strategy has a high certainty of substantial net benefit. But the USPSTF also recommends selective screening for those aged 76-85, with a weaker C recommendation (JAMA. 2016 Jun 21;315[23]:2564-75).

What are the practical implications of that recommendation for selective screening after age 75?

Investigators at Harvard Medical School and the University of Oslo recently took a closer look. Their population-based, prospective, observational study included 1,355,692 Medicare beneficiaries aged 70-79 years at average risk for colorectal cancer who had not had a colonoscopy within the previous 5 years.

The investigators demonstrated that the benefit of screening colonoscopy decreased with age. For patients aged 70-74, the 8-year risk of colorectal cancer was 2.19% in those who were screened, compared with 2.62% in those who weren't, for an absolute 0.43% difference. The number needed to be screened to detect one additional case of colorectal cancer was 283. Among those aged 75-79, the number needed to be screened climbed to 714 (Ann Intern Med. 2017 Jan 3;166[1]18-26).

Moreover, the risk of colonoscopy-related adverse events also climbed with age. These included perforations, falls while racing to the bathroom during the preprocedural bowel prep, and the humiliation of fecal incontinence. The excess 30-day risk for any adverse event in the colonoscopy group was 5.6 events per 1,000 patients aged 70-74 and 10.3 per 1,000 in 75- to 79-year-olds.

In a similar vein, Mara A. Schonberg, MD, of Harvard Medical School, Boston, has shed light on the risks and benefits of biannual mammographic screening for breast cancer in 70- to 79-year-olds, a practice recommended in American Cancer Society guidelines for women who are in overall good health and have at least a 10-year life expectancy.

She estimated that 2 women per 1,000 screened would avoid death due to breast cancer, for a number needed to screen of 500. But roughly 200 of those 1,000 women would experience a false-positive mammogram, and 20-40 of those false-positive imaging studies would result in a breast biopsy. Also, roughly 30% of the screen-detected cancers would not otherwise become apparent in an older woman's lifetime, yet nearly all of the malignancies would undergo breast cancer therapy (J Am Geriatr Soc. 2016 Dec;64[12]:2413-8).

Dr. Schonberg's research speaks to Dr. Wallace.

"It's breast cancer therapy: It's procedures; it's medicalizing the patient's whole life and creating a high degree of angst when she's 75 or 80," he said.

Dr. Wallace reported having no financial conflicts regarding his presentation.

bjancin@frontlinemedcom.com

An interview with incoming CHEST President, John Studdard, MD, FCCP

John Studdard, MD, FCCP, has been a member of the American College of Chest Physicians for 36 years, and, this November, he will be inaugurated as CHEST President. This will not be Dr. Studdard's first time in a presidential role for CHEST, as he served as CHEST Foundation President in 2013 and 2014. Currently, Dr. Studdard serves as a pulmonologist at Jackson Pulmonary in Jackson, Mississippi. Being a physician and being as heavily involved with an organization as Dr. Studdard is takes a lot of prioritizing, hard work, and dedication. Get to know CHEST's new President through this interview.

Born and raised in Mississippi, Dr. Studdard says there were four factors that inspired him to become a physician:

1. I have always loved people and working with them, and I always admired the respect that physicians received in my community.
2. We generally enjoy doing what we are pretty good at...I am pretty good at math and science, and these were important components in pre-med curriculum in my day.
3. I am competitive and decided if it was going to be hard to get into medical school, then I wanted to go to medical school.
4. My dad always told my brother and me that we would be doctors when we grew up, because we were going to be our own boss. I have been in private practice for 36 years, and that is not the case, not if you are doing it right. I obviously love medicine, and my dad was great in that he paid for our education…but he called the shots.

What are some of the biggest challenges you have encountered throughout your career?

Private practice makes you gain more independence and autonomy; you have to become more agile, more efficient, and you have awfully big workloads. However, you give up the academic stimulation of being in an academic center. It is a tough discipline in the private practice of medicine to try to stay up to date. Whether going to the CHEST Annual Meeting, reading our journal *CHEST*, or looking at CHEST education online products, those of us in the clinical practice of pulmonary, critical care, and sleep medicine are more dependent than any group on what our clinical educators write and teach.

How do/did you balance work and your personal life?

We are busy in practice, particularly when taking on volunteer opportunities, and that time comes out of something: time with family, hobbies, it has to come from somewhere. But it is not unique to those of us in medicine. My daughter is a 33-year-old mother to a 20-month-old beautiful granddaughter of ours and is pregnant with another child, and she and her husband both work full time. Our son and his wife also both work and must find ways to balance work/life issues. So work-life balance, particularly in today's world, is more difficult than ever for everyone. I am blessed that my wife is the daughter of a general surgeon, and she understood a little bit about stressors in a physician's life – sometimes she seems to understand more than others—she is a unique person. Work-life balance is all about priorities – our priority was our family. We spent a ton of time with our children, great vacations, rarely missed a program or ballgame (there were lots of them), and frequently that involved going to work early in the morning, coming home early in the evening, and going back to the hospital to finish up late at night. A lot of being a good parent is being lucky. We either did a lot of things right, or were lucky, or a combination of both, because I think our kids turned out pretty darn well.

What has been your favorite project throughout your involvement with CHEST?

Early in my days as a member of CHEST, a mentor of mine from training at the Mayo Clinic, Dr. Doug Gracey, gave me the opportunity to join the CHEST Government Relations Committee, which he chaired. After a few years, I was given the opportunity to serve as its Chair. We became heavily involved in the tobacco wars, as some people called them. Our Attorney General in Mississippi at the time, Mike Moore, and a plaintiff's attorney in Mississippi, Dick Scruggs, whom I knew from some work I had done from the defense side of asbestos litigation, took a lead role in the Attorney General's Master Settlement - a group of attorney generals suing the tobacco industry (basically, state's Medicaid was suing the tobacco industry for reimbursement of funds). It was a completely different approach. The tobacco industry turned its nose up at it at first – they did not think it had a chance to fly, but it did. CHEST got involved early on, and then a big a group of people, including Tobacco Free Kids, the American Cancer Society, and many others in the public health space, got involved. CHEST represented the public health community during part of the negotiations that led to the Attorney General's Master Settlement. We should be very proud of the role CHEST played in this critical public health effort. If I can look back at my time spent in CHEST leadership, and see it as fondly as I do when I look back at my time just being a part of our CHEST Foundation, I will feel incredibly fulfilled.

What made you want to be President of CHEST?

I believe it is always important to give back to the people who gave you something. CHEST has given me a ton over the last 36 years, so giving back to CHEST is easy.

What are you looking forward to as President of CHEST?

On a personal level, I am looking forward to what we are doing right now, meeting new people, and learning from young people.

Because of my background and upbringing, I have a passion for diversity and inclusion; I think we need to continue to talk about, learn about, care about, be open about, and be transparent about diversity of thought, inclusion, and care disparity. The word "diversity" means something different to every person, and, for that, we have to have respect.

Continued on page 62

#Winning: Are you in it to win it at CHEST 2017?

CHEST 2017 offers several contests and opportunities to win great prizes! Are you ready to take home the prize?

CHEST Events App Game: *Click Game*

Do you like scavenger hunts? How about prizes? In our CHEST Events app, you will find the game Click filled with a list of photo challenges. To participate, simply log in and earn your challenge badges by submitting photos to your profile. As you complete each challenge throughout the duration of CHEST 2017, your badges will accumulate, and we will award sweet treats to the person(s) with the highest number of badges on the last day of the annual meeting. Winners can stop by the press room, Metro Toronto Convention Centre, **Room 706**, to collect prizes on Wednesday, November 1, by 2:00 PM local time.

CHEST® Annual Meeting 2017

Rules of participation

- To participate, you must be a registered attendee on-site at CHEST 2017.
- The contest begins Saturday, October 28 at 12:00 PM EST, and ends Wednesday, November 1, at 10:00 AM EST.
- Prize must be picked up in the Press Room, **Room 706**, between the hours of 10:00 AM and 2:00 PM, November 1.
- Questions about the Click photo contest should be directed to socialmedia@chestnet.org

Are you a VITweep?

Get active on Twitter, and share your latest highlights for #CHEST2017! Sitting in on an interesting session? Having a great time visiting the posters? Let us know! The most active tweeters for the day will receive a special prize!

Share your selfies!

See a selfie spot and take advantage of it! We know there's more to your trip than lectures and keynote speakers, and we want to see it!

Throughout the convention center, you'll find many designated areas to snap and share photos of yourself and colleagues! Be sure to find them all and share your images on Twitter or Instagram using our #CHEST2017 hashtag. We'll choose our favorite photo of the day and reshare your picture with our social media followers. Don't miss your chance to be featured!

Don't miss out on CHEST Bingo

Take advantage of one of the many opportunities in the Exhibit Hall during CHEST. Play CHEST Bingo daily, starting Monday, October 30, through Wednesday, November 1, for a chance to win a prize!

How to play:
Find your bingo card in the program guide that you will receive during registration. Get each bingo letter to spell out C-H-E-S-T as you visit each of the five sponsors' booths. You will then have a chance to win a $75 gift certificate to the CHEST bookstore. There will be a winner drawn every night!

Win an iPad®!

This year, attendees will have the opportunity to win a refurbished iPad for playing one of our Simulation Center's arcade style GAMEs (Games Augmenting Medical Education). Last year, we gave away 15 refurbished iPad 2s; this year, we hope to give away 30 refurbished iPad 2s!

iPads will be awarded for the following:

- One each day for the fastest time on Aspirated!
- One each day for whoever has played the most games and Virtual Patient Tours (VPTs).
- Several for playing the games Peer Pressure and Nodal Nemesis.

Please refer to the program schedule in the CHEST Events app for dates and times of the GAMEs and VPTs.

Changes to CPT® codes coming January 2018

BY MIKE NELSON, MD, FCCP
CHEST Physician Editorial Board Member

There will be a number of changes to Current Procedural Terminology (CPT®) codes of interest to pulmonary/critical care providers in January 2018. A thorough understanding of these changes is important for appropriate coding and reimbursement for the services described by these codes.

There are two changes in the CPT codes for bronchoscopy involving **31645** and **31646**. CPT code **31645** describes a therapeutic bronchoscopy, eg, removal of viscous, copious or tenacious secretions from the airway. It had previously included wording that suggested it was used for abscess drainage, and this has been removed. If a therapeutic bronchoscopy procedure is repeated during the same hospital stay, then CPT code **31646** should be utilized. If a therapeutic bronchoscopy procedure is performed in the non-hospital setting and later repeated, then CPT code **31646** would be used for both procedures.

CPT code **94620** *Pulmonary stress testing; simple (eg, 6-minute walk test, prolonged exercise test for bronchospasm with pre- and post-spirometry and oximetry)* has been deleted and replaced by two new codes. CPT code **94617** *Exercise test for bronchospasm, including pre- and postspirometry, electrocardiographic recording(s), and pulse oximetry* describes the procedure used to assess for exercise-induced bronchospasm. CPT code **94618** *Pulmonary stress testing (eg, 6-minute walk test), including measurement of heart rate, oximetry, and oxygen titration, when performed,* describes the typical simple pulmonary stress test. After January 1, 2018, if CPT code **94620** is used, the claim will be denied. CPT code **94621** *Cardiopulmonary exercise testing, including measurements of minute ventilation, CO_2 production, O_2 uptake, and electrocardiographic recordings* has been reworded to better describe the procedure of cardiopulmonary exercise testing. Additionally, there are numerous parentheticals appended that list the CPT codes that may not be used in conjunction with **94617**, **94618**, and **94621**. Please refer to the 2018 CPT manual for further information on these exclusions.

NEW PRESIDENT // *continued from page 59*

As Dr. Studdard prepares to take on his new role in CHEST leadership this October, he is optimistic about what the future will bring and about the things that he will learn. He considers himself incredibly lucky to be in the position that he is in, and he values each relationship he has made during his involvement with CHEST. He left us with a quote from Wyatt Cooper:

"The only immortality we can be sure of is that part of ourselves we invest in others—the contribution we make to the totality of man, the knowledge we have shared, the truths we have found, the causes we have served, the lessons we have lived."

NETWORKS

Transbronchial cryobiopsy, updated guidelines for chronic cough in children, PD-1 inhibition

Interventional Chest/ Diagnostic Procedures

Cryobiopsy for ILD: Careful stewardship needed

Interest in transbronchial cryobiopsy has accelerated rapidly in recent years. This procedure is performed by advancing a cryoprobe into the peripheral lung via flexible bronchoscopy, where lung tissue freezes and adheres to the probe and is subsequently extracted as a cryobiopsy. The number of cryobiopsy-related publications has increased exponentially since it was described in 2009 (Babiak A, et al. *Respiration.* 2009;78[2]:203). This interest stems from reports of high diagnostic yields in patients with interstitial lung disease (ILD) while maintaining complication rates similar to that of conventional bronchoscopic biopsy.

DR. LENTZ

DR. MALDONADO

Traditional bronchoscopic biopsies are notoriously insensitive; a specific diagnosis can be established in fewer than a third of cases (Sheth JS, et al. *Chest.* 2017;151[2]:389). As such, surgical lung biopsy continues to be recommended but is associated with significant mortality (2%) and morbidity (30%) in patients with ILD (Hutchinson JP, et al. *AR-JCCM.* 2016;193[10]:1161). Cryobiopsy, which appears to rival surgical lung biopsy in terms of ability to contribute to a specific diagnosis, is, therefore, a highly promising alternative (Tomassetti S, et al. *AJRCCM.* 2016;193[7]:745).

As cryobiopsy is increasingly adopted around the world, however, troubling reports of serious complications have surfaced. Most notable is the recently reported experience of the initial 25 cases performed at the University of Pennsylvania, in which almost one in four patients suffered serious complications (DiBardino DM, et al. *Ann Am Thorac Soc.* 2017;14[6]:851). The authors pointed to lack of a predefined procedural protocol, as well as several choices relating to the specific technique used, including inconsistent use of fluoroscopy, lack of prophylactic bronchial blocker placement, and predominant use of laryngeal mask airways as potential contributing factors. Indeed, many variations of the basic cryobiopsy procedure have been described (Lentz RJ, et al. *J Thoracic Dis.* 2017;9[7]:2186), with no formal guidance or training available to inform advanced bronchoscopists interested in this procedure.

It is incumbent on the interventional pulmonology and ILD specialist communities to be responsible stewards of this promising procedure. Implementation of three parallel efforts to standardize and rigorously study this procedure should be considered as soon as possible: creation of expert consensus guidelines establishing best-practices for safe and effective biopsy technique; a training requirement before independent performance of the procedure; and creation of an international cryobiopsy registry to facilitate higher-quality research into optimal technique and outcomes. We owe this to our patients.

Robert J. Lentz, MD
NetWork Member
Fabien Maldonado, MD, FCCP
NetWork Member

Pediatric Chest Medicine

Chronic cough in children: New guidelines

A chronic cough is a common complaint among children whose parents seek medical evaluation. Chronic wet cough can indicate an underlying illness; therefore, an early diagnosis can lead to prevention of complications of the disease and improvement in quality of life.

CHEST is a leading resource in evidence and consensus-based guidelines on important topics affecting children. The most recent guidelines entitled Management of Children with Chronic Wet Cough and Protracted Bacterial Bronchitis (*Chest.* 2017;151(4):884-890) and Use of Management Pathways or Algorithms in Children with Chronic Cough (*Chest.* 2017;151(4):875-873) are updates from the 2006 CHEST guidelines on chronic cough in children.

The present updates utilized the CHEST methodological guidelines with chronic wet or productive cough and Grading of Recommendations Assessment, Development, and Evaluation framework and also performed a systematic review addressing key questions concerning the management of childhood disease for children 14 years and younger.

Guidance provided by the expert panel focused on recommendations to answer six key questions concerning the management of children 14 years and younger with a chronic wet cough unrelated to established chronic lung disease. The recommendations are:

1. Chronic cough is defined as the presence of a cough 4 weeks or longer in duration.
2. Assessment of the effect of the cough on the child and the family be undertaken as part of clinical consultation.
3. Evaluation of a chronic cough should be done with a systematic approach with pediatric-specific cough management protocols or algorithms.
4. Chest radiograph and, when age appropriate, spirometry with bronchodilator be undertaken as evaluation; tests for pertussis infection only to be performed if clinically suspected.
5. Chronic wet cough with no specific clinical features should receive antibiotics for 2 weeks targeted for common respiratory bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*).
6. When cough persists despite 2 weeks of appropriate antibiotics, it is recommended to continue for an additional 2 weeks.
7. Additional tests (eg skin prick test, Mantoux, bronchoscopy, chest CT scan) should be individualized in accordance with the clinical setting and child's clinical symptoms and signs.

The panel recognizes the need for prospective studies to assess current algorithms outcomes of children with chronic cough. Both articles can be found on the guidelines section of the CHEST site.

John Bishara, DO
Fellow-in-Training Member

Pulmonary Physiology, Function, and Rehabilitation

Functional imaging of the lung

Quantifying heterogeneity of ventilation and gas exchange in lung diseases remains a clinical challenge. Conventional pulmonary function test is insensitive to regional changes. The multiple inert gas elimination technique can quantify ventilation-perfusion distribution, but it requires invasive instrumentation (eg, pulmonary artery catheterization) and is not practical for clinical use. Computed tomography (CT) scans delineate spatial changes in lung structures but do not directly measure changes in ventilation and gas exchange. With its radiation, it is difficult to apply CT scanning repeatedly in patients. More recently, MR imaging techniques have been developed to directly "visualize" and quantify regional lung function (Kruger SJ, et al. *J Magn Reson Imaging.* 2016;43(2):295; Roos JE, et al. *Magn Reson Imaging Clin N Am.* 2015;23(2):217). These techniques employ inhalation of gases, such as oxygen, perfluorinated gases, and hyperpolarized ^{3}He and ^{129}Xe. Hyperpolarized ^{3}He has been studied the most; however, the dwindling supply of ^{3}He gas and its rising cost have prevented its further development. ^{129}Xe has abundant supply and has emerged to be the inert gas of choice for MR imaging. Hyperpolarized ^{129}Xe can measure ventilation, like hyperpolarized ^{3}He. In addition, Xe diffuses into alveolar barrier (interstitium and plasma) and red blood cells, where it exhibits distinct resonant frequency shifts that can be captured by MR. Therefore, in one test, information on pulmonary ventilation and gas transfer can be obtained. To date, the results from MR imaging studies have provided new insights into the pathophysiology of obstructive

Continued on page 68

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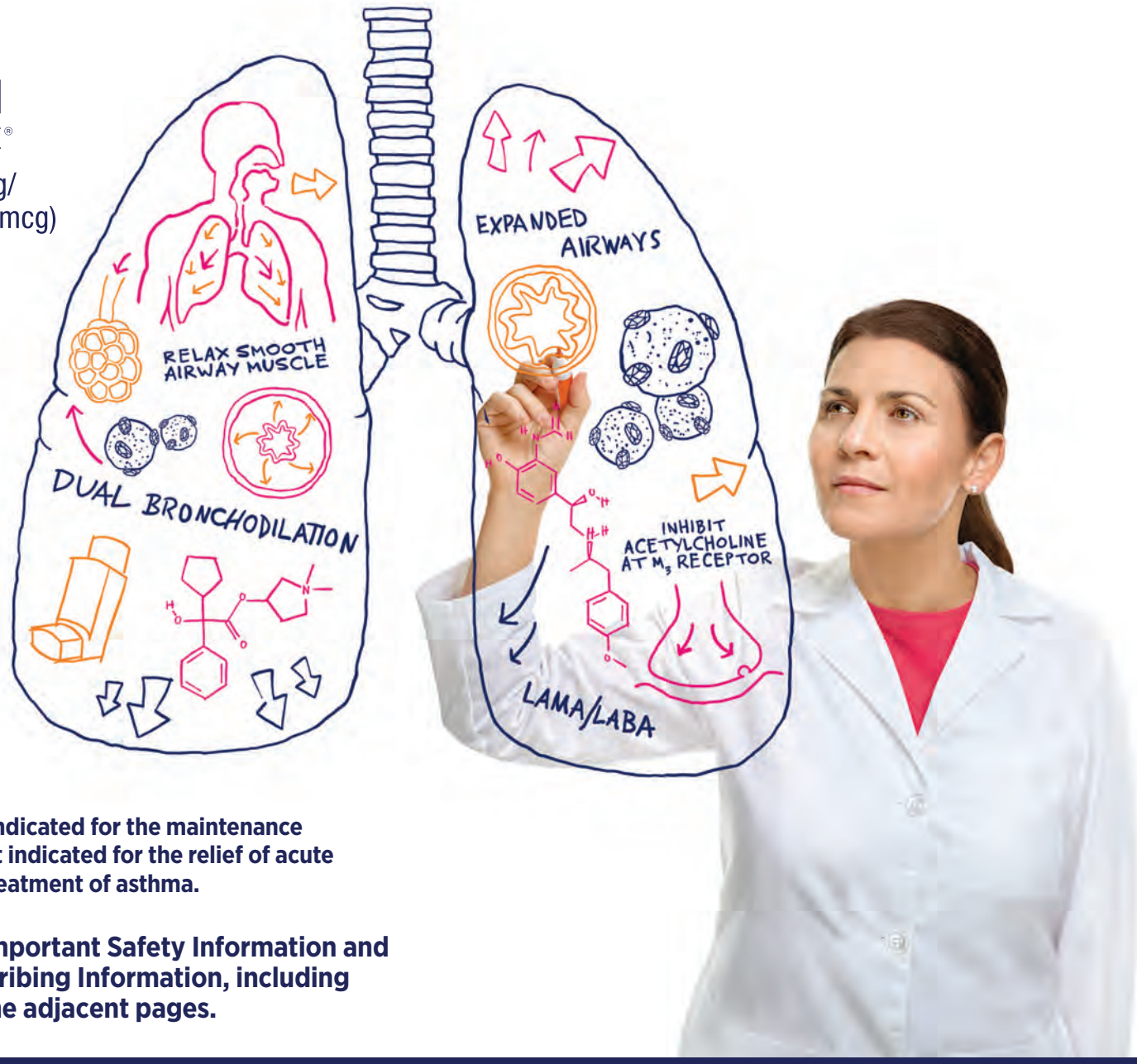
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



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.

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

WARNINGS AND PRECAUTIONS

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

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

DRUG INTERACTIONS

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

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

INTELLIGENT FORMULATION*

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

MAXIMIZE BRONCHODILATION†

Improved lung function‡ vs placebo including[1]

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

In a separate study vs placebo

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

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

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

LEARN MORE AT DUALBRONCHODILATION.COM

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

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

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

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

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

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

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

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

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

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

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

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

AstraZeneca

BEVESPI AEROSPHERE™

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Asthma-Related Death

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

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

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

Deterioration of Disease and Acute Episodes

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

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

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

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

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

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

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

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

Cardiovascular Effects

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

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

ADVERSE REACTIONS

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

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

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

Clinical Trials Experience

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

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

24-Week Trials

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

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

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

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

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

Long-Term Safety Extension Trial

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

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

DRUG INTERACTIONS

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

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

Non-Potassium Sparing Diuretics

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

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

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

Beta-Blockers

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

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

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

Glycopyrrolate

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

Formoterol Fumarate

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

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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

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Continued from page 63

and restrictive lung diseases. With continuous development, MR imaging of the lung could become a clinically useful tool in the near future.

Yuh-Chin T. Huang, MD, MHS, FCCP
Steering Committee Member

Thoracic Oncology

Immune-mediated pneumonitis and PD-1 inhibition

Inhibitors of the programmed cell death 1 receptor (PD-1) have shown significant promise in the treatment of advanced stage malignancy. With the recent expansion of indications for use of these agents, the number of patients treated will continue to grow. Clinicians must be aware of their potential for serious adverse side effects, including dermatitis, colitis, and potentially life-threatening pneumonitis.

The development of pneumonitis secondary to PD-1 inhibitions is reported to occur in 2% to 5% of patients and can present at any time during therapy, with 1% of patients developing grade 3 or higher pneumonitis.[1,2] The most common symptoms are dyspnea and cough, though one-third

Continued on page 71

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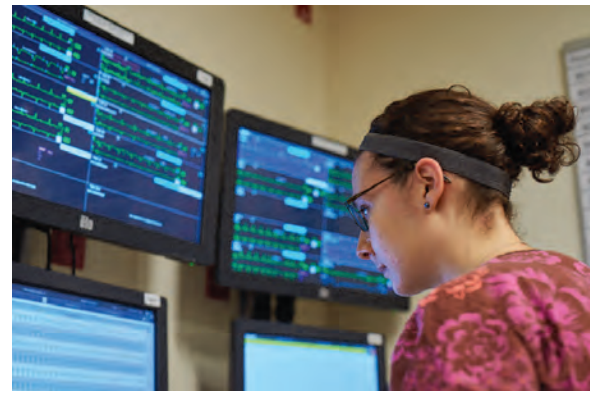

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NETWORKS // *continued from page 68*

of patients are asymptomatic at presentation.[2] Radiographic and pathologic features vary greatly and include organizing pneumonia, interstitial pneumonitis, hypersensitivity pneumonitis, or diffuse alveolar damage.[3]

While pneumonitis due to PD-1 inhibition is reportedly uncommon, the increasing number of patients expected to receive these medications will predictably result in increasing overall frequency of pneumonitis cases. In addition, the lack of large prospective randomized trials and reliance on radiographic rather than pathologic data in diagnosing immune-mediated pneumonitis gives one pause. Given the variability of presentation, lack of routine pathologic data, and increasing use of dual agents (eg, PD-1 and CTLA-4), chest physicians and medical oncologists should have a high index of suspicion yet practice equipoise in patients receiving immunotherapy who develop unexplained pulmonary symptoms or infiltrates. More research is needed to help improve the multidisciplinary diagnosis and treatment of this potentially serious complication.

David Maurice Chambers, MD
Fellow-in-Training Member
Jason Atticus Akulian, MD, MPH
Steering Committee Member

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Pulmonary Vascular Disease

Pulmonary Arterial Hypertension Associated With SLE

While pulmonary arterial hypertension (PAH) commonly complicates scleroderma (SSc), it is a rare complication of other connective tissue diseases (CTD), such as systemic lupus erythematosus (SLE). In the few prospective studies that utilize right-sided heart catheterization (RHC), the estimated prevalence of PAH in SLE is about 4%. However, since the prevalence of SLE is 10 to 15 times greater than SSc in the United States, the true prevalence of SLE-PAH may be higher than previously thought, and, thus, clinically relevant. Despite this, little is known about SLE-PAH.

A recent retrospective study from the French Pulmonary Hypertension Registry has added significantly to our understanding of this complication of SLE. Hachulla and colleagues studied 51 patients with RHC-proven SLE-PAH compared with 101 SLE control subjects without PAH. While the authors did not find any relevant differences in the demographics between groups, they did find a significantly higher prevalence of SSA and SSB antibodies in SLE-PAH. Interestingly, the presence of anti-U1 RNP antibody appeared to be less common in SLE-PAH patients; this lack of association is in contrast to prior studies in mixed CTD patients with anti-U1 RNP antibodies in which the prevalence of PAH can be as high as 60%. Further, none of the SLE-PAH patients demonstrated an acute response to vasodilator challenge during RHC, emphasizing that this maneuver does not need to be performed in SLE patients at risk of PAH. Trends toward improved survival in SLE-PAH patients treated with hydroxychloroquine are preliminary and hypothesis-generating but require confirmation in larger clinical studies.

Stephen Mathai, MD, FCCP
Chair
Leena Palwar, MD
Fellow-in-Training Member

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This Month in *CHEST*

Editor's Picks

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

A Multicenter, Randomized Trial of Ramped Position vs Sniffing Position During Endotracheal Intubation of Critically Ill Adults.
By Dr. M. W. Semler, et al.

Sleep Apnea and Hypertension: Are There Sex Differences? The Vitoria Sleep Cohort.
By Dr. I. Cano-Pumarega, et al.

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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.

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