VOL. 12 • NO. 8 • AUGUST 2017

# CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Courtesy Dr. Krishna Sundar

Blood pressure–lowering therapy is an important treatment for patients with sleep apnea, according to researchers.

## PAP doesn't cut rates of cardiovascular events, death

**BY MARY ANN MOON**
*Frontline Medical News*

Positive airway pressure, whether delivered continuously (CPAP) or as adaptive servoventilation, doesn't reduce the rate of cardiovascular (CV) events or death in patients who have sleep apnea, according to a report published online July 11 in JAMA.

Positive airway pressure (PAP) relieves the symptoms of sleep apnea and has been reported to improve cardiovascular risk factors such as hypertension, insulin resistance, and endothelial dysfunction. However, whether the treatment improves "hard" vascular outcomes such as stroke and MI has never been established, said Jie Yu, MD, of the department of cardiology, Peking University and the Ministries of Health and Education, Beijing, and his associates.

They performed a systematic review of the literature and a meta-analysis of 10 randomized clinical trials that compared PAP against standard care or a sham treatment and had at least 6 months of follow-up for CV events. The meta-analysis involved 7,266 participants who had either obstructive (5,683 patients) or central (1,583 patients) sleep apnea. There were 356 major adverse CV events and 613 deaths during a median follow-up of 6-68 months.

The use of PAP showed no significant association with a range of outcomes: major adverse CV

**PAP DIDN'T IMPROVE BLOOD PRESSURE** // *continued on page 7*

## Azithromycin improves QOL in asthmatics

*Drug cut exacerbations*

**BY DOUG BRUNK**
*Frontline Medical News*

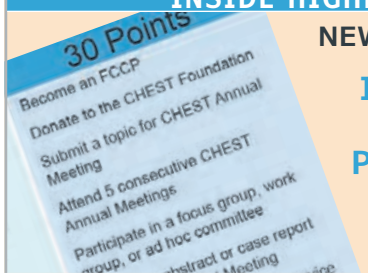
Adults with persistent symptomatic asthma who took azithromycin as an add-on therapy experienced fewer exacerbations and had improved quality of life, compared with their peers who took a placebo, a multicenter, randomized trial demonstrated.

"Macrolide antibiotics have antibacterial, antiviral, and anti-inflammatory effects, and are reported to be beneficial in both eosinophilic and noneosinophilic subtypes," a group of Australian researchers wrote online July 4 in The Lancet (doi: org/10.1016/S0140-6736[17]31281-3). "Systematic reviews of randomized, controlled trials report benefits of macrolides on asthma symptoms but [we] are unable to draw conclusions about the effects on other endpoints, including exacerbations, due to lack of data, heterogeneity of results, and inadequate study design and sample size."

Led by Peter G. Gibson, MBBS, of Hunter Medical Research Institute, New South Wales, Australia, researchers at eight clinical sites con-

**ADD-ON THERAPY CUTS EXACERBATIONS** // *continued on page 4*

**INSIDE HIGHLIGHT**

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**Introducing CHEST Participation Points**

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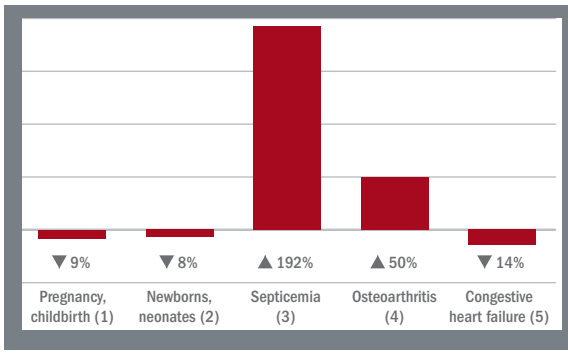


**Reasons for inpatient stays shift**

*The reasons for inpatient stays have shifted. See 2014's most frequent diagnoses for hospital stays, following pregnancy/childbirth and newborns and neonates, on page 7.*

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# HELP PRESERVE MORE LUNG FUNCTION

## Reduce lung function decline with Esbriet[1–4]

### BROAD PATIENT POPULATION

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

### DEMONSTRATED EFFICACY

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

IPF=idiopathic pulmonary fibrosis.

*Baseline characteristics (including clinical characteristics, demographics, and select comorbidities) were well balanced across treatment groups, with 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624).[1,2]

†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).[1,4] 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]

## 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.

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## ESTABLISHED SAFETY AND TOLERABILITY


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

## COMMITTED TO PATIENTS

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

## WORLDWIDE PATIENT EXPERIENCE

**More than 31,000 patients have taken pirfenidone worldwide[1,2‖]**

**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 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**

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

# Add-on therapy cuts exacerbations // *continued from page 1*

ducted a randomized trial to test the hypothesis that the macrolide antibiotic azithromycin reduces asthma exacerbations and improves quality of life in patients with symptomatic asthma on inhaled maintenance therapy. To be eligible for the trial, known as Asthma and Macrolides: the Azithromycin Efficacy and Safety Study, or AMAZES, patients had to be at least 18 years of age, be using an inhaled corticosteroid and long-acting bronchodilator, and have no hearing impairment or abnormal prolongation of the corrected QT interval. Primary efficacy endpoints were the total number of asthma exacerbations (severe and moderate) over 48 weeks and asthma quality of life based on responses to the Asthma Quality of Life Questionnaire (Chest. 1999 May;115[5]:1265-70). Of the 420 patients, 213 were allocated to take 500 mg azithromycin three times weekly and 207 were allocated to placebo. In all, 168 patients in the azithromycin group completed 48 weeks of treatment, compared with 166 in the placebo group. Their median age was 60 years, 76% had

*Continued on page 7*

## VIEW ON THE NEWS

### The impact on community microbial resistance remains unclear

Since microbial resistance is a well known side effect of antibiotic use, add-on therapy with azithromycin in asthma needs to be restricted to those patients with the highest unmet medical need (for example, frequent exacerbators) and to time periods with the greatest risk of exacerbations (such as winter). Biomarkers that predict the therapeutic response to macrolides might facilitate optimal patient selection. Further research is needed to elucidate the most important mechanism of action of these pleiotropic drugs. Macrolides have anti-inflammatory, antibacterial, and antiviral effects. However, the authors did not observe a reduction in inflammatory cell counts in sputum to support a definite anti-inflammatory effect. Azithromycin also was effective in patients with and without potentially pathogenic microorganisms in sputum cultures at baseline. Since azithromycin reduced both asthma exacerbations and respiratory infections, the benefits of azithromycin might be caused by preventing viral-induced attacks in asthma. Azithromycin stimulates phagocytosis of microbes and dead cells by macrophages (i.e., efferocytosis), an effect that is likely to be independent of the nature of the accompanying neutrophilic or eosinophilic airway inflammation.

Dr. Gibson and his colleagues have clearly shown that add-on therapy with azithromycin is effective and safe in adult patients with uncontrolled asthma despite treatment with inhaled corticosteroids and long-acting beta-agonists. Azithromycin benefited patients with both eosinophilic and noneosinophilic asthma. However, the effects of long-term therapy with macrolides on community microbial resistance remain a public health concern. Future studies with potentially safer nonantibiotic macrolides in uncontrolled severe asthma are warranted. Since the antimicrobial effects probably contribute to the overall efficacy of macrolides, the beneficial effects of nonantibiotic macrolides might be intermediate between macrolide antibiotics and placebo.

*This text is excerpted from a commentary published online July 4 in The Lancet (doi. org/10.1016/S0140-6736[17]31547-7). Guy Brusselle, MD, is with the department of respiratory medicine at Ghent (Belgium) University Hospital and Ian Pavord, MD, is with the University of Oxford's Nuffield Department of Medicine, in England. Both authors disclosed having received honoraria and other financial support from numerous pharmaceutical companies.*

# Frequent bronchiectasis exacerbations linked to higher mortality

BY MITCHEL L. ZOLER
*Frontline Medical News*

WASHINGTON – Bronchiectasis patients with three or more exacerbations per year had twice the mortality during 5-year follow-up as patients with no recent exacerbations, in a prospective registry of nearly 2,600 European bronchiectasis patients.

A multivariate analysis showed this statistically significant doubled death rate after adjustment for baseline demographic and clinical differences between patients with no exacerbations during the year before they entered the registry, James D. Chalmers, MD, said at an international conference of the American Thoracic Society.


DR. CHALMERS


DR. AKSAMIT

Having had frequent exacerbations at a rate of three or more annually prior to enrollment was common, with 37% of the 2,596 bronchiectasis patients in the registry having this history, said Dr. Chalmers, a pulmonologist at the University of Dundee, Scotland. This 37% prevalence contrasted with a 19% U.S. prevalence of bronchiectasis patients having two or more exacerbations per year among 2,114 patients enrolled in a 13-center U.S. registry that was reported during the same session by Timothy R. Aksamit, MD, a pulmonologist at the Mayo Clinic in Rochester, Minn. Dr. Aksamit contended that the U.S. registry tried to exclusively enroll patients with bronchiectasis and no other disorder, possibly explaining the prevalence difference between Europe and the United States.

The European registry included patients with bronchiectasis seen in 10 centers in seven European countries and Israel. They averaged 67 years of age. While more than a third had a history of at least three exacerbations a year, one-quarter had no exacerbations during the year before they entered the study.

The prospective study also showed that, among patients with three or more exacerbations annually, the risk for a subsequent exacerbation was five times higher than among patients with no recent exacerbations.

The U.S. registry reported by Dr. Aksamit had 2-year follow-up data for 1,049 of the enrolled patients, a subgroup that closely matched the entire population initially enrolled. The 2-year follow-up showed an overall average exacerbation rate of 0.75 episodes per year, but this was driven largely by the subgroup of patients who entered the registry with a history of two or more exacerbations per year, who then averaged about 2.6 exacerbations during follow-up. In contrast, patients who entered the registry with a history of fewer than two exacerbations per year averaged fewer than a third of an exacerbation per year during follow-up.

The European bronchiectasis registry was partially funded by Bayer. Dr. Chalmers has been a consultant to Bayer and to AstraZeneca, Basilea, Grifols, Napp, and Raptor and has received research funding from Aradigm, AstraZeneca, Bayer, GlaxoSmithKline, and Pfizer.

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## VIEW ON THE NEWS

**Eric Gartman, MD, FCCP, comments:** The longitudinal outcomes of patients within both of these bronchiectasis cohorts demonstrate that there is a subset of patients with this condition who are prone to exacerbation and that this high exacerbation rate portends a very poor prognosis. As such, increased focus should be placed on this particular group of patients in an attempt to prevent exacerbations and subsequent clinical decline.



IN THIS ISSUE




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

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# Septicemia admissions almost tripled from 2005 to 2014

**BY RICHARD FRANKI**
*Frontline Medical News*

Admissions for septicemia nearly tripled from 2005 to 2014, as it became the third most common diagnosis for hospital stays, according to the Agency for Healthcare Research and Quality.

There were more than 1.5 million hospital stays with a principal diagnosis of septicemia in 2014, an increase of 192% over the 518,000 stays in 2005. The only diagnoses with more admissions in 2014 were pregnancy/childbirth with 4.1 million stays and newborns/neonates at almost 4 million, although both were down from 2005. That year, septicemia did not even rank among the top 10 diagnoses, the AHRQ reported.

Osteoarthritis was the fourth most common diagnosis in 2014 with almost 1.1 million stays, an increase of almost 50% from 2004, when it was the seventh most common diagnosis. Admissions for the fifth most common diagnosis in 2014, congestive heart failure, were down by over 14% from 2005, data from the National Inpatient Sample show.

Pneumonia, which was the third most common diagnosis in 2005, dropped by 32% and ended up in sixth place in 2014, while admissions for coronary atherosclerosis, which was fourth in 2005, decreased by 63%, dropping out of the top 10, by 2014, the AHRQ said.

Septicemia was the most common diagnosis for inpatient stays among those aged 75 years and older and the second most common for those aged 65-74 and 45-64. The leading nonmaternal, non–neonatal diagnosis in the two youngest age groups, 0-17 and 18-44 years, was mood disorders, and the most common cause of admissions for those aged 45-64 and 65-74 years was osteoarthritis, the AHRQ reported.

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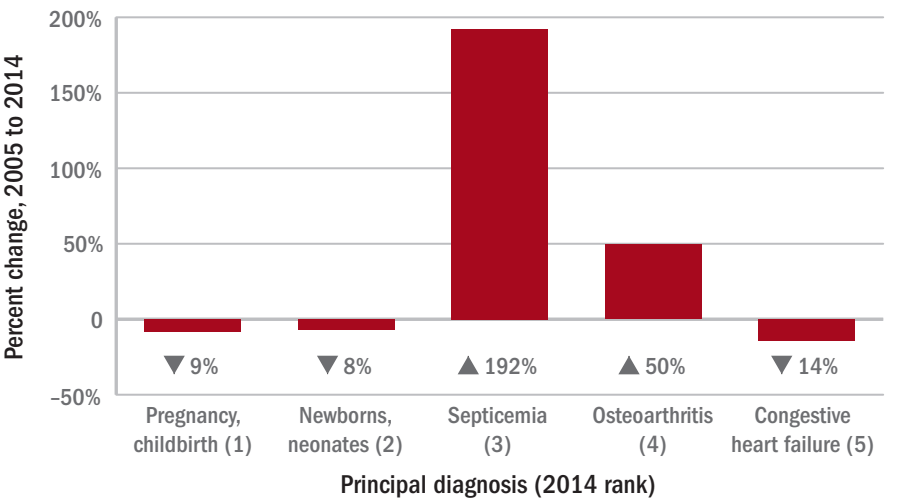
FIVE MOST COMMON DIAGNOSES FOR INPATIENT STAYS, 2014

**Change in the number of admissions from 2005 to 2014**




**Note:** Based on data from the National Inpatient Sample.
**Source:** Agency for Healthcare Research and Quality

## PAP didn't improve blood pressure

// *continued from page 1*

events (relative risk, 0.77; *P* = .19), major adverse CV events plus hospitalization for unstable angina (RR, 0.92; *P* = .54), cardiovascular death (RR, 1.15; *P* = .30), all-cause mortality (RR, 1.13; *P* = .08), noncardiovascular death (RR, 0.85; *P* = .33), acute coronary syndromes (RR, 1.00; *P* = .99), stroke (RR, 0.90; *P* = .47), and heart failure (RR, 1.03; *P* = .60). This lack of treatment benefit persisted regardless of length of follow-up, adherence to treatment, or baseline score on the apnea-hypopnea index, the investigators said (JAMA. 2017 Jul 11. doi: 10.1001/jama.2017.7967).

PAP also failed to improve blood pressure, body mass index, any lipid parameter, glycemia, or quality-of-life scores on the EQ-5D. It did improve sleepiness and some measures of physical and mental well-being.

"The evidence from these [randomized clinical trials] suggests that the association [between] sleep apnea and vascular outcomes and death ... may represent disease processes that cannot be ameliorated by PAP delivered at the average intensity achieved in these clinical trials or by currently feasible methods in clinical practice," Dr. Yu and his associates said.

Their findings also "emphasize the importance of proven therapies, such as blood pressure lowering, lipid lowering, and antiplatelet therapy, in patients with sleep apnea, who should be treated according to established guidelines for patients at elevated cardiovascular risk," they added.

This study was supported by the National Health and Medical Research Council of Australia. Dr. Yu reported having no relevant financial disclosures. His associates reported ties to numerous industry sources.

### VIEW ON THE NEWS

**Clinical – if not statistical – significance?**

The estimated relative risk for the association between PAP and the composite outcome of acute coronary events, stroke, or vascular death was 0.77 in the study by Yu et al. It did not reach statistical significance but is similar to the estimated risk reduction associated with antiplatelet therapy, statins, and beta-blockers in preventing recurrent vascular events.

This magnitude of benefit could be of substantial clinical importance. Far from discouraging further research, this meta-analysis should be an impetus for more studies examining whether treatment of sleep apnea reduces vascular disease risk.

*Daniel J. Gottlieb, MD, is in the medical service at the VA Boston Healthcare System and in the division of sleep medicine at Harvard Medical School, Boston. He reported receiving personal fees from VIVUS. Dr. Gottlieb made these remarks in an editorial accompanying Dr. Yu's report (JAMA. 2017;318:128-30).*

*Continued from page 4*

atopic asthma, and 38% were ex-smokers.

The researchers observed a significant reduction in the incidence of total asthma exacerbations in the azithromycin-treated group: 1.07/patient-year, compared with 1.86/patient-year in the placebo group, which translated into an incidence rate ratio of 0.59 (*P* less than .0001). Specifically, 127 patients in the placebo group (61%) experienced at least one asthma exacerbation, compared with 94 patients in the azithromycin group (44%; *P* less than .0001). A significant improvement in asthma-related quality of life was also seen among patients in the azithromycin group (adjusted mean difference of 0.36; *P* = .001).

Though the mechanism of the antiviral effect of macrolides is not yet determined, Dr. Gibson and his associates noted that respiratory viral infection is associated with severe exacerbations in eosinophilic asthma and causes most respiratory infections. "There is a known interaction between eosinophilic airway inflammation, exacerbation rate, and impaired innate antiviral immunity," they wrote. "Since we observed a benefit of azithromycin on both asthma exacerbations and respiratory infections, we speculate that azithromycin might be acting to prevent viral-induced episodes in asthma."

"Given the major impact of asthma exacerbations on patients and the community and the ongoing risk posed by these events in patients who remain symptomatic on maintenance therapy, we consider that azithromycin is a valuable addition to existing regimens for treating asthma," the researchers concluded. "The long-term effects of this therapy on community microbial resistance require further evaluation."

The overall rates and types of serious adverse events seen in both groups were not significantly different from each other, with serious adverse events having occurred in 16 (8%) patients treated with azithromycin and 26 (13%) patients given the placebo.

The study was funded by the National Health and Medical Research Council of Australia and the John Hunter Hospital Charitable Trust. The authors reported having no financial conflicts directly related to the study.

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# RELEASE THE POTENTIAL OF NUCALA

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

## Indication

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

## Important Safety Information

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity Reactions**

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

**Acute Asthma Symptoms or Deteriorating Disease**

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

**Opportunistic Infections: Herpes Zoster**

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

**Reduction of Corticosteroid Dosage**

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

**Parasitic (Helminth) Infection**

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

**ADVERSE REACTIONS**

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

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

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

## Benefits of NUCALA:

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

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

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

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

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

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

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

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

Visit **NUCALAHCP.COM** to learn more

## Important Safety Information (cont'd)

### USE IN SPECIFIC POPULATIONS

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

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

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

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



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

**BRIEF SUMMARY**

**NUCALA®**
**(mepolizumab) for injection, for subcutaneous use**

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

## 1 INDICATIONS AND USAGE

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

Limitations of Use

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

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

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

### 5.2 Acute Asthma Symptoms or Deteriorating Disease

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

### 5.3 Opportunistic Infections: Herpes Zoster

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

### 5.4 Reduction of Corticosteroid Dosage

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

### 5.5 Parasitic (Helminth) Infection

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

## 6 ADVERSE REACTIONS

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

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

### 6.1 Clinical Trials Experience

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

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

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-term Safety

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

### 6.2 Immunogenicity

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

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

### 6.3 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

## 7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Clinical Considerations

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

Data

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

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

### 8.2 Lactation

Risk Summary

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

### 8.4 Pediatric Use

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

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

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

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

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

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

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

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

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

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

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

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

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

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Research Triangle Park, NC 27709


Revised 2/2017 NCL:2BRS

# Tool predicts antimicrobial resistance in sepsis

**BY HEIDI SPLETE**
*Frontline Medical News*

Use of a clinical decision tree predicted antibiotic resistance in sepsis patients infected with gram-negative bacteria, based on data from 1,618 patients.

Increasing rates of bacterial resistance have "contributed to the unwarranted empiric administration of broad-spectrum antibiotics, further promoting resistance emergence across microbial species," said M. Cristina Vazquez Guillamet, MD, of the University of New Mexico, Albuquerque, and her colleagues (Clin Infect Dis. cix612. 2017 Jul 10. doi: 10.1093/cid/cix612).

The researchers identified adults with sepsis or septic shock caused by bloodstream infections who were treated at a single center between 2008 and 2015. They developed clinical decision trees using the CHAID algorithm (Chi-squared Automatic Interaction Detection) to analyze risk factors for resistance associated with three antibiotics: piperacillin-tazobactam (PT), cefepime (CE), and meropenem (ME).

*"[We] found good overall agreement between the accuracies of the [multivariable logistic regression] models and the decision tree analyses for predicting antibiotic resistance," the researchers said.*

Overall, resistance rates to PT, CE, and ME were 29%, 22%, and 9%, respectively, and 6.6% of the isolates were resistant to all three antibiotics.

Factors associated with increased resistance risk included residence in a nursing home, transfer from an outside hospital, and prior antibiotics use. Resistance to ME was associated with infection with *Pseudomonas* or *Acinetobacter* spp, the researchers noted, and resistance to PT was associated with central nervous system and central venous catheter infections.

Clinical decision trees were able to separate patients at low risk for resistance to PT and CE, as well as those with a risk greater than 30% of resistance to PT, CE, or ME. "We also found good overall agreement between the accuracies of the [multivariable logistic regression] models and the decision tree analyses for predicting antibiotic resistance," the researchers said.

The findings were limited by several factors, including the use of data from a single center and incomplete reporting of previous antibiotic exposure, the researchers noted. However, the results "provide a framework for how empiric antibiotics can be tailored according to decision tree patient clusters," they said.

# Ribaxamase prevented *C. difficile* infections by protecting microbiome

**BY MICHELE G. SULLIVAN**
*Frontline Medical News*

VIENNA – An investigational beta-lactamase reduced *Clostridium difficile* infections by 71% in patients receiving extended antibiotic therapy for respiratory infections but not by killing the opportunistic bacteria.

Rather, ribaxamase prevented *C. difficile* infections (CDI) by breaking down excess therapeutic antibiotics in the gut before they could injure an otherwise healthy microbiome, John Kokai-Kun, PhD, said at the European Society of Clinical Microbiology and Infectious Diseases annual congress.

"Up to 50% of an antibiotic dose is excreted into the small intestine, where it starts to disrupt the bowel microbiome and predisposes you to pick up *C. difficile*," said Dr. Kokai-Kun, vice president of nonclinical affairs at Synthetic Biologics, Rockville, Md. "Ribaxamase is designed to block this cascade. If we protect the microbiome, any *C. difficile* that finds its way in would not find a gut conducive to the germination of vegetative cells."

Ribaxamase is an oral enzyme that breaks the lactam ring in penicillins and cephalosporins. It's formulated to release at a pH of 5.5 or higher, an environment that begins to develop in the upper small intestine near the bile duct – the same place that excess antibiotics are excreted.

"The drug is intended to be administered during, and for a short time after, intravenous admin istration of specific beta-lactam–containing antibiotics," Dr. Kokai-Kun said. Ribaxamase doesn't work on carbapenem-type antibiotics, he noted, and Synthetic Biologics is working on an effective enzyme for those as well.

In early human studies, ribaxamase was well tolerated and didn't interfere with the pharmacokinetics of therapeutic antibiotics (Antimicrob Agents Chemother. 2017 Mar;61[3]:e02197-16). It's also effective in patients who are taking a proton pump inhibitor, he said.

Dr. Kokai-Kun reported the results of a phase 2b study of 412 patients who received IV ceftriaxone for lower respiratory infections. They were assigned 1:1 to either 150 mg ribaxamase daily or placebo throughout the IV treatment and for 3 days after.

The primary endpoint was prevention of *C. difficile* infection. The secondary endpoint was prevention of non–*C. difficile* antibiotic-associated diarrhea. An exploratory endpoint examined the drug's ability to protect the microbiome. Patients were monitored for 6 weeks after treatment stopped.

The cohort was a mean 70 years old. One-third of patients also received a macrolide during their hospitalization, and one-third were taking proton pump inhibitors. The respiratory infection cure rate was about 99% in both groups at both 72 hours and 4 weeks.

Eight patients in the placebo group (3.8%) and two in the active group (less than 1%) developed *C. difficile* infection. That translated to a statistically significant 71% risk reduction, with a *P* value of .027, Dr. Kokai-Kun said. Ribaxamase did not hit its secondary endpoint of preventing all-cause diarrhea or antibiotic-associated diarrhea that was not caused by *C. difficile* infection.

Although not a primary finding, ribaxamase also inhibited colonization by vancomycin-resistant enterococci, which occurred in about 70 (40%) patients in the placebo group and 40 (20%) in the ribaxamase group at both 72 hours and 4 weeks.

All patients contributed stool samples at baseline and after treatment for microbiome analysis. That portion of the study is still ongoing, Dr. Kokai-Kun said.

Synthetic Biologics sponsored the study and is developing ribaxamase. Dr. Kokai-Kun is the company's vice president of nonclinical affairs.

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Michele G Sullivan/Frontline Medical News

**Dr. John Kokai-Kun**

## VIEW ON THE NEWS

**Daniel Ouellette, MD, FCCP, comments:** Aggressive treatment of septic patients with antibiotics has become the cornerstone of modern sepsis management. Like all such treatments, adverse effects confound clinical outcomes. Intensive care units have experienced epidemics of *C. difficile* colitis related to antibiotic use. The oral agent ribaxamase shows promise in this regard. This beta-lactamase breaks down surplus antibiotics in the gut and may offer needed adjunctive therapy to our sepsis regimens. Further study will be needed to confirm positive effects on clinical endpoints.

# AR-301 holds promise for *S. aureus* pneumonia

**BY DAMIAN MCNAMARA**
*Frontline Medical News*

NEW ORLEANS – Monoclonal antibody therapies have already upended treatment strategies in cancer, dermatology, and multiple inflammatory diseases, and infectious disease may be next.

That's because a single injection of a monoclonal antibody in development, AR-301, appeared to be safe and effective as an adjunct treatment for severe pneumonia caused by *Staphylococcus aureus*, according to a new study. The monoclonal antibody attacks the alpha-toxin secreted by *S. aureus*, thereby helping to protect immune cells.


Damian McNamara/Frontline Medical News

**Dr. Celine Gonzalez**

Researchers assessed 48 patients between May 2012 and May 2016 in a randomized, double-blind, placebo-controlled trial. Each participant received a single injection of placebo or AR-301 (at one of four doses) to test the antibody's tolerability and effectiveness.

"We know *S. aureus* pneumonia is a big problem. There is a lot of antibiotic resistance, and that is why we need new treatments," Celine Gonzalez, MD, of the Dupuytren Central University Hospital in Limoges, France, said in an interview.

"Animal studies have shown the monoclonal antibody seems to be useful. This is the first in-human study to use a monoclonal antibody to treat hospital-acquired pneumonia due to *Staphylococcus aureus*," Dr. Gonzalez said in a late-breaking poster presentation at the annual meeting of the American Society for Microbiology.

Treatment started within 36 hours of onset of severe pneumonia. Severity was based on a mean $PaO_2/FiO_2$ of 147 and/or a need for catecholamine. Six cases of pneumonia were related to MRSA and the remaining 42 to methicillin-susceptible *S. aureus*. The mean APACHE II score was 18.7, the mean Clinical Pulmonary Infection Score was 9.6, and the mean Sequential Organ Failure Assessment score was 6.9.

Participants were recruited from

*Continued on following page*

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13 ICUs in four countries. About 80% of participants were men. Their mean age was 56 years, and mean body mass index was 29 kg/m$^2$. Concurrent antibiotic treatment choice and duration were at the investigator's discretion.

*S. aureus* infection was considered eradicated if a follow-up culture was negative, a result achieved by 63% of the 16 placebo patients and 75%-88% of the AR-301-dosage groups.

***"Animal studies have shown the monoclonal antibody seems to be useful. This is the first in-human study to use a monoclonal antibody to treat hospital-acquired pneumonia due to* Staphylococcus aureus*," Dr. Celine Gonzalez said.***

Eradication was also based on observed clinical success in the absence of a confirmatory culture. This was achieved by 38% in the placebo group and 13%-25% of the monoclonal antibody cohorts. A total of seven placebo patients and 15 AR-301 patients met eradication by these criteria.

Side effects were primarily minor and transient, Dr. Gonzalez said. Of the 343 total adverse events reported, only 8 (2.3%) were considered treatment related, she added.

"In infectious disease, it's the beginning" for monoclonal antibody therapy, Dr. Gonzalez said. "But, it appears to be the future because … it is a more specific treatment, and there is no resistance."

The study suggests adjunctive treatment with AR-301 appears safe for treatment of hospital-acquired bacterial pneumonia, she noted.

The next step will be to confirm the findings in a larger, follow-up study that includes more efficacy outcomes, Dr. Gonzalez added.

Dr. Gonzalez reported having no relevant disclosures. The study's principle investigator is a scientific advisor for Aridis Pharmaceuticals, which is developing AR-301.

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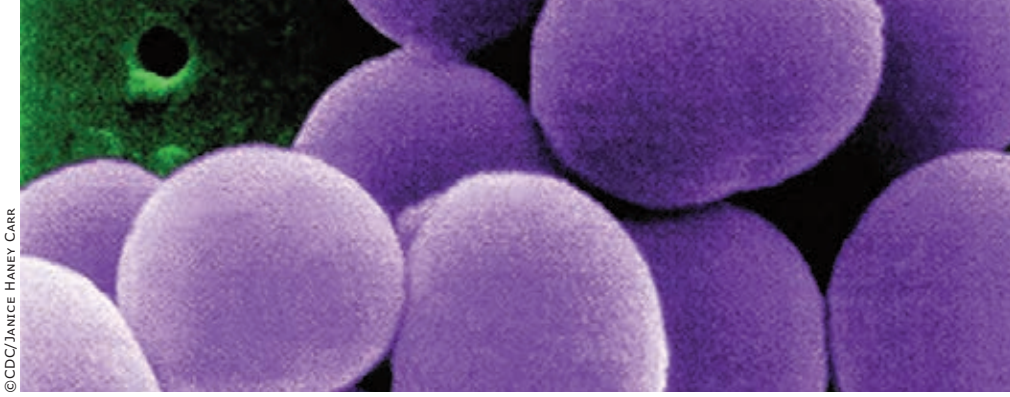

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# RV contractility improved in scleroderma-PAH

**BY M. ALEXANDER OTTO**
*Frontline Medical News*

A combination of ambrisentan (Letairis) and tadalafil (Cialis) improves regional and global right ventricular contractility in patients with scleroderma-associated pulmonary arterial hypertension, according to an open-label investigation of 23 patients.

The project was a follow-up to a previous report showing that the upfront combination – tadalafil 40 mg and ambrisentan 10 mg oral once daily – improved hemodynamics, right ventricular (RV) structure and function, and functional status in treatment-naive patients after 36 weeks and "may represent a very effective therapy for this patient population" (Am J Respir Crit Care Med. 2015 Nov 1;192[9]:1102-10).

DR. MERCURIO

Survival in scleroderma pulmonary arterial hypertension (PAH) depends mostly on RV function, so investigators in the follow-up study wanted to take a closer look at how the combination affected the heart. They reviewed conventional echocardiograph imaging and RV strain analyses for the 23 of the 24 patients in the original trial for which it was available (Am J Respir Crit Care Med. 2017 Jun 29. doi: 10.1164/rccm.201704-0789LE).

At baseline, the subjects had normal left ventricular (LV) size and function, with borderline left atrial enlargement and mild LV diastolic dysfunction. Their right heart chambers were significantly dilated, with RV hypertrophy. Conventional RV function parameters – tricuspid annular systolic plane excursion (TAPSE) and fractional area change (FAC) – were impaired. RV systolic pressure (RVSP) was severely elevated. There was also a marked reduction of global RV longitudinal systolic strain (RVLSS), compared with normal values, mainly because of a reduction in midventricular and apical RVLSS, with relative hyperkinesis of basal RVLSS.

*Continued on following page*

# Amplatzer devices outperform oral anticoagulation

**BY BRUCE JANCIN**
*Frontline Medical News*

PARIS – Percutaneous left atrial appendage closure with an Amplatzer device in patients with nonvalvular atrial fibrillation was associated with significantly lower rates of all-cause and cardiovascular mortality, compared with oral anticoagulation, in a large propensity score–matched observational registry study.

Left atrial appendage closure (LAAC) also bested oral anticoagulation (OAC) with warfarin or a novel oral anticoagulant (NOAC) in terms of net clinical benefit on the basis of the device therapy's greater protection against stroke and systemic embolism coupled with a trend, albeit not statistically significant, for fewer bleeding events, Steffen Gloekler, MD, reported at the annual congress of the European Association of Percutaneous



*Continued from previous page*

After 36 weeks of treatment, right heart chamber sizes were significantly reduced. There was also a decrease in RV free wall thickness, which coincided with a significant reduction in RV mass on cardiac MRI. TAPSE, FAC, and global RVLSS improved significantly, and RVSP decreased significantly. LV end-diastolic and end-systolic diameters and volumes increased significantly.

The changes "may represent transition from maladaptive RV remodeling ... to a more physiological and adaptive RV remodeling;" however, "the effects of treatment should be interpreted with caution, as this was an open-label study without a placebo or a single-drug control group," said investigators led by Valentina Mercurio, MD, a postdoc fellow at Johns Hopkins University, Baltimore.

Subjects were about 60 years old on average, and most were women. The majority shifted from World Health Organization PAH functional class 3 to 2 during the original trial. Mean 6-minute walk tests increased from 341 m to 401 m.

Gilead and United Therapeutics provided the ambrisentan and tadalafil. Dr. Mercurio reported funding from both companies and Merck. The original study was sponsored by United Therapeutics.

aotto@frontlinemedcom.com

## VIEW ON THE NEWS

**Jason Lazar, MD, FCCP, comments:** Dual therapy is standard therapy for PAH but not for secondary pulmonary hypertension. Dual oral therapy represents a novel approach for treatment, and very few studies have demonstrated any drug to benefit secondary pulmonary hypertension.

Cardiovascular Interventions.

The Watchman LAAC device, commercially available both in Europe and the United States, has previously been shown to be superior to OAC in terms of efficacy and noninferior regarding safety. But there have been no randomized trials of an Amplatzer device versus OAC. This lack of data was the impetus for Dr. Gloekler and his coinvestigators to create a meticulously propensity-matched observational registry.

Five hundred consecutive patients with AF who received an Amplatzer Cardiac Plug or its second-generation version, the Amplatzer Amulet, during 2009-2014 were tightly matched to an equal number of AF patients on OAC based on age, sex, body mass index, left ventricular ejection fraction, renal function, coronary artery disease status, hemoglobin level, $CHA_2DS_2$-VASc score, and HAS-BLED score. During a mean 2.7 years, or 2,645 patient-years, of follow-up, the composite primary efficacy endpoint, composed of stroke, systemic embolism, and cardiovascular or unexplained death occurred in 5.6% of the LAAC group, compared with 7.8% of controls in the OAC arm, for a statistically significant 30% relative risk reduction. Disabling stroke occurred in 0.7% of Amplatzer patients versus 1.5% of controls. The ischemic stroke rate was 1.5% in the device therapy group and 2% in the OAC arm.

All-cause mortality occurred in 8.3% of Amplatzer patients and 11.6% of the OAC group, for a 28% relative risk reduction. The cardiovascular death rate was 4% in the Amplatzer group, compared with 6.5% of controls, for a 36% risk reduction.

The composite safety endpoint, comprising all major procedural adverse events and major or life-threatening bleeding during follow-up, occurred in 3.6% of the Amplatzer group and 4.6% of the OAC group, for a 20% relative risk reduction that is not significant at this point because of the low number of events. Major, life-threatening, or fatal bleeding occurred in 2% of Amplatzer recipients versus 5.5% of controls, added Dr. Gloekler of University Hospital in Bern, Switzerland.

The net clinical benefit, a composite of death, bleeding, or stroke, occurred in 8.1% of the Amplatzer group, compared with 10.9% of controls, for a significant 24% reduction in relative risk in favor of device therapy.

Of note, at 2.7 years of follow-up only 55% of the OAC group were still taking an anticoagulant: 38% of the original 500 patients were on warfarin, and 17% were taking a NOAC. At that point, 8% of the Amplatzer group were on any anticoagulation therapy.

Discussion of the study focused on that low rate of medication adherence in the OAC arm. Dr. Gloekler's response was that, after looking at the literature, he was no longer surprised by the finding that only 55% of the control group were on OAC at follow-up.

"If you look in the literature, that's exactly the real-world adherence for OACs. Even in all four certification trials for the NOACs, the rate of discontinuation was 30% after 2 years – and these were controlled studies. Ours was observational, and it depicts a good deal of the problem with any OAC in my eyes," Dr. Gloekler said.

Patients on warfarin in the real-world Amplatzer registry study spent on average a mere 30% of time in the therapeutic international normalized ratio range of 2-3.

Dr. Gloekler reported receiving research funds for the registry from the Swiss Heart Foundation and Abbott.

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# Biomarker distinguishes ARDS, acute heart failure

**BY MITCHEL L. ZOLER**
*Frontline Medical News*

WASHINGTON – Plasma levels of an interleukin-33 receptor that's involved in inflammation regulation appeared able to discriminate between acute respiratory distress syndrome and acute decompensated heart failure in an analysis with 72 patients.

In a second study, high plasma levels of the same interleukin-33 receptor, soluble suppressor of tumorgenicity 2 (sST2), identified acute respiratory distress syndrome (ARDS) patients who were sicker and more responsive to conservative fluid management, Sean D. Levy, MD, said at an international conference of the American Thoracic Society.

While further validation of sST2 is needed, its future as a clinically useful biomarker also depends on development of a test that could be easily and repeatedly used at the bedside, said Dr. Levy, a pulmonologist at New England Deaconess Medical Center in Boston. "We're not quite there yet," he explained. The sST2 test he used for his studies is sold by Critical Diagnostics.

In order to assess the ability of sST2 to reliably distinguish patients with ARDS from those with acute decompensated heart failure, he and his associates selected 72 patients seen at the Massachusetts General Hospital in Boston with an initial diagnosis of acute decompensated heart failure accompanied by bilateral lung infiltrates and acute hypoxemia respiratory failure requiring endotracheal intubation and mechanical ventilation. The investigators measured the sST2 level in a plasma specimen from each patient. In addition, after each patient either left the hospital or died, their case underwent review by two critical care physicians who retrospectively rediagnosed the patients as either having ARDS or acute decompensated heart failure. This divided the cohort into 30 patients with ARDS and 42 with true acute heart failure. The two subgroups matched up fairly closely for most clinical measures and comorbidities, but APACHE III (Acute Physiology and Chronic Health Evaluation III) scores averaged significantly higher in the ARDS patients.

*The plasma levels of sST2 showed a dramatic split between the two subgroups.*

**DR. LEVY**

The plasma levels of sST2 showed a dramatic split between the two subgroups. The 30 patients retrospectively diagnosed with ARDS had an average level of 386 ng/mL with an interquartile range of 318-611 ng/mL. The 42 acute decompensated heart failure patients averaged a sST2 level of 148 ng/mL, with an interquartile range of 84-225 ng/mL. The area under the receiver operator curve for discriminating between ARDS and acute heart failure using a cutpoint of 271 mg/mL was 0.86, showing "good" discrimination, Dr. Levy said. This cutpoint had a sensitivity of 83% and specificity of 88% for correctly distinguishing between ARDS and acute heart failure.

In a second analysis, Dr. Levy and his associates looked at the ability of sST2 levels to separate out patients with acute lung injury who had a more robust response to either the conservative or liberal fluid-management strategies tested in the Fluid and Catheter Treatment Trial (FACTT), run by the National Heart, Lung, and Blood Institute's ARDS Clinical Trials Network. The primary outcome of FACTT was death from any cause 60 days after entry, and this showed no significant difference between conservative (restricted fluids and increased urine output) and liberal (the reverse) fluid management strategies in acute lung injury patients (N Engl J Med. 2006 Jun 15;354[14]:2564-75). From among the 1,001 patients enrolled in FACTT, 826 had specimens available for measuring sST2 (Crit Care Med. 2013 Nov;41[11]:2521-31). The researchers applied the sST2 cut point they derived in the first analysis to the FACTT cohort and identified 133 (16%) patients with a low sST2 level and 693 (84%) with a high level. The patients with high sST2 had significantly higher APACHE III scores, worse acidemia, and worse renal function.

Patients with high sST2 levels had a significant increase in ventilator-free days on conservative fluid management, compared with liberal management, while the two management strategies produced virtually identical results in the patients with low levels of sST2. Patients with high sST2 also had a significantly quicker time to extubation on a conservative strategy, compared with the liberal strategy, and again this correlation did not exist among patients with low sST2. However, as in the overall trial, a conservative strategy had no discernible impact on 60-day mortality, compared with the liberal strategy, even in the subgroup with high sST2.

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# More pulmonary patients getting palliative care

**BY RICHARD FRANKI**
*Frontline Medical News*

Patients referred to palliative care are most likely to have cancer, but the proportion has gone down since 2009 as other diagnoses have increased, according to a report from the National Palliative Care Registry.

In 2015, cancer patients made up 26% of the patients referred to palliative care, compared with 35% in 2009. The situation was reversed for the next three most common diagnoses in 2015: Cardiac diagnoses rose from 5% in 2009 to 13%, pulmonary diagnoses increased from 6% to 12%, and neurologic diagnoses went from 3% to 8%, the report showed.

Referrals by specialty were led by hospital medicine, which accounted for 48% of all patients referred to palliative care in 2015, with internal medicine/family medicine next at 14%, followed by pulmonary/critical care at 13% and oncology at 7%.

An increase in overall palliative care penetration was seen from 2009 to 2015, as the percentage of annual hospital admissions seen by a palliative care team increased from 2.7% to 4.8%. Over that same period, the percentage of palliative care patients who died in the hospital decreased from 29% to 22%, according to the report.

In 2015, there were 420 palliative care programs participating in the registry, which is a joint project of the Center to Advance Palliative Care and the National Palliative Care Research Center.

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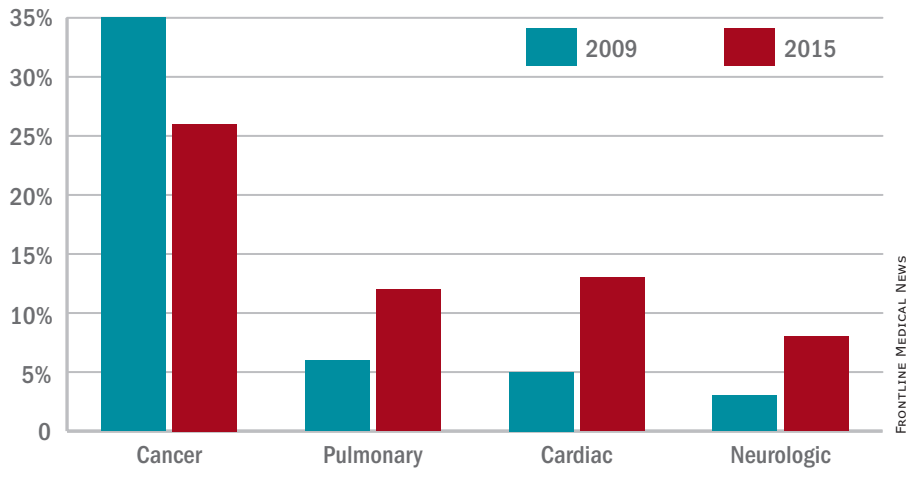
**Leading diagnosis groups referred to palliative care**




FRONTLINE MEDICAL NEWS

**Note:** Based on data from the National Palliative Care Registry.
**Source:** Center to Advance Palliative Care, National Palliative Care Research Center

## VIEW ON THE NEWS

**Daniel Ouellette, MD, FCCP, comments:** "But doc, isn't hospice just for cancer patients?"

My 80-year-old patient has COPD, requires oxygen at 4 L/min at rest, and cannot walk to his mailbox despite being on a maximum bronchodilator regimen. Too old to be a candidate for lung transplant, I have few additional medical treatments to offer him. I hope that I can help him have comfort during the last days of his life. My response to him is: "Not any longer." The study from the National Palliative Care Registry demonstrates that pulmonary physicians and their patients are increasingly aware that palliation plays an important role in the management of patients with end-stage respiratory disease.

# Patients report issues with home $O_2$

**BY KATIE WAGNER LENNON**
*Frontline Medical News*

WASHINGTON – Patient education in the use of home oxygen halves the number of system use issues reported by patients, based on results of a survey of nearly 2,000 patients.

Pulmonary clinicians and patients report "intolerable barriers to home oxygen services," lead researcher Susan S. Jacobs, RN, MS, said in a poster session at an international conference of the American Thoracic Society. These barriers include insufficient oxygen supply, inadequate and physically unmanageable portable options, and equipment malfunction.

In their study, Ms. Jacobs and her colleagues sought to determine the frequency and types of problems experienced by adult home oxygen users in the United States. Survey respondents were recruited via efforts by the ATS Public Advisory Roundtable. Links to the survey were posted on various patient advocacy websites, and flyers were posted at clinics and pulmonary rehabilitation programs asking patients to participate in an online, 60-item survey developed by the ATS Nursing Oxygen Working Group. Participants included 1,926 patients, but not all patients responded to every question.

"We've demonstrated that, if the patients are educated by a health-care professional, the problems with oxygen go down, Ms. Jacobs, who is a nurse coordinator in the division of pulmonary and critical care medicine at Stanford (Calif.) University, said in an interview. "While physicians can provide oxygen for their patients, the patient oxygen education will most likely lie with the nurses and respiratory therapists."

Of patients who responded to the survey question "Do you have oxygen problems?" 51% (899) said yes. On average, these patients said they had experienced 3.5 types of problems with their systems.

Patients who were educated by a health-care professional reported fewer problems and were more likely to report having no problems with their oxygen system. Of the patients who received oxygen therapy instruction from a health-care professional, 76 (57%) did not report having any issues with their system. In contrast, of the patients who received no instruction, 116 (64%) said they had problems with their oxygen.

Most survey participants (1,113 patients) received oxygen therapy instruction from an oxygen delivery person instead of a health-care professional. This group's opinions about their oxygen systems were split, with 51% (563 patients) experiencing issues with their systems. The other 49% reported no problems.

Survey participants most frequently complained that their equipment was not working; 499 selected this response to the question, "What types of oxygen problems do you have?"

Many patients also reported being unable to spend as much time out of their homes as they wanted. This limitation resulted from their lack of access to functioning, manageable, high-flow, portable oxygen systems, according to the researchers. Further, 43% of patients reported that their portable system limited their activity outside the home frequently or all of the time.

"Most of the reported problems were related to respondents not having portable systems that let them be out of their house for more than 2-4 hours or [to systems that] were too heavy for the patients to lift up and down their stairs and out of their cars, and they had problems operating them," Ms. Jacobs said.

The survey respondents also reported experiencing delivery problems, not being able to change the company providing them with oxygen, receiving incorrect or delayed orders from a physician, or being unable to get liquid oxygen. These responses were provided by 267, 177, 166, and 68 patients, respectively.

*"We've demonstrated that, if the patients are educated by a health-care professional, the problems with oxygen go down, said Susan Jacobs, who is a nurse coordinator in the division of pulmonary and critical care medicine at Stanford University.*

COURTESY SUSAN JACOBS

**Susan S. Jacobs instructs a patient on how to use home oxygen.**

"There is a lot of confusion for the physicians as well as the nurses about what types of systems the patients can use [and] the pros and cons of each system. There's lots of confusion and time spent about getting the initial orders right, getting them set up with a supplier, and ensuring the patient gets the equipment that was ordered. There is a lot of back and forth, which results in a delay to the patient, and the patients are upset because they are waiting for their oxygen supply," she explained. "So, I think that physicians are very much wanting clarification to streamline the process and identify what patient systems are appropriate, which are high flow, [and] what their patients' needs are to help physicians spend less time on this and help the patients get their oxygen set up in a timely manner."

The study participants came from all 50 states and were 64 years of age on average and mostly women. A high percentage (39%) of the sample had chronic obstructive pulmonary disease, while 26% had interstitial lung diseases, 18% had pulmonary arterial hypertension, 8% had alpha-1 antitrypsin deficiency, and 4% had lymphangioleiomyomatosis.

Ms. Jacobs noted that she thought patients would benefit from greater physician knowledge of their prescribing options.

"A physician can dictate exactly what system they want. ... You can try to give [patients] a lighter system, a backpack, a smaller tank, more tanks per week, depending on their lifestyle and their needs. But physicians, a lot of times, like all of us and our patients, [are] not aware of all these choices," she said during the interview.

An online resource providing all of the pros and cons of the different types of portable oxygen systems that would be appropriate for physicians, nurses, and patients, as well as an examination of the quality standards of the oxygen suppliers, are needed, she noted

Ms. Jacobs reported no financial disclosures.

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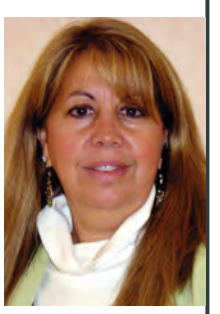
## VIEW ON THE NEWS



**Vera A. De Palo, MD, MBA, FCCP, comments:** The authors point out that there are a multitude of reasons that a patient may have difficulty with oxygen therapy. Their work would seem to indicate that conversation between the care team members (patient/family, physician, and respiratory therapy provider) can help reduce the questions and difficulties that a patient and his/her family may have after the prescribed therapy has been delivered. Any action that would enhance the likelihood of compliance with the prescribed therapy would be a benefit to our patients.

# 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

# Algorithm for identifying IPF has low PPV

**BY M. ALEXANDER OTTO**
*Frontline Medical News*

ICD-9 codes were poor at picking out idiopathic pulmonary fibrosis patients from administrative databases for epidemiologic studies, but a new tool could improve diagnostic accuracy, according to Kaiser Permanente and University of California, San Francisco, investigators.

"In the age of large administrative databases and electronic medical records, there is rich opportunity to conduct population-based studies" of disease behavior, outcomes, health care use, and other matters, but researchers first need to be able to accurately identify patients with idiopathic pulmonary fibrosis (IPF) in large data sets, said investigators led by Brett Ley, MD, an assistant professor of medicine at UCSF.

The research community has traditionally relied on claims for specific IPF diagnostic codes – ICD-9 code **516.3** or ICD-9-CM code **516.31** – to identify patients, but the approach had never been validated. To see how well it works, the investigators applied it to the nearly 5.4 million adults in the Kaiser Permanente Northern California system during 2000-2014. After patients with interstitial lung disease-associated codes entered on or after the day of the last IPF code were excluded, the algorithm identified 2,608 patients as having IPF (Ann Am Thorac Soc. 2017 Jun;14[6]:880-7).

Next, the investigators randomly

## VIEW ON THE NEWS

**Case validation is key**

This study glaringly displays potential problems with using ICD codes for research purposes and calls into question results from a handful of studies that yielded epidemiological estimates for idiopathic pulmonary fibrosis. We are reminded that practitioner-generated diagnostic codes of IPF recorded in the medical record are subject to inaccuracies, which can be illuminated by the "gold standard" – multidisciplinary adjudication.

Moving forward, particularly as longitudinal, nationwide IPF registries come online, patient-level case validation should be employed. As we move into the era of ICD-10, the study should serve as a call to improve IPF case ascertainment accuracy for any investigators choosing to use large data analytic strategies. Doing so will mute the background noise and allow us to better hear the signals of this complex disease.

*Evans R. Fernandez Perez, MD, is a pulmonologist at National Jewish Health, Denver. He made his comments in an editorial, and reported speaker's fees from Boehringer Ingelheim and Genentech (Ann Am Thorac Soc. 2017 Jun;14[6]:829-30).*

selected 150 of those patients and examined their medical records, procedure codes, CTs, and other patient-level data to see how many of them really had IPF. The results weren't good. The positive predictive value of the IPF code-based algorithm was only 42.2%, with a sensitivity of 55.6%.

The widely used code-based IPF algorithm does "not generate accurate estimates of IPF incidence and prevalence. ... Over half of the patients identified as having IPF ... did not have IPF on case review. Alarmingly, whereas half of the misclassified cases had an alternative [interstitial lung disease] diagnosis, the other half had no clinical or radiologic evidence of ILD [interstitial lung disease] at all." The algorithm also "likely misses a substantial proportion of patients who do have IPF," Dr. Ley and his colleagues said.

"We can only speculate about the reasons. ... It seems likely to be due to a combination of misdiagnosis at the clinical level and miscoding at the administrative level," they said.

To try to improve the situation, the team tweaked the algorithm to include only patients 50 years or older who had at least two **516.3** or **516.31** claims 1 month or more apart and a chest CT procedure code beforehand. They again excluded ILD-associated claims on or after the day of the last IPF code.

Although the sensitivity of the

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modified algorithm was lower than the original, it had a more robust positive predictive value of 70.4% in the derivation cohort and 61.8% in the validation cohort, both derived from the 150 patients used to validate the original algorithm.

"By making a few simple, empirically derived changes to the IPF algorithm," it's possible to "more reliably [identify] patients" with IPF. "We believe the modified IPF algorithm will be useful for population-based studies of IPF ... that require high diagnostic certainty," the investigators concluded.

The traditional algorithm found an incidence of 6.8 cases per 100,000 person-years, which was on the low end of previous reports, perhaps because of the relative health and youth of the 5.4 million patient pool. As in past studies, IPF incidence increased with older age and was highest in white patients and men.

The researchers called for further study of whether the more specific codes will allow for improved case classification of IPF.

The work was funded by the National Institutes of Health. Dr. Ley reported speaker's fees from Genentech, and another author was an employee of Genentech. The senior author Harold Collard, MD, an associate professor in UCSF's division of pulmonary and critical care medicine, reported personal fees from various companies.

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# GI disorder risk may rise in poorly controlled asthma

**BY BRIAN HOYLE**
*Frontline Medical News*

SAN FRANCISCO – Pediatric patients who have asthma that is poorly controlled may be more likely to have functional gastrointestinal (GI) disorders, which feature chronic GI distress that has several causes, according to a study of patients treated at one hospital.

Female sex and increased anxiety were influential factors.

"This study suggests a high prevalence of functional GI disorders among patients with persistent asthma. Moreover, patients with functional GI disorders had poor asthma control and increased anxiety. Clinicians should consider functional GI disorders in patients with poor asthma control and assess for anxiety as indicated," Ruben J. Colman, MD, a pediatric resident at SBH Health System, New York, said at the Pediatric Academic Societies meeting.

The prospective, cross-sectional study recruited patients aged 4-20 years at the emergency department, pediatric inpatient unit, and ambulatory clinics at St. Barnabas Hospital, a 422-bed, not-for-profit, acute care community hospital. Those with persistent asthma, which was evident by an ongoing history of daily inhaled corticosteroid medication, were enrolled.

Functional GI disorders including functional abdominal pain, irritable bowel syndrome, and functional dyspepsia were evaluated. The study was prompted by the knowledge that these conditions are a common cause of chronic GI symptoms in children, and from the findings of a retrospective study of 30,000 patients in Europe that reported a higher prevalence of asthma in those with functional GI disorders, compared with those without chronic GI distress (Aliment Pharmacol Ther. 2014 Aug;40[40]:382-91). Data are scarce in North America concerning asthma control and functional GI disorders in both pediatric and adult populations.

The validated Questionnaire on Pediatric Gastrointestinal Symptoms–Rome III version was used to assess functional GI disorders. Asthma control was assessed using the childhood Asthma Control Test

*Continued on following page*



## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** It is so important to understand what comorbidities our patients may have, and this article highlights gastrointestinal concerns for our asthma patients. It is an excellent prospective study in a wide range of ages, and I hope that this research will be expanded to benefit our patients and help us to manage their health more effectively.

# State e-cigarette laws linked to reduced youth use

**BY TARA HAELLE**
*Frontline Medical News*

Several state regulations governing the sales or use of e-cigarettes and related products were associated with lower proportions of youth trying or regularly using vaping products, a new study found.

Restricting sales of electronic vapor products to minors, however, was not linked to a lower risk of vaping among teens.

"It may be too soon to tell if the state level restrictions are having an impact," said lead author Sarah A. Keim, PhD, of Nationwide Children's Hospital in Columbus, Ohio, in an interview. "However, it was reassuring to see these early indicators that they may be having an effect so early on, and so these findings were not surprising."

Dr. Keim and her associates investigated possible associations between various state laws related to vaping products, all passed before 2015, and youth use of the products. They relied on 2015 data from 35 state-specific surveys of youth regarding use of vaping products and from the Youth Risk Behavior Survey from the Centers for Disease Control and Prevention, a nationally representative, biannual survey of students in grades 9-12. The Tobacco Control Laws Database of the American Nonsmokers' Rights Foundation provided information on state laws related to electronic vapor products.


DR. KEIM

Among the 200,513 teens whose responses were included in the study, 44% had ever used any kind of electronic vapor product. Rates were similar between girls and boys for ever having tried one or currently using one, Dr. Keim reported at the Pediatric Academic Societies annual meeting.

Experimentation began young for most: 35% of respondents tried an e-cigarette before age 14 years, and 18% under age 14 currently use vaping products. By age 17, half of all kids had tried an e-cigarette or related product, and a quarter were currently using them.

The researchers looked at associations with each of the following types of laws:

- Statewide prohibition of vaping products on school property or in workplaces, which includes Arizona, New Hampshire, Vermont, and Virginia for schools and North Dakota for workplaces.
- Prohibition of sales to minors under age 18 years, present in 24 states.
- Prohibition or restriction of sales of e-cigarette products from vending machines, present in 17 states.
- Prohibition or restriction of self-service displays of vaping products, present in 11 states.
- Prohibition or restriction of sampling of electronic vapor products, present in Arizona, Delaware, Kentucky, Maryland, New Hampshire, North Carolina, Oklahoma, and South Carolina.

For most of the regulations, teens had a reduced likelihood of trying or currently using vaping products after adjusting for age, ethnicity, grade level, race, region, and sex. Risk of ever trying a vaping product was 12% lower in states that prohibited their use on school grounds or in workplaces, 6% lower in states that barred sales to those under age 18, and 7% lower in states that restricted or prohibited self-service vaping displays.

The risk of youth currently using electronic vapor products was 5% lower in states with the school grounds and workplace restrictions,


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and 13% lower in states that restricted self-service displays. Laws restricting minor sales were unrelated to the risk of current vaping among youth. Restricting vending machine sales of vaping products had no association with the risk of a teen ever trying vaping, but it was linked to a 7% lower risk of current use of the products among teens. All these associations were statistically significant based on confidence interval values.

A statistically significant risk increase in vaping use occurred for teens in states that restricted or outlawed sampling of vaping products.

### VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** This report highlights how much we need to learn about e-cigarettes and consequences for all at-risk groups, including teens. Plus, we need to learn it FAST!



*Continued from previous page*

(ACT) questionnaire, with scores exceeding 30, less than 19, and less than 14, indicating well-controlled, not well-controlled, and poorly controlled asthma, respectively. Anxiety was assessed using the Beck Anxiety Inventory, with increasing scores indicating increasing anxiety.

The 110 enrolled patients had a mean age of 10 years. Age was similar between the 18 patients with functional GI disorders – representing a prevalence rate of 16% – and the 92 without such disorders at 12 and 10 years, respectively. Those with functional GI disorders were predominantly female, compared with the patients without a functional GI disorder (72% vs. 45%; *P* less than .03). The GI distress in the 18 patients comprised 10 cases of abdominal pain disorders and 13 cases of upper GI tract disorders, with 3 patients having an overlap of 2-3 functional GI disorders.

Patients with functional GI disorders had a lower mean ACT score, compared with those without (12 vs. 15; $P = .03$). Functional GI disorders also were associated with higher anxiety scores (34 vs. 14; *P* less than .01).

Asthma control significantly predicted the presence of functional GI disorders in univariate analysis (odds ratio, 0.9; 95% confidence interval, 0.80-0.99; $P = .03$). However, this significance was lost in a multivariate analysis that adjusted for asthma control, anxiety, and sex. The multivariate analysis revealed continued significant associations between functional GI disorders and anxiety (OR, 1.1; 95% CI, 1.01-1.10; *P* less than .01) and female sex (OR, 3.3; 95% CI, 1.00-10.56; *P* less than .05).

Dr. Colman speculated that the apparent association of asthma with chronic GI distress could reflect asthma-related inflammation that exacerbates the GI disorders.

# SYNDROMIC TESTING FROM BIOFIRE:

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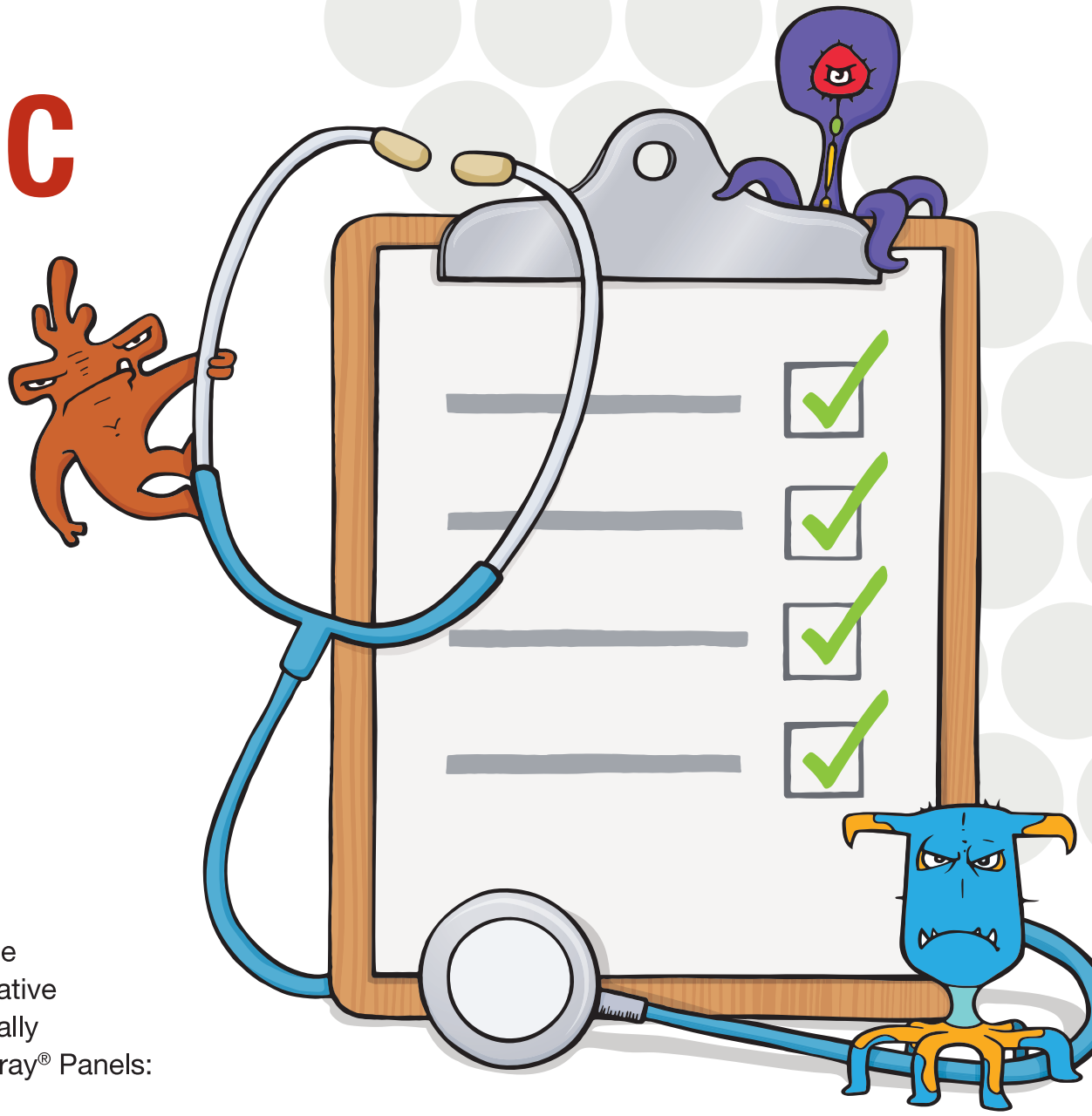

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# EHR price alert doesn't reduce lab orders

**BY M. ALEXANDER OTTO**
*Frontline Medical News*

Displaying Medicare allowable fees in the electronic health record at the time of order entry did not significantly reduce the number of inpatient lab tests at three Philadelphia hospitals.

In a study involving 98,529 patients and 142,921 admissions, Medicare payment information popped up randomly in the EHR when standard tests including complete blood cell counts, metabolic panels, and liver function tests were ordered. The costs of the labs varied depending on their extent. The message mentioned that "the dollar amount represents Medicare reimbursement for the test. Actual costs to the consumer may vary by patient insurance status." Just over a third of the patients were actually on Medicare; most had private insurance.

The idea of the study was to see if cost information would curb unnecessary testing, and save money. "There is growing interest in using price transparency to influence medical decision making toward higher-value care," Mina Sedrak, MD, and her colleagues said in a paper presented at the annual meeting of the Society of General Internal Medicine.

It didn't work out that way. Four tests ordered per patient-day when the messages appeared, and 2.34 when they did not. With messaging, the mean lab fee per patient-day was $38.85, versus $27.59 without it. In an adjusted analyses comparing the intervention to the control group, there were no significant changes in overall test ordering (0.05 tests ordered per patient-day, $P = .06$) or associated fees when pricing information was displayed ($0.24 per patient-day; $P = .47$).

In a subset analysis, the investigators did find a small decrease in orders for the most expensive labs and a small but significant increase in orders for the least expensive ones when physicians aware of cost (top quartile of tests based on fee value: -0.01; $P = .04$; bottom quartile: 0.03, $P = .04$).

Despite the overall negative results, there's still a likely role for cost information in value improvement programs; what the study shows is that

## VIEW ON THE NEWS

**Michael E. Nelson, MD, FCCP, comments:** One also needs to consider the effects of information overload and alert fatigue, both of which have been well-documented since the advent of EMRs. Most interesting is the fact that knowledge of the price actually was associated with a slight increase in test ordering, although not statistically significant. It would be even more interesting to conduct a similar study providing the knowledge to both the patient and the physician.

there's a better way to use it, according to Dr. Sedrak, currently of the City of Hope Comprehensive Cancer Center in Duarte, Calif., and colleagues.

The investigators made several suggestions when reviewing their work.

"First, the price transparency intervention in this study was always displayed regardless of the clinical scenario. The presence of this information for appropriate tests may have diminished its impact when tests were inappropriate. Future efforts may consider more selective targeting of price transparency." It might also be a good idea to price out different testing options for providers, and use actual charges and other more on-point forms of cost estimates, they said, instead of Medicare fees that have little to do with what many patients are actually charged. Targeting only the most expensive tests might also help (JAMA Intern Med. 2017 Apr 21. doi: 10.1001/jamainternmed.2017.1144).

The investigators also noticed a problem when labs are ordered to repeat automatically; clinicians did not see the price information every day, and so missed cost information "when it would be most salient."

The mean age in the study was 54.7 years; 52% of the patients were white, 39% black, and 57% women. The mean length of stay was about 6 days, and over 80% of the patients were discharged home.

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# Proposal would exempt most from MACRA/QPP

**BY GREGORY TWACHTMAN**
*Frontline Medical News*

More than half of physicians could be spared from participating in Medicare's new value-based payment programs in 2018, thanks to a Centers for Medicare & Medicaid Services proposal exempting some physicians.

The proposed 2018 update to the Quality Payment Program (QPP), the payment system created as part of the Medicare Access and CHIP Reauthorization Act (MACRA), would increase the low-volume threshold for participation, exempting practices that receive $90,000 or less in Medicare Part B payments or have 200 or fewer Medicare patients. These would be exempt from participation in either the Merit-based Incentive Payment System (MIPS) or Advanced Alternative Payment Model (APM) tracks of the QPP.

According to the proposed rule, released June 20, the CMS "estimates that approximately 572,000 eligible clinicians would be required to participate in MIPS in the 2018 MIPS performance period. ... After restricting the population of eligible clinician types who are not newly enrolled, the proposed increase in the low-volume threshold is expected to exclude 585,560 clinicians who do not exceed the low-volume threshold."

The CMS is estimating there will be 554,846 MIPS-eligible clinicians in payment year 2020, and most of them will receive either a positive or neutral payment adjustment because of their participation.

Overall, 96.6% of MIPS-eligible physicians will engage in quality reporting in 2020, with 96.1% receiving either a bonus to their Medicare Part B payments or no adjustment, according to CMS estimates. For all eligible clinicians, 76.8% will receive a bonus payment, with all payment bonuses totaling $673.3 million, while those losing money will see their Medicare payments reduced by $173.3 million. The overall aggregate impact will be a 0.9% increase in Part B payments to clinicians.

However, different practice sizes will have different experiences. For example, practices with 1-15 eligible clinicians (114,424 total eligible clinicians in this group) will see in the aggregate a 0.7% increase, while practices with 16-24 eligible clinicians (22,296) will see a 0.4% increase in the aggregate. Practices of 100 or more clinicians (318,841) stand to see the biggest bump in their Medicare payments, with a 1.4% bonus based on the provisions in the proposal.

Ten percent of practices with 1-15 MIPS-eligible clinicians and 10.9% of practices with 16-24 MIPS-eligible clinicians are estimated to receive a decrease in their Medicare payments based on the proposal, while 0.8% of clinicians in practices of 100 or more are expected to see the penalty.

Comments on the proposed update to the QPP are due to the CMS by Aug. 21, 2017.

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# Letter to *CHEST* Leaders, Members, and Friends

***Dear CHEST Leaders, Members, and Friends:***

The Forum of International Respiratory Societies (FIRS) is an organization comprised of the world's leading international professional respiratory societies presenting a unifying voice to improve lung health globally. Its members are: the American College of Chest Physicians (CHEST), American Thoracic Society (ATS), Asian Pacific Society of Respirology (APSR), Asociación Latino Americana De Tórax (ALAT), European Respiratory Society (ERS), International Union Against Tuberculosis and Lung Diseases (The Union), the Pan African Thoracic Society (PATS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and the Global Initiative for Asthma (GINA). FIRS has more than 70,000 professional members; the physicians and patients they serve magnify our efforts, allowing FIRS to speak for lung health on a global scale.

FIRS is working with the World Health Organization and the United Nations to make sure lung health is represented in national health agendas. FIRS' position paper on electronic nicotine delivery systems was presented at a side-event at the United Nations High-Level Meeting (UNHL) in New York in 2014 and is now a world standard. At the recent World Health Assembly meeting (May 2017) in Geneva, FIRS launched its Global Impact of Lung Disease report that called for a global clean air standard, strong anti-tobacco laws, and better health care for patients with respiratory disease.

FIRS will be reviewing the new WHO Global Air Quality Guidelines and will help promote them globally through advocacy and messaging, as well as by providing air quality expertise. FIRS will be involved at the Coimbra meeting (Sept 26-29) on improving the urban environment, the Montevideo UN High-Level (UNHL) meeting on chronic disease (Oct 18-20), and the UN Ministerial Meeting in Moscow on tuberculosis, and it is preparing for the 2018 UNHL meetings on antibiotic drug resistance, tuberculosis, and chronic diseases.

**At the World Health Assembly, FIRS proclaimed September 25 as World Lung Day and hopes to use this as a rallying point for advocacy related to respiratory health or air quality.** Lung Disease is the only major chronic disease that does not have a World Day. FIRS produced a Charter for Lung Health (www.firsnet.org/publications/charter) and hopes to have 100,000 persons sign on to it. FIRS also seeks to have lung-health organizations sign on and develop activities that can be carried out to celebrate lung health. Uruguay was the first country to sign the charter. The logos of the organizations who have signed the charter are on the FIRS website at firsnet.org. Activities being planned include editorials, newsletters, and letters-to-the-editor articles, legislative proclamations, social media exposure, and free spirometry, smoking cessation guidance, and carbon monoxide testing, but FIRS is looking for many more ways to celebrate healthy lungs on September 25 and many more partners!

Sixty-five million people suffer from chronic obstructive pulmonary disease and 3 million die of it each year, making it the third leading cause of death worldwide; 10 million people develop tuberculosis and 1.4 million die of it each year, making it the most common deadly infectious disease; 1.6 million people die of lung cancer each year, making it the most deadly cancer; 334 million people suffer from asthma, making it the most common chronic disease of childhood; pneumonia kills millions of people each year, making it a leading cause of death in the very young and very old. At least 2 billion people are exposed to toxic indoor smoke; 1 billion inhale polluted outdoor air; and 1 billion are exposed to tobacco smoke, and the tragedy is that many conditions are getting worse. We cannot sit still and allow this to happen.

FIRS proposes a multipronged campaign to combat lung disease to bring together all people concerned with lung health. It starts with naming September 25 World Lung Day and calling on respiratory health organizations to pledge to improve lung health and help identify ways to celebrate this day.

Please sign up, and share this call for action with your professional, advocacy, and social networks, and those of your friends and families. Please do your part as global citizens to improve lung health. To do so, organizations should indicate they wish to sign on and send their logo to Betty Sax, FIRS Secretariat, betty.sax@ersnet.org. Organizations should also encourage individuals to sign on and show that they are committed to increasing awareness and action to promote global lung health.

Thank you.

Gerard Silvestri, MD, MS, FCCP
CHEST President
Darcy Marciniuk, MD, FCCP
CHEST FIRS Liaison

## *CHEST*® journal — new online home


We are excited to share that the journal *CHEST*® has a new website with improved navigation, better search capabilities, alert sign-ups, and more multimedia elements. We are asking members to take a few minutes to activate their new account.

In order to maintain continuous access to the online journal, members will have to register for a free account and claim their subscription. If you go to chestjournal.org, CHEST members can then complete a 1- to 2-minute registration process.

"This is an exciting time for the journal, and I personally believe that online users will be very pleased with what the new web version has to offer," says Dr. Richard Irwin, *CHEST*'s Editor in Chief.

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## This Month in *CHEST:* Editor's picks

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

**GIANTS IN CHEST MEDICINE:**
**Steven E. Weinberger, MD, FCCP**
*By Dr. J. Mandel*

**EDITORIAL**
**Precision Medicine Urgency: The Case of Inhaled Corticosteroids in COPD**
*By Drs. S. Suissa and P. Ernst*

**ORIGINAL RESEARCH**
**Physician Assessment of Pretest Probability of Malignancy and Adherence With Guidelines for Pulmonary Nodule Evaluation**
*By Dr. N. T. Tanner, et al.*

**The Long-Term Effect of Bacille Calmette-Guérin Vaccination on Tuberculin Skin Testing: A 55-Year Follow-Up Study**
*By Dr. J. D. Mancuso, et al.*


**Clinical Characteristics of Pertussis-Associated Cough in Adults and Children: A Diagnostic Systematic Review and Meta-Analysis**
*By Dr. A. Moore, et al.*

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).

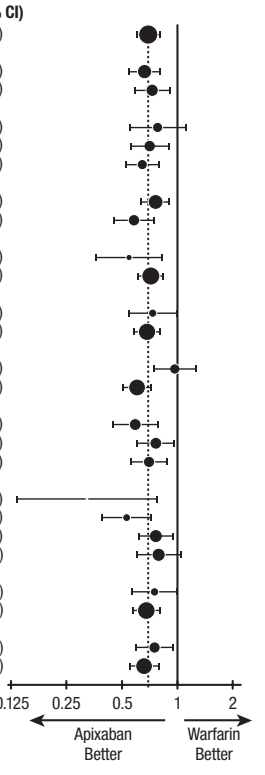
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§ 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]*.

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
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1356615A2 / 1356514A1 Rev July 2016

432US1603587-13-01

# CHEST Membership News

*We're Rewarding You*

### Introducing CHEST Participation Points

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We're happy to introduce CHEST Participation Points, designed to increase member recognition and reward you for participating and contributing to our diverse community. Wherever you are in your career, you can earn points for the things you do within the CHEST community.

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Point accrual started on July 5, so you've already been earning points. If you are an FCCP, you began with 30 points awarded for becoming FCCP—that's only 20 points away from the first tier of prizes. To accrue or redeem points, you must be an active member and current with your dues.

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| Volunteer in CHEST booth | First time membership renewal | Participate in a focus group, work group, or ad hoc committee |
| Attend CHEST Annual Meeting | Attend 3 consecutive CHEST Annual Meetings | Submit an abstract or case report for CHEST Annual Meeting |
| Serve as abstract/case report grader for CHEST Annual Meeting | Participate in a CHEST webinar | Participate in a community service event |
| | | Participate in the mentorship program |

## INDEX OF ADVERTISERS





# Vaccination: An Important Step in Protecting Health

Patients with chronic lung conditions, like COPD and asthma, need to take extra steps to manage their condition and ensure the healthiest possible future. One important step that may not always be top of mind is vaccination, which can protect against common preventable diseases that may be very serious for those with respiratory conditions. CDC recommends adults with COPD, asthma, and other lung diseases get an annual flu vaccine, as well as stay up to date with pneumococcal and other recommended vaccines. Additional vaccines may be indicated based on age, job, travel locations, and lifestyle.

COPD and asthma cause airways to swell and become blocked with mucus, making it hard to breathe. Certain vaccine-preventable diseases can make this even worse. Adults with COPD and asthma are at increased risk of complications from influenza, including pneumonia and hospitalization. They are also at higher risk for invasive pneumococcal disease and more likely to develop infections including bacteremia and meningitis. Each year, thousands of adults needlessly suffer, are hospitalized, and even die of diseases that could be prevented by vaccines. Despite increased risks, less than half of adults under 65 years with COPD and asthma have received influenza and pneumococcal vaccination (National Health Information Survey 2015).

*One important step that may not always be top of mind is vaccination, which can protect against common preventable diseases that may be very serious for those with respiratory conditions.*

Find the latest recommended adult immunization schedule at www.cdc.gov/vaccines/hcp/adults.

CRITICAL CARE COMMENTARY

# Conscience Rights, Medical Training, and Critical Care

## *A Medical Student Perspective*

BY ANA-MARIA DUMITRU, PHD; BENJAMIN W. FRUSH, MA; CHRIS RADLICZ, MS, MPH; PHILIP ALLEN, BS; MARTIN T. BROWN, BS; JEREMY BANNON, BSC; AND JOHN Y. RHEE, MPH

***"No provision in our Constitution ought to be dearer to man than that which protects the rights of conscience against the enterprises of the civil authority."*** – *Thomas Jefferson* (Washington HA. *The Writings of Thomas Jefferson*. New York: Biker, Thorne, & Co. 1854,; Vol 3:147.)

What is the proper role of conscience in medicine? A recent article in the New England Journal of Medicine (Stahl & Emmanuel. *N Engl J Med*. 2017; 376(14):1380) is the latest to address this question. It is often argued that physicians who cite conscience in refusing to perform requested procedures or treatments necessarily infringe upon patients' rights. However, we feel that these concerns stem from a fundamental misunderstanding of what conscience is, why it ought to be respected as an indispensable part of medical judgment (Genuis & Lipp . *Int J Family Med*. 2013; Epub 2013 Dec 12), and how conscience is oriented toward the end goal of health, which we pursue in medicine.

By failing to define "conscience,"

*Continued on following page*

### EDITOR'S NOTE:

When I invited Dr. Wes Ely – the coauthor of a recent article regarding physician-assisted suicide – to write a Critical Care Commentary on said topic, an interesting thing happened: he declined and suggested that I invite a group of students from medical schools across the country to write the piece instead. The idea was brilliant, and the resulting piece was so insightful that the CHEST® journal editorial leadership suggested submission to the journal, and the accepted article will appear in the September issue. Out of that effort, the idea for the present piece was born. The result is an opportunity to hear the students' voices, not only to stimulate discussion on conscientious objection in medicine but also to remind the ICU community that our learners have their own opinions and that through dialogues such as this, we might all learn from one another.

*Lee Morrow, MD, FCCP*

*Continued from previous page*

the crux of the argument against conscience rights is built on the basis of an implied diminution of conscience from an imperative moral judgment down to mere personal preference. If conscience represents only personal preference – if it is limited to a set of choices of the same moral equivalent as the selection of an ice cream flavor, with no need for technical expertise—then it would follow that a physician ought to simply comply with the patient's decisions in any given medical situation. However, we know intuitively that this line of reasoning cannot hold, if followed to its conclusion. For example, if a patient presenting with symptoms of clear rhinorrhea and dry cough in December asks for an antibiotic, through this patient-sovereignty model, the physician surely ought to provide the prescription to honor the

***Conscience ought to be respected as an indispensable part of medical judgment.***

patient's request. The patient would have every right to insist on the antibiotic, and the physician would be obliged to prescribe accordingly. We, as students, are trained, however, that it would be morally and professionally fitting, even obligatory, for the physician to refuse this request, precisely through exercise of his/her professional conscience.

If conscience, then, is not simply a subject of one's personal preferences, how are we to properly understand it? Conscience is "a person's moral sense of right and wrong, viewed as acting as a guide to one's behavior" (Conscience. Oxford Dictionary. Oxford, Oxford University Press. 2017). It exhibits the commitment to engage in a "self-conscience activity, integrating reason, emotion, and will, in self-committed decisions about right and wrong, good and evil" (Sulmasy. *Theor Med Bioeth*. 2008; 29(3):135). Whether or not a person intentionally seeks to form his/her conscience, it continues to be molded through the regular actions of daily life. The actions we perform – and those we omit – constantly shape our individual consciences. One's conscience can indeed err due to emotional imbalance or faulty reasoning, but, even in these instances, it is essential to invest in the proper shaping of conscience in accordance with truth and goodness, rather than to reject the place of conscience altogether.

By attributing appropriate value to an individual's conscience, we thereby recognize the centrality of conscience to identity and personal integrity. Consequently, we see that forcing an individual to impinge on his/her conscience through coercive means incidentally violates that person's autonomy and dignity as a human being capable of moral decision-making.

*The actions we perform – and those we omit – constantly shape our individual consciences.*

In the practice of medicine, the free exercise of conscience is especially relevant. When patients and physicians meet to act in the pursuit of the patient's health, they begin the process of conscience-mediated shared decision-making, rife with the potential for disagreement. Throughout this process, a physician should not violate a patient's conscience rights by forcing medical treatment where it is unwanted, but neither should a patient violate a physician's conscience rights by demanding a procedure or treatment that the physician cannot perform in good conscience. Moreover, to insert an external arbiter (eg, a professional society) to resolve the situation by means of contradiction of conscience would have the same violating effect on one or both parties.

One common debate as to the application of conscience in the setting of critical care focuses on the issue of physician-assisted suicide and euthanasia (PAS/E) (Rhee J, et al. *Chest*. 2017;152[3]. Accepted for Sept 2017 publication). Those who would deny physicians the right to conscientiously object to PAS/E depict this as merely an issue of the physician's personal preference. Given the distinction between pref-

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erence and conscience, however, we recognize that much more is at play. For students and practitioners who hold that health signifies the "well-working of the organism as a whole," (Kass L. *Public Interest*. 1975; 40(summer):11-42) and feel that the killing of a patient is an action that goes directly against the health of the patient, the obligation to participate in PAS/E represents not only a violation of our decision-making dignity, but also subverts the critical component of clinical judgment inherent to our profession. The conscientiously practicing doctor who follows what they believe to be their professional obligations, acting in accordance with the health of the patient, may reasonably conclude that PAS/E directly contradicts their obligations to pursue the best health interests of the patient. As such, their refusal to participate can hardly be deemed a simple personal preference, as the refusal is both reasoned and reasonable. Indeed, experts have concluded that regardless of the legality of PAS/E, physicians must be allowed to conscientiously object to participate (Goligher et al. *Crit Care Med*. 2017; 45(2):149).

As medical students who have recently gone through the arduous medical school application process, we are particularly concerned with the claim that if one sees fit to exercise conscientious objection as a practitioner, they should leave medicine, or choose a field in medicine with few ethical dilemmas. To crassly exclude students from the pursuit of medicine on the basis of the shape of their conscience would be to unjustly discriminate by assigning different values to genuinely held beliefs. A direct consequence of this exclusion would be to decrease the diversity of thought, which is central to medical innovation and medical progress. History has taught us that the frontiers of medical advancement are most ardently pursued by those who think deeply and then dare to act creatively, seeking to bring to fruition what others deemed impossible. Without conscience rights, physicians are not free to think for themselves. We find it hard to believe that many physicians would feel comfortable jettisoning conscience in all instances where it may go against the wishes of their patients or the consensus opinion of the profession.

Furthermore, as medical students, we are acutely aware of the importance of conscientious objection due to the extant hierarchical nature of medical training. Evaluations are often performed by residents and physicians in places of authority, so students will readily subjugate everything from bodily needs to conscience in order to appease their attending physicians. Evidence indicates that medical students will even fail to object when they recognize medical errors performed by their superiors (Madigosky WS, et al. *Acad Med*. 2006; 81(1):94).

It is, therefore, crucial to the proper formation of medical students that our exercise of conscience be safeguarded during our training. A student who is free to exercise conscience is a student who is learning to think independently, as well as to shoulder the responsibility that comes as a consequence of free choices.

Ultimately, we must ask ourselves: how is the role of the physician altered if we choose to minimize the role of conscience in medicine? And

do patients truly want physicians who forfeit their consciences even in matters of life and death? If we take the demands of those who dismiss conscience to their end – that only those willing to put their conscience aside should enter medicine – we would be left with practitioners whose group think training would stifle discussion between physicians and patients, and whose role would be reduced to simply acquiescing to any and all demands of the patient, even to their own detriment. Such a group of people, in our view, would fail to be physicians.

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PULMONARY PERSPECTIVES®

# Immigrants in Health Care

BY NITIN PURI, MD, FCCP
*Pulmonary Perspectives Section Editor*

July 4th was bittersweet for me, this year. Independence days of my childhood were spent grilling, sitting by the campfire on the lakes and rivers of Northern Michigan, watching the fireworks turn the night sky red, white, and blue. These fond memories were a painful reminder that others like me may not have the privilege to experience such joy, secondary to their background.



I don't remember the first time that I heard the tale of my parents coming to America. They were both medical students from India, who received brightly colored brochures from American hospitals inviting them to come further their medical training. Due to the deficit of physicians in the United States, the hospitals even loaned money to medical students, so they would do their residencies in America. My parents took advantage of this opportunity and embarked on a journey that would define their lives. Often, my mother would talk about my father leaving for the hospital on Friday morning only to return to his wife and two toddlers on Monday afternoon. As a child, I remember my uncles taking bottles of milk to the hospital to make chai to fuel through their grueling overnight calls. These immigrant tales were the backdrop of my childhood, the basis of my understanding of America. I was raised in an immigrant community of physicians who were grateful for the opportunities that America offered them. They worked hard, reaped significant rewards, and substantially contributed to their communities. Maybe, I am just nostalgic for my childhood, but this experience, I believe, is still an integral part of the American dream.

The recent choice to restrict immigration from specific nations is disturbing at best and reminiscent of an America that I have never known. More than 7,000 physicians from Libya, Iran, Somalia, Sudan, Syria, and Yemen are currently working in the United States, providing care for more than 14 million people. An estimated 94% of American communities have at least one doctor from one of the targeted countries. These physicians are more likely to work in rural and underserved communities and provide essential services.[1] They are immigrants who have come to America to better their lives and, in turn, have bettered the lives of those around them. They are my parents. Not all physicians are good people or are worthy of the American dream, but America is a better place for welcoming those who are willing to work hard to make a better life for themselves. An important criticism of the effect of migration of medical professionals to the United

States has been the loss of human capital to their respective nations, but never the ill-effect they have had on the nations they have emigrated to.

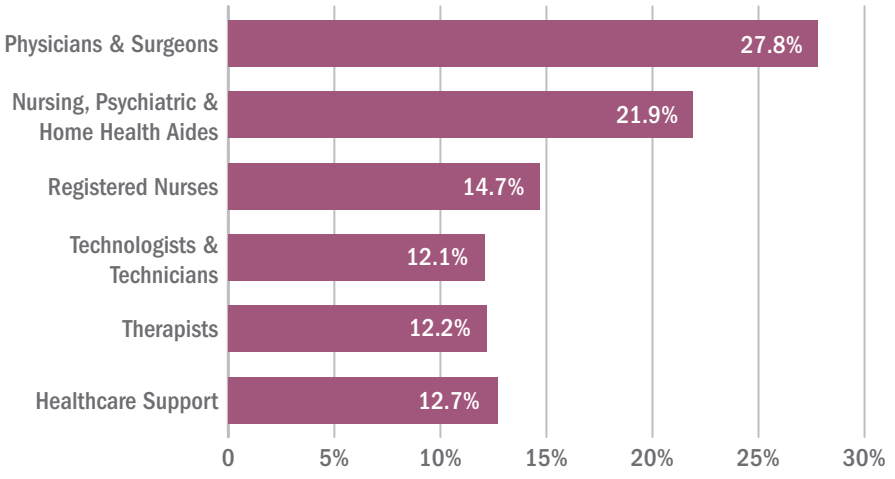
The 2015 Educational Commission for Foreign Medical Graduates (ECFMG) reported that a quarter of practicing physicians in the United States are international medical graduates (IMGs) and a fifth of all residency applicants were IMGs.[2] Measuring the impact of the IMGs who have come to America is difficult to quantify but can be assessed by countless anecdotes and success stories. Forty-two percent of researchers at the seven top cancer research centers in the United States are immigrants. This is impressive considering that only about a tenth of the United States population is foreign born. Twenty-eight American Nobel prize winners in Medicine since 1960 are immigrants and taking a broader view as seen in Figure 1, almost 28% of physicians and 22% of RNs in the United States are foreign born.[3,4] That does not take into account those like myself, first generation children who chose to enter this field of work out of respect for what their parents had accomplished.

The American College of Chest Physicians (CHEST), over the past 15 years, has had several Presidents who are American immigrants. One of them, Dr. Kalpalatha K. Guntupalli, President 2009-2010, I have met, and I was humbled by the experience. She is brilliant, kind, and modest and without her knowing, she has served as one of the role models for my career.

I applaud CHEST for standing with other member organizations to oppose the immigration hiatus (Letter to John F. Kelly, Secretary of Homeland Security. Feb 7, 2017). The medical organizations made four concrete proposals:

- Reinstate the Visa Interview Waiver Program, as the suspension of this program increases the risk for significant delays in new and renewal visa processing for trainees from any foreign country;
- Remove entry restrictions of physicians and medical students from the seven designated countries that have been approved for J-1, H-1B or F-1 visas;
- Allow affected physicians to obtain travel visas to visit the United States for medical conferences, as well as other medical and research related events; and
- Prioritize the admission of refugees with urgent medical needs who had already been checked and approved for entry prior to the executive order.

FIGURE 1
**Foreign-Born Share of Healthcare Workers by Occupation, 2010**




**Source:** Adapted from American Community Survey 5-year estimates (2010-2014) and IPUMS-USA, University of Minnesota, www.ipums.org.

These recommendations were good but not broad enough. The decision to bar immigration for any period of time, from any country, is an affront to the American dream with long-lasting consequences, most importantly, the loss of healthcare services to the American populace. My Congressman knows how I feel about this, does yours?

1. Fivethirtyeight.com/features/trumps-new-travel-ban-could-affect-doctors-especially-in-the-rust-belt-and-appalachia/.Accessed July 18, 2017.
2. Masri A, Senussi MH. Trump's executive order on immigration—detrimental effects on medical training and health care. N Engl J Med. 2017; 376(19): e39.
3. http://www.immigrationresearch-info.org/report/immigrant-learning-center-inc/immigrants-health-care-keeping-americans-healthy-through-care-a.Accessed July 27, 2017.
4. http://www.nfap.com/wp-content/uploads/2015/05/International-Educator.May-June-2015.pdf.Accessed July 27, 2017 (not available on Safari).

# Catching Up With Our CHEST Past Presidents

*Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians, leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's strategic initiatives. Let's check in with Dr. Goldberg.*

**ALLEN I. GOLDBERG, MD, MASTER FCCP**
*President 1998-1999*

I arrived in Toronto in 1998 to start my term as President of the American College of Chest Physicians. (I had always loved Toronto, where I had spent months training in pediatric critical care at "Sick Kids" [Toronto's Children's Hospital] and collaborating with Audrey King on disability issues and public policy in Ontario.) CHEST 1998 in Toronto was equally exciting. What I remember - with humility – was that being CHEST President is not about "you." It is about "The President," who is honored and revered by all members for what CHEST truly represents … excellence in healthcare education, communication, and information. Everyone came up to me to respect and honor the role … including awesome Past Presidents who lovingly shared their insights and experience and others (including many who became future presidents) to volunteer their assistance. I was in awe of these leaders and how they demonstrated selfless service.

And so I began my year of presidential service leadership. What I remember best is the respect all around the world for CHEST and what it does to unite people into actions that improve health globally. The President serves CHEST members to facilitate working together, which makes a difference. My presidential year culminated in the 65th anniversary conference in Chicago in 1999. All year, I had worked with my mentor (C. Everett Koop, MD, FCCP(Hon), to plan an opening ceremony that would be inspirational and unforgettable. For years, we had shared personal/private conversations. This time, we planned to communicate in public to inspire others and help them understand key issues we considered critical for the future of health care and global health.


**Dr. Koop presided over a student competition to design innovations in communication of information about asthma. This event was held at Northwestern-Kellogg School of Management, sponsored by the CHEST Foundation (Dr. Goldberg far right).**

Soon after my Presidential term, I took 2 years off for sabbatical to work more closely with Dr. Koop (2000-2002). Then, I retired to continue to focus on our work together and as personal caregiver for my wife, Evi Faure, MD, FCCP. Dr. Koop and I met many times and also held more public presentations, including the 2003 Surgeons' General National Meeting on Overcoming Health Disparities at Howard University arranged with CHEST Past President Dr. Alvin Thomas.

All our joint efforts focused on the importance of **Communication in Health Care**. We shared the belief that communication of health information would create the "informed patient and family" who would then work together in partnership with health-care professional team members. We thought that this would be the best way to improve and reform health-care delivery. We sought to provide information (the "what") in ways that it would be trusted, understandable, and easily usable (the "how) for patients and families (the "who"). Our goal was to use evolving digital technology and personal health communicators who would facilitate information exchange. This would enable patients/families to make decisions and take actions to manage their health and identify and obtain the resources they needed (the "why") at times of need (the "when"). This concept was built on our long-term shared commitment and belief in patient self-help and self-management.

My greatest learning was the importance of mentorship – both for the mentor and mentee. This fosters communication that enables learning and growth in our abilities to serve others by the profession we love.

http://www.chestnet.org/News/Blogs/CHEST-Thought-Leaders/2013/06/Dr-Koops-Legacy-Reflections-on-Mentorship

http://www.chestnet.org/News/Blogs/CHEST-Thought-Leaders/2013/08/The-Legacy-of-Dr-Koop-Reflections-on-Our-Fireside-Chat

**Dr. Allen I. Goldberg (left) attends Dr. C. Everett Koop's wedding and congratulates him on his marriage. "Dr. Koop was remarried at age 94. I was delighted to attend this special event," Dr. Goldberg said.**

# CHEST Joint Congress in Basel, Switzerland

Members of CHEST leadership, faculty, and staff traveled to Basel, Switzerland, in June, to participate in the CHEST Joint Congress, which was co-hosted with the Swiss Respiratory Society, Schweizersche Gesellschaft Fur Pneumologie (SPG). Overall, there were approximately 1,100 total attendees, representing over 40 countries, who enjoyed the scientific program and gained valuable chest medicine knowledge. Among the many topics presented were diagnosis and treatment of ILD; biologics for severe asthma; EBUS for molecular analysis; and ICS in COPD. Plus, hands-on, interactive workshops were offered for learning or reviewing more procedural skills. We invite you to view webcasts of five of the Basel sessions at bit.ly/chestsgp2017.

The CHEST Joint Congress in Basel represented the second collaborative scientific conference endeavor with a third party, the first being the CHEST Conference held in Amsterdam May 6-9, COPD: Current Excellence and Future Development.


**CHEST President, Gerard Silvestri, MD, FCCP, at the CHEST booth in Basel.**

# *New Tools in Campaign to Fight Asthma*

The Allergy & Asthma NetWork, the nation's leading patient education and advocacy organization for people with allergy and asthma, has once again joined forces with the CHEST Foundation in an effort to empower patients suffering from severe asthma.

The campaign's focus is to educate health-care providers, patients, parents of asthmatics, and the public about the most current treatment options for asthma, highlight the importance of referring to specialists to improve patient outcomes, and bring to light the role of the entire health-care team in the care of a patient with severe or difficult-to-control asthma.

This is the second year of this growing campaign, and there are several new and exciting materials.

## Severity Assessment Tool

Available online and in print, the severity assessment tool was designed to help a patient, and the clinician, understand the severity of their asthma. Not only does the tool evaluate the severity of their condition, but it also helps the patient become more aware of their symptoms. The seven-question assessment includes questions on usage of quick-relief or rescue inhalers, visits to the ED/hospital, physical activity, controller medication, and quality of sleep.

## Patient and Caregiver Testimonials

The campaign features several patient and caregiver testimonials that tell the stories of patients and

*Continued on following page*

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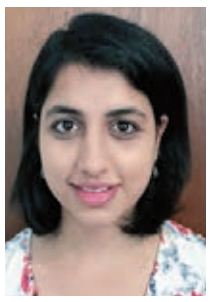
NETWORKS

# Health-care weaponization, PTSD, depression in caregivers

## Disaster Response

### The tragic weaponization of health care

The Syrian conflict has highlighted the dangers to health-care workers (HCWs) in humanitarian crises. The Lancet-American University of Beirut Commission on Syria reports on the weaponization of health care in Syria – a strategy of depriving people of their health-care needs. Targeting of HCWs was recognized early in the Syrian war with targeting of health-care facilities being frequently reported throughout the conflict. HCWs facing extreme supply shortages have been reported to resort to desperate measures: using urine bags with added anticoagulants for blood collection and crafting homemade external fixators for fractures. Sadly, the Syrian conflict is not unique. The International Committee of the Red Cross (ICRC) documented 2,398 episodes of violence directed at health facilities in 11 countries affected by armed conflict between 2012 and 2014 alone. In Syria and elsewhere, the exodus of trained medical personnel, due to lack of medical training in trauma, emergency medicine, and intensive care, puts populations at further risk in these regions. The International Red Cross and Red Crescent Movement has started the Health Care in Danger (http://http://healthcareindanger.org) initiative to highlight this weaponization of health, supporting efforts by HCWs to advocate for their rights and their patients' rights at a global level. This highlights the needs for CHEST members responding to humanitarian crises to ensure they have appropriate training to work in these environments and deploy with an organization that can provide adequate safeguards.



DR. MISHRA

DR. MAVES

*Dr. Maves is a military service member. The opinions expressed herein are his own and do not necessarily reflect the official opinions of the Department of the Navy, Department of Defense, or the US Government.*

*Rashmi Mishra, MD*
*Fellow-in-Training Member*
*Ryan Maves, MD, FCCP*
*Steering Committee Member*

## Practice Operations

### The House AHCA /Senate BCRA compared with ACA (Affordable Care Act)

Health-care costs are a fundamental driver of insurance costs, which leads to challenges to coverage affordability for millions of families. There is ongoing debate whether the current law (Affordable Care Act [ACA/Obamacare]) and the republican alternatives (American Healthcare Act [AHCA] and Better Care Reconciliation Act [BCRA]) do enough to address the cost challenges. Here is a brief summary of the key similarities and differences.

**Similarities:** (1) Children will be covered up to age 26. (2) Coverage of pre-existing conditions continues (high risk pools will be subsidized by a state government but premiums are up to twice as much as individual coverage). (3) Tax credit (based on age and family size rather than income level). (4) Insurance can charge older customers more than younger (up to 3X under ACA, 5X under AHCA/BCRA). (5) No annual or lifetime payout limit (but states may apply waivers allowing insurers to apply limits).

DR. BASSILY-MARCUS

**Differences:** (1) Insurance will no longer be mandatory (no individual or employer mandates, but there is a 30% increase in premiums for 1 year for not maintaining individual continuous coverage). (2) Medicaid expansion (expanded under ACA to 133% of poverty level income) will stop in 2020. (3) Restriction on "Abortion Funding" (any facility that offers abortion will not receive federal funding) for 1 year. (4) Taxes on health care will be removed (including taxes on prescription drugs, OTC, premiums, and medical devices). (5) Allowing policies for major illness or injury (with elimination of the requirement to cover ten essential health benefits, allowing states to modify).

Health-care reform undoubtedly is complicated, and there are a lot of questions in the air about the future of health care under the Trump Administration. Few certainties: change is coming, MACRA is here to stay.

*Adel Bassily-Marcus, MD, FCCP*
*NetWork Chair*

## Transplant

### Posttraumatic Stress Disorder Post-Lung Transplant

The majority of transplant physicians are mainly concerned with issues posttransplant that are focused on the graft function. But recently, neurocognition and posttransplant posttraumatic stress disorder have been found to have significant impact on quality of life and mortality after transplantation. Posttraumatic stress disorder (PTSD) is described as re-experiencing a traumatic event in addition to having avoidant and hyperarousal symptoms, which last for a period of at least 1 month. Studies of PTSD in solid organ transplant recipients have revealed a significantly higher prevalence of PTSD symptoms (10% to 17%) compared with the general population (prevalence of 3.5% to 6%). In one study of heart transplant recipients, patients who met the criteria for PTSD in the first year posttransplant had a higher risk for 3-year mortality (OR=13.74) [Dew et al. *J Heart Lung Transplant.* 1999;18[6]:549-562].

Lung transplant recipients are at a high risk for developing PTSD due to exposure to several traumatic events, such as a life-threatening exacerbation of the underlying lung disease, undergoing transplant surgery, intensive care unit stay, delirium and episodes of infection, and acute and chronic rejection. However, data regarding the prevalence and risk factors for PTSD post-lung transplant are limited.

The prevalence of PTSD post lung transplantation has been reported to

*Continued from previous page*

parents of children with severe asthma.

"What we want people to understand, is that at the time of Ben's passing, he was on a preventive med. He was going to the doctor routinely. We had actually just been to the asthma doctor. We were seeing somebody, had an action plan, and everybody knew what they had to do. Even with all of that, it still came to this. Benjamin still lost his life, and we never knew this was something that could happen," stated Cristin Buckley, mother of Benjamin Buckley who was 7 years old at the time of his death. These testimonial videos will be used to raise awareness of the condition, and the importance of managing and monitoring symptoms.

### Shared Decision Making Tool

The American College of Allergy, Asthma, and Immunology (ACAAI), the Allergy & Asthma Network, and CHEST Foundation have partnered to develop a shared decision-making tool for adults with severe asthma. This tool will be launched at CHEST 2017 in October. Available online and in print, it was created for patients and clinicians to work together to improve self-management skills, choose the best treatment plan for the patient, and increase adherence. This patient-centered approach in clinical settings improves patient satisfaction of care and overall outcomes.


### Thank You to Our Supporters

The CHEST Foundation and Allergy and Asthma Network would like to thank our generous supporters, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis for making this campaign possible. It is through supporters, who are active participants in helping grow this campaign, that these important materials are able to have an impact on patient outcomes and create long-lasting social change.

To view the campaign materials, visit us at asthma.chestnet.org.

be 12.6% to 15.8%. In lung transplant recipients with clinically significant PTSD symptomatology; the presence of symptoms of re-experiencing (29.5%) and arousal (33.8%) were more common than avoidant symptoms (18.4%) [Gries et al. *J Heart Lung Transplant*. 2013; 32[5]: 525-532]. In another study by Dew et al, in 178 lung transplant recipients, all PTSD occurred in the early months posttransplant with a median duration of symptoms of 12 months (IQR 7.2 to 18.5 months) [Dew et al. *Gen. Hosp Psychiatry.* 2012;34:127-138]. A higher burden of PTSD is noted in patients who are younger, have a lower income, have a previous history of a traumatic event, and have bronchiolitis obliterans (Gries et al. *J Heart Lung Transplant*. 2013;32[5]:525-532).

DR. AHYA

The challenges that remain include determining the true prevalence of PTSD in the lung transplant recipient in the LAS era using standard diagnostic criteria, documenting the adverse effects of PTSD on medical compliance, morbidity, and mortality; and developing interventions to mitigate the adverse effects of PTSD through well-designed multicenter prospective studies.

*Vivek Ahya, MD*
*Steering Committee Member*

## Women's Health

### Caregiver Burden in the ICU and Beyond

Family members of patients in the ICU who transition to the role of caregivers following discharge are at high risk for psychosocial distress. Post-intensive care syndrome-family (PICS-F) describes the symptoms of depression, posttraumatic stress, and anxiety commonly found in this population (Davidson et al. *Crit Care Med.* 2012;4(2):618-624). Women are more commonly called upon to adopt the role of caregiver for family members with chronic medical conditions or mental illnesses. Worldwide estimates indicate that 57% to 81% of all caregivers are women (Sharma et al. *World J Psych.* 2016;6[2]:7-17).

Family burden begins during the acute phase of critical illness. As surrogate decision-makers, they frequently face decisional conflict and decisional regret, especially in scenarios that limit life-sustaining therapies (Long et al. *Curr Opin Crit Care.* 2016;22:613-620). The prevalence of PICS-F is high as family members attempt to balance their role in the ICU with personal obligations (Choi et al. *J Korean Acad Nurs.* 2016;[46]2:159-167). Those who perceive that they are not receiving complete information from the medical team, and who do not find their physician comforting, have been shown to suffer a greater symptom burden (Davidson et al).

With the growing older adult population, and increased ICU survival, family members are often called upon to serve as caretakers to the chronically critically ill (Choi et al.). These caregivers have more depressive symptoms, worse health outcomes, and significant professional and personal lifestyle disruptions (Cameron, et al. *N Engl J Med.* 2016;[374]19:1831-1841). In many caregivers, depressive symptoms persist at 1 year after ICU admission, with rates comparable to caretakers of patients with dementia (Haines et al. *Crit Care Med.* 2015;(43)5:1112-1120). Caregivers who are younger, female, minorities, and those with pre-existing depression are at especially high risk for worse mental health outcomes (Davidson et al; Cameron et al).

DR. PISANI

DR. BOURNIVAL

Caregivers of ICU survivors are vulnerable and undersupported. Interventions such as ICU diaries, telephone-based mindfulness exercises, and stress management strategies have shown promise in alleviating PICS-F symptoms (Choi et al.). During the acute ICU stay, how medical providers communicate, and how we help family members make sense of what has happened and their new roles as caregivers have an impact (Davidson et al.). From an individual in a study of psychosocial morbidity in caregivers of ICU survivors: "Leaving the hospital is not the end for some people. The next place is just as hard, sometimes worse" (Haines et al. Further studies are needed to identify interventions that will truly address this population's unique needs.

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

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

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

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


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