Celebrating 10 Years
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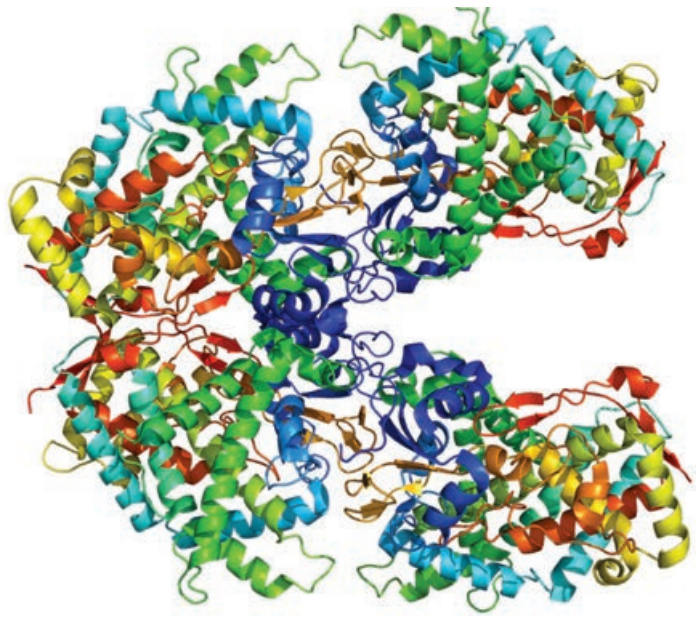

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High metabolizers of cytochrome P450 2A6 (CYP2A6) are more likely to form DNA adducts and are at higher risk of lung cancer.

Using DNA adducts to find high-risk smokers

BY PATRICE WENDLING
Frontline Medical News

SAN DIEGO – Using large-scale epidemiology studies and DNA adducts data, researchers are one step closer to identifying young smokers particularly susceptible to the carcinogenic effects of smoking.

"This is not lung cancer screening; this is not early detection of lung cancer; this is detection of susceptible, high-risk individuals, so they can be targeted for cessation, surveillance, and prevention," said Stephen S. Hecht, Ph.D., professor of cancer prevention at the University of Minnesota Masonic Cancer Center in Minneapolis.

While nicotine itself is not a carcinogen, each puff of tobacco smoke delivers more than 70 established carcinogens, including the potent lung-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Some of these carcinogens are excreted, but many will undergo metabolic activation and interact with a patient's DNA.

The product of this interaction, called DNA adducts, causes persistent miscoding during DNA replication, leading to the thousands of mutations we see in lung

See **Adducts** • *page 26*

Intensified therapy for TB meningitis did not aid survival

Levofloxacin and more rifampin fell short.

BY MARY ANN MOON
Frontline Medical News

Intensified antituberculosis therapy doesn't appear to improve survival in adults with tuberculous meningitis, compared with standard treatment, according to a report published online in the New England Journal of Medicine.

This result, from a 3-year randomized double-blind placebo controlled clinical trial involving 817 adults in Vietnam, contradicts findings from previous small studies which suggested that increasing the rifampin dose and adding a fluoroquinolone to the standard regimen might improve outcomes, said Dr. A. Dorothee Heemskerk of the Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam, and her associates.

Current guidelines recommend at least 2 months of therapy with four antituberculosis agents, followed by treatment with rifampin (10 mg/kg) and isoniazid for an additional 7-10 months. "However, these recommendations are based on data from pulmonary tuberculosis and do not take into account the differential ability of antituberculosis drugs to penetrate the

See **TB meningitis** • *page 14*

Real-world NOAC adherence is poor

BY BRUCE JANCIN
Frontline Medical News

ORLANDO – Adherence to the novel oral anticoagulants (NOACs) is surprisingly poor in clinical practice, Xiaoxi Yao, Ph.D., reported at the American Heart Association scientific sessions.

Her retrospective study of nearly 65,000 patients with atrial fibrillation who initiated therapy with apixaban, dabigatran, rivaroxaban, or warfarin showed that during a median 1.1 years of follow-up fewer than half of all patients were treatment adherent, with adherence defined as possession of sufficient medication to cover at least 80% of days.

Adherence rates, while uniformly suboptimal, nevertheless varied considerably: lowest at 38.5% for dabigatran, followed by 40.2% for warfarin, 50.5% for rivaroxaban, and 61.9% for apixaban.

This poor adherence to NOACs in real-world clinical practice is surprising in light of the drugs' greater conve-

See **NOACs** • *page 4*

INSIDE

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Indication

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

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

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

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

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

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

Start preserving more lung function for patients with IPF[4]

- Esbriet had a significant impact on lung function vs placebo in ASCEND[3,4†]
  - —**48% relative reduction in risk of a meaningful decline in lung function at 52 weeks for patients on Esbriet** vs placebo (17% vs 32%; 15% absolute difference; *P*<0.001)
  - —**2.3× as many patients on Esbriet maintained their baseline function at 52 weeks** vs placebo (23% vs 10% of patients; 13% absolute difference; *P*<0.001)
- Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[3,4†]
  - —**Patients on Esbriet maintained an average of 193 mL more lung function at 52 weeks** vs placebo (–235 mL vs –428 mL; *P*<0.001)
- **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**[3,5]
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide[2]

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

ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

*Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.

†The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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

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

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

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

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

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

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

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

References: 1. Raghu G, Rochwerg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*. 2015;192(2):e3-e19. **2.** Data on file. Genentech, Inc. **3.** Esbriet Prescribing Information. InterMune, Inc. October 2014. **4.** 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. **5.** 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.

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Real-world adherence is poor

NOACs *from page 1*

nience, with fewer drug interactions than warfarin and no need for laboratory monitoring, observed Dr. Yao of the Mayo Clinic in Rochester, Minn.

It's possible, although speculative, that the NOACs' greater convenience paradoxically contributes to the low adherence rates, since unlike warfarin, NOACs don't require regular interactions with the health care system for INR monitoring. And then there is the hefty cost of the novel agents, she added.

The study population consisted of 3,900 patients with atrial fibrillation who initiated oral anticoagulation with apixaban (Eliquis), 10,235 who started on dabigatran (Pradaxa), 12,366 on rivaroxaban (Xarelto), and 38,190 on warfarin. The analysis utilized claims data from a large U.S. commercial insurance database.

Adherence rates were better among patients with greater stroke risk as reflected by their CHA2DS2-VASc scores. For example, at the high end of the adherence spectrum, the adherence rate for apixaban was 50%

in patients with a CHA_2DS_2-VASc score of 0-1, rising to 62% with a score of 2-3 and 64% with a score of 4 or more. The corresponding adherence rates for dabigatran were 25% in patients with a CHA_2DS_2-VASc of 0-1, 40% among those with a score of 2-3, and 42% in patients with a score of 4 or higher.

Dr. Yao and her coinvestigators were interested in whether lower adherence to oral anticoagulation was associated with worse outcomes. This proved to be the case with regard to stroke rate for patients with a CHA_2DS_2-VASc score of 2 or more, where a clear dose-response relationship was evident between the event rate and cumulative time off oral anticoagulation during follow-up.

Among patients with a CHA_2DS_2-VASc of 2 or 3, the stroke rate was nearly twice as high among those off oral anticoagulation for a total of 3-6 months and three times greater if off therapy for more than 6 months than in those with a total time off of less than 1 week. The stroke rate was even higher in patients with a CHA_2DS_2-VASc of 4 or more who had suboptimal adherence.

An unexpected finding was that among patients with a CHA_2DS_2-VASc score of 2 or more there was no significant relationship between cumulative time off oral anticoagulation and the risk of major bleeding. Unless they were off treatment for a total of 6 months or more; only then was the major bleeding risk lower than in patients whose total time off therapy was less than a week, she said.

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. Yao: Adherence was better in those with high CHA_2DS_2-VASc scores.

Also, one would expect that when patients are off oral anticoagulation they should be at significantly lower risk of intracranial hemorrhage than when on-therapy, but this proved not to be the case.

For patients at substantial stroke risk as indicated by a CHA_2DS_2-VASc score of at least 2, this finding about off-treatment bleeding risk actually constitutes a good argument for sticking to their medication, in Dr. Yao's view.

"Physicians and patients often fear bleeding, especially intracranial hemorrhage, but we found that for patients at higher risk for stroke there is little difference in intracranial hemorrhage risk whether you're on or off of oral anticoagulation. So higher-risk patients should definitely adhere to their medication because of the stroke prevention benefit. However, in low-risk patients with a CHA_2DS_2-VASc of 0-1, the benefits of oral anticoagulation may not always outweigh the harm," she said.

Dr. Yao reported having no financial conflicts of interest regarding her study.

bjancin@frontlinemedcom.com

Acetazolamide: No decline in ventilation duration

BY MARY ANN MOON
Frontline Medical News

Acetazolamide failed to reduce the duration of invasive mechanical ventilation in chronic obstructive pulmonary disease (COPD) patients who had pure or mixed metabolic alkalosis, according to results from a clinical trial published online Feb. 2 in JAMA.

Acetazolamide is a carbonic anhydrase inhibitor used as a respiratory stimulant in patients who have COPD and metabolic alkalosis. Recent studies suggested that high doses of the drug (1,000 mg/day or more) might shorten the duration of mechanical ventilation in critically ill COPD patients who require invasive mechanical ventilation, by markedly lowering serum bicarbonate and raising minute ventilation, said Dr. Christophe Faisy of the medical intensive care unit, European Georges Pompidou Hospital, Paris, and his associates.

To test this hypothesis, Dr. Faisy and his associates in the DIABOLO trial assessed 380 adults with COPD who were being treated at 15 French ICUs. One patient was receiving ventilation through a tracheotomy tube and the rest through endotracheal intubation.

These study participants were randomly assigned in a double-blind fashion to receive either 500 mg acetazolamide twice daily or 1,000 mg acetazolamide twice daily if they were concomitantly receiving loop diuretics (187 patients), or a matching placebo (193 patients), administered as a slow intravenous injection.

Patients in the active-treatment group achieved larger reductions in serum bicarbonate and had fewer days with metabolic acidosis. Nevertheless, the primary efficacy outcome – the duration of invasive ventilation – did not differ significantly between the two study groups. The median duration of ventilation was 136.5 hours with acetazolamide and 163.0 hours with placebo, which is clinically substantial but did not reach statistical significance, the investigators said (JAMA. 2016 Feb 2. doi: 10.1001/jama.2016.0019).

The active-treatment group achieved larger reductions in serum bicarbonate and had fewer days with metabolic acidosis. Nevertheless, the duration of invasive ventilation did not differ significantly between the two study groups.

Acetazolamide didn't exert a respiratory stimulant effect as measured by changes in respiratory rate, tidal volume, or minute ventilation. And there were no significant differences between the two study groups in secondary outcomes such as time to weaning off ventilation, rate of successful weaning, number of spontaneous breathing trials, use of tracheotomy or noninvasive ventilation after extubation, unplanned extubations, episodes of ventilator-associated pneumonia, laboratory values, length of ICU stay, or in-ICU mortality.

In addition, rates of adjunctive treatment using loop diuretics, glucocorticoids, beta-agonists, or catecholamines were the same between the two study groups, and left ventricular ejection fraction at weaning from ventilation also was the same. The rate of serious adverse events also was comparable.

"Taken together, these findings indicate that the inhibition of the renal carbonic anhydrase enzyme and the resulting serum bicarbonate reduction did not trigger a sufficient respiratory-stimulating effect to affect outcomes of critically ill patients with COPD," Dr. Faisy and his associates wrote.

However, they noted that in both study groups the median duration of invasive mechanical ventilation was shorter than had been anticipated when the trial was designed, which likely decreased the statistical power of the primary endpoint. "It is possible that the study was underpowered to establish statistical significance," the researchers said.

It is also possible that higher doses of acetazolamide may have exerted a greater effect on respiratory parameters. However, higher doses also may have increased the workload of the respiratory muscles and induced respiratory muscle fatigue, they added.

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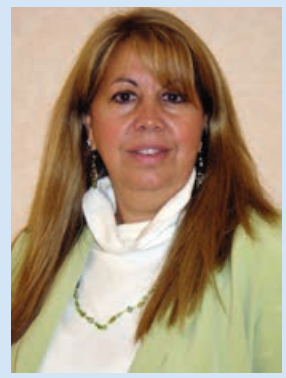

Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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Editorial Offices 5635 Fishers Lane, Suite 6100, Rockville, MD 20852, 240-221-2400, fax 240-221-2548
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Coils improve severe emphysema, but at a cost

BY MARY ANN MOON
Frontline Medical News

Bronchoscopically placed nitinol coils to reduce lung volume markedly improved quality of life and modestly improved walk distance and lung function in a preliminary study of patients with severe emphysema, which was published online in JAMA.

The magnitude and severity of serious and nonserious adverse effects were far less than has been reported for more invasive lung volume reduction surgery in this patient population. However, the short-term financial costs of coil placement were substantial, said Dr. Gaetan Deslee of University of Reims (France) Hospital and his associates.

Nitinol coils are shape-memory devices delivered into subsegmental airways to reduce regional parenchymal volume, which increases expansion of adjacent nontargeted lung. This increases the nontargeted tissue's elastic recoil and reestablishes small-airway tethering, which improves expiratory flow and reduces air trapping.

The procedure was compared with usual care in 100 patients with severe emphysema who were treated and followed for 1 year at 10 university hospitals across France. Both groups underwent pretreatment pulmonary rehabilitation and received inhaled bronchodilators with or without inhaled corticosteroids and with or without supplemental oxygen at the discretion of their treating physicians. Then patients were randomly assigned – 50 to receive the coils and 50 to receive usual care.

The coils were inserted under general anesthesia, and approximately 10 coils were placed per targeted lobe. Most patients later underwent the procedure on the opposite side, so that 47 patients received bilateral and 3 received unilateral coils during 97 bronchoscopies. The mean procedure time was 54 minutes, and the treatment significantly decreased lung hyperinflation.

The primary efficacy endpoint, improvement in 6-minute walk test scores after 6 months, was evaluable for 44 patients in each study group. A total of 18 patients (36%) who underwent coil placement and 9 (18%) who received usual care improved their scores by at least 54 m, which was a significant difference, the investigators said (JAMA. 2016 Jan 12. doi: 10.1001/jama.2015.17821).

In addition, all secondary endpoints were significantly better after coil placement than after usual care at both 6 months and 12 months. This included forced expiratory volume in 1 second, forced vital capacity, residual volume, and residual volume/total lung capacity, scores on the Medical Research Council dyspnea scale, and scores on a measure of health-related quality of life.

A cost-benefit analysis at 1 year showed that the mean increase in expenditures was $47,908 per person in the coil group, compared with the usual-care group. The 1-year incremental cost-effectiveness ratio was $782,598 per quality-adjusted life year (QALY). Assuming that the quality of life gains would be maintained over 3 years and that the costs of follow-up care would be identically low in both study groups, this ratio would decrease to $270,000 per QALY at 3 years.

However, neither of these cost-effectiveness ratios would be considered economical enough to warrant adopting this technology in most countries, Dr. Deslee and his associates noted.

At least one serious adverse event developed in 52% of the coil group and in 38% of the usual-care group, and there were four deaths (8%) in the coil group and three deaths (6%) in the usual-care group. The most frequent adverse event was pneumonia, which resolved with medical care in all cases. "The mechanism involved in pneumonia may result from local airway irritation, subsegmental airway closure, tension-induced inflammation, or local ischemia rather than from an infectious mechanism," the researchers said.

This study was limited in that coil placement was not compared with either a sham or control procedure, patients were not blinded to treatment assignment, the sample size was relatively small, and follow-up was short. Larger studies using more rigorous statistical methods are needed "to draw a definitive conclusion regarding the long-term efficacy of coil treatment," they added.

VIEW ON THE NEWS

Clinically important QOL benefits

The improvement in health-related quality of life scores in this study represents a mean response of approximately three times the established minimal clinically important difference. By comparison, trials of pharmacologic interventions rarely achieve even the minimal clinically important difference.

Despite the high cost-effectiveness ratio of more than $700,000 per QALY – when ratios of $50,000 to $100,000 per QALY are commonly deemed to be the maximal acceptable limit – clinicians shouldn't hesitate to use this treatment if these findings are confirmed in larger trials. Bronchoscopically placed nitinol coils are largely palliative, but the response is meaningful and offers realistic hope to patients who have few other treatment choices.

Dr. Frank C. Sciurba, Dr. Divay Chandra, and Dr. Jessica Bon are all in the division of pulmonary, allergy, and critical care medicine at the University of Pittsburgh. Dr. Sciurba reported receiving grants from PneumRX, maker of the coils used in this study, and PulmonX. Dr. Sciurba, Dr. Chandra, and Dr. Bon made these remarks in an editorial accompanying Dr. Deslee's report (JAMA 2016;315:139-41).

Closed compressions adequate in traumatic cardiac arrest

BY M. ALEXANDER OTTO
Frontline Medical News

SAN ANTONIO – Open-chest cardiac massage offers no benefit over closed-chest compressions in patients with traumatic cardiac arrest, according to a prospective observational study from the University of Maryland Shock Trauma Center in Baltimore.

The investigators compared 16 open-chest cardiac massage (OCCM) patients with 17 closed-chest compression (CCC) patients delivered directly to the level 1 trauma center in cardiac arrest. The open-massage group received closed compressions for a mean of 66 seconds before being converted to open massage for reasons that weren't captured by the data.

End-tidal carbon dioxide ($ETCO_2$) – the standard for determining the effectiveness of chest compressions and return of spontaneous circulation – was used as a surrogate for cardiac output and adequacy of resuscitation. Continuous high-resolution $ETCO_2$ measurements were collected every 6 seconds in both groups.

When periods of OCCM were compared to equivalent periods of CCC, there were no differences in the initial, final, peak, or mean $ETCO_2$ values, and there was no difference in return of spontaneous circulation (OCCM, 23.5% versus CCC, 38.9%; $P = .53$).

"Unless the patient has a thoracic injury that you need to get into the chest to fix, we didn't see any benefit in opening the chest just to massage the heart. The data suggest that maybe we shouldn't be so aggressive in doing open cardiac massage. There's renewed interest in performing endovascular balloon occlusion techniques for the aorta to obtain hemorrhage control; if you do that and you do closed-chest compressions, it's just as effective as opening up the chest and doing cardiac massage," said Dr. Matthew Bradley, a trauma surgeon at the Shock Trauma Center, at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

Most of the patients were men, and there was a higher percentage of penetrating trauma in the OCCM group (81% versus 47%; $P = .04$).

The results were the same, however, in subgroup analyses limited to blunt and penetrating trauma.

All of the open massage patients died, but there were a few survivors in the CCC group.

Dr. Bradley didn't think the closed versus open approach was the reason for the survival difference.

Resuscitative endovascular balloon occlusion of the aorta patients were excluded from the trial to prevent confounding.

The investigators have no relevant disclosures.

aotto@frontlinemedcom.com

SELECTED IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

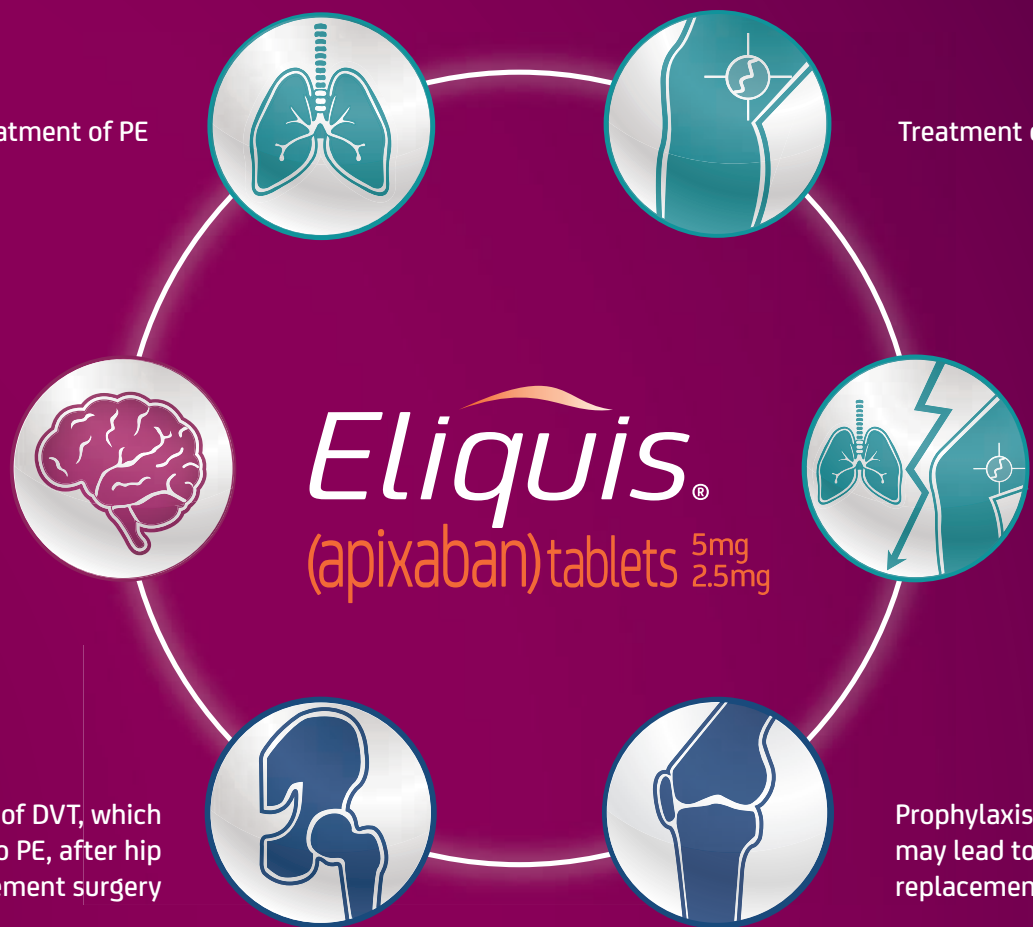
DRUG INTERACTIONS

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

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

Bristol-Myers Squibb Pfizer

Approved for 6 indications



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

hcp.eliquis.com

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

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

DRUG INTERACTIONS (CONT'D)

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

PREGNANCY CATEGORY B

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

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

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

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

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see Warnings and Precautions]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

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

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

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

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

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

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

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

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

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

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PULMONARY PERSPECTIVES: Why don't we advocate for ambulation?

BY DR. SANDEEP J. KHANDHAR, FACS

Thoracic surgeons are procedurally focused

Thoracic surgery has seen significant changes over the past decade with an ever-increasing procedural focus. As a minimally invasive thoracic surgeon, I have been part of this transformation. Minimally invasive approaches can often replace thoracotomy incisions—considerably reducing morbidity, shortening recovery, and returning patients back to productive lives faster (Villamizar et al. *J Thoracic Cardiovasr Surg.* 2009;138:419.

Thoracic surgery evolved this way for the primary purpose of improving care for our patients. As a surgical community, we have spent endless hours toiling to create smaller and fewer incisions, design and modify instruments, improve visualization, find unique ways to seal tissue, shorten procedural time, and make operations more cost effective. While we have made significant strides in the operative arena, the perioperative care of these patients remains much the same. Perhaps, the classical surgical focus on technique has caused us to miss the big picture.

Do what makes sense

Applying basic physiologic principles and common sense, our team believed that early postoperative ambulation would improve outcomes and was an essential part of optimal postoperative recovery (Leithauser. *J International Coll Surg.* 1949;12[3]:368). Anticipated benefits of early postoperative ambulation include:

1. Decrease narcotic necessity - Upright positioning places less mechanical strain on the intercostal space, thereby relaxing the intercostal muscles that have been cut during surgery (minimally invasive or open). Less pain results in less narcotic use. Limitation of narcotics allows for the avoidance of related complications.

a. Narcotics decrease respiratory drive that is inherently detrimental after operating on the lungs, as it promotes pooling of secretions, increases atelectasis, and poses an aspiration risk.

b. Narcotics diminish wakefulness, thereby limiting ambulation, promoting suboptimal patient position, increasing pain, and thereby creating the need for more narcotics.

c. Narcotics often result in constipation, significantly affecting time to full recovery and optimal patient satisfaction.

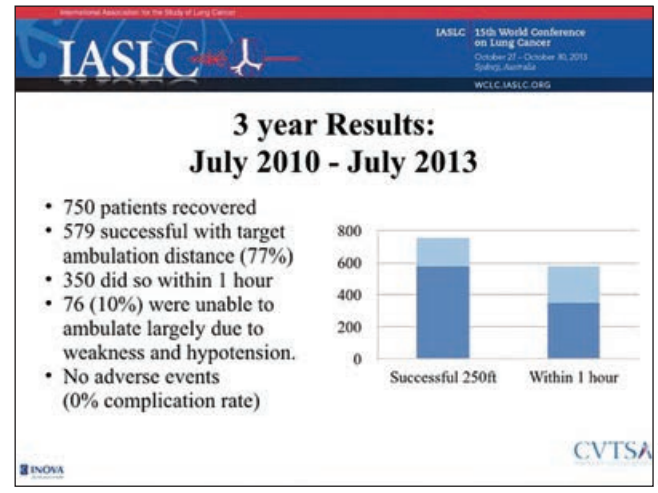
2. Decrease pneumonia risk - Ambulation facilitates mobilization of secretions and improved pulmonary toilet. This prevents pooling of secretions and superimposed bacterial proliferation.

3. Decrease deep venous thrombosis (DVT) and, therefore, pulmonary embolism (PE) risk - In thoracic surgery, while there is minimal local trauma, mobility directly combats venous stasis and malignancy becomes the only remaining risk factor from Virchow's triad (stasis, trauma, hypercoaguable state, such as malignancy). We have observed that early postoperative ambulation is so successful that we do not routinely use any chemical DVT prophylaxis in our patients, before or after surgery.

4. Decrease atrial arrhythmias - Ambulation allows for optimal distribution of fluids, therefore, limiting peripheral edema, subsequent redistribution, atrial stretch, and the concomitant risk of atrial arrhythmias.

5. Decrease in postoperative hypotension - There is a peripheral vasodilatory effect from general anesthesia that may cause relative hypotension postoperatively. Fluid administration to combat this is detrimental in a patient who has undergone lung resection. Early ambulation improves peripheral vasomotor tone, increases venous return, and improves blood pressure, reducing the need for exogenous fluid administration.

6. Overall improved sense of well being - Patients tend to feel better walking and have a greater sense of confidence that they are recovering.



DR. KHANDHAR

Building a pathway

When we began our multidisciplinary thoracic oncology program, we were given a mandate from administration to create metrics by which we could track our progress. Publicly reported cardiac surgery metrics, such as delivery of aspirin and beta-blockers or tracking readmission rates for CHF existed, but none existed in thoracic surgery. This represented an opportunity to create goals and then demonstrate success. We arbitrarily decided that our goal was to walk every patient 100 meters (distance from our postanesthesia care unit to the doors of the ICU and back) within 1 hour of extubation.

Overcoming obstacles

Much as is chronicled in Lillehai's paper (*J Heart Valve Dis.* 1995; 4(suppl II):S106), we were at the first stage in the Evolution of an Idea - people said "it won't work." Therefore, our initial challenges surrounding this initiative revolved around safety and feasibility. Our nurses felt unsafe walking patients so soon after surgery because it was not what they were used to doing. Education, a small focused unit, and appropriate staffing were the keys to overcoming these initial challenges. Nurses saw the benefits immediately, and the commitment propagated to the point of competition to see who could ambulate their patient farther and faster.

Results that speak for themselves

We retrospectively reviewed our 3-year experience in 2013 and we presented that data at the World Conference on Lung Cancer, held in Sydney, Australia. Our goal was to demonstrate the safety and feasibility of the approach, and we had done so in 750 patients. The response to our findings was a mixture of incredulousness and cautious optimism. We pressed on.

Validation and retrospection

Our culture has changed. Postoperative ambulation has been effectively inculcated into our postanesthesia care unit and our inpatient unit. The expectations have been set, and they are well established. At this point, a prospective, randomized study seems unethical given the logical progression from physiologic principles and mechanistic understanding. In order to limit variability, we retrospectively analyzed 208 consecutive patients undergoing thoracoscopic lobectomy from 2010 to 2014 and compared them to the most recently available 3-year data within the Society of Thoracic Surgeons (STS) database. There were no significant differences in the baseline patient characteristics, although it should be noted that the STS database included both open and thoracoscopic interventions, as the database is not yet further stratified. In spite of this limitation, the differences in lengths of stay, atrial arrhythmias, and pneumonia rates still seem remarkable.

Conclusions

Early postoperative ambulation should be considered in any thoracic surgical setting. The benefits to the patient and the program are far reaching and result in better outcomes, higher patient satisfaction, and more nursing integration and foster a collaborative relationship between medical personnel and administration (Schatz. *AORN Journal.* 2015;102:482).

Characteristic	Observed N (%) (N = 208)	STS Average N (%) (N = 27,542)	P
Length of stay in days, median (IQR*)	1.0 (1.0-1.0)	5.0 (3.0-7.0)	
Atrial arrhythmia requiring treatment	9 (4.3)	3,002 (10.9)	.002
Pneumonia	1 (0.5)	1,157 (4.2)	.008
Pulmonary embolism	1 (0.5)	138 (0.5)	.967
DVT requiring treatment	3 (1.4)	165 (0.6)	.118
Prolonged air leak >5 days	19 (9.1)	2,947 (10.7)	.467
30-day mortality	0 (0.0)	386 (1.4)	.086

*Interquartile range

Note: Ns for STS average based on the total N and reported proportion.

Source: Dr. Khandar

FRONTLINE MEDICAL NEWS

Dr. Khandhar is Medical Director and Chief, Thoracic Surgery, Inova Fairfax Hospital; Director, Thoracic Oncology Program, Inova Health System; and Clinical Assistant Professor, Virginia Commonwealth University and Inova Fairfax Residency Program, Falls Church, Virginia.

Specialized centers benefit severe asthma patients

BY MARY ANN MOON
Frontline Medical News

FROM CHEST

After attending specialized centers for severe, refractory asthma, British patients had improved asthma control, decreased use of emergency health care services, reduced medication usage, and improved quality-of-life measures, according to a report in Chest.

These specialized centers perform multiple assessments to determine the cause of persistent symptoms and develop a targeted treatment approach for each patient. Alternative diagnoses are ruled out, and comorbid conditions such as allergies are identified and treated, said Dr. David Gibeon of Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, both in London, and his associates.

Of 346 patients who were referred to these centers and followed for a median of 286 days, more than half had a contributing disorder requiring treatment, such as gastroesophageal reflux (55%) or allergies (71%).

Significantly fewer patients required an unscheduled emergency dept. or primary care visit after attending the specialized centers (66%) than they had in the preceding year (88%). Also, the average number of such visits decreased from four to one, and hospitalization declined from 48% to 38% (Chest. 2015;148[4]:870).

Serum total IgE levels dropped, forced expiratory volume in 1 second measures improved, and the number of courses and doses of oral corticosteroids declined. In addition, scores on two measures of asthma-related quality of life significantly improved.

It is possible that patients' multiple contacts with health care professionals may have exerted a placebo-type effect. Future research should examine how different components of such programs – including the treatment of comorbidities, weight loss, clinical psychological support, and asthma education – contribute to improved outcomes, the researchers wrote.

The study received no funding. Dr. Gibeon had no relevant financial disclosures.

VIEW ON THE NEWS

Better outcomes

What we can take from this first prospective study of Difficult Asthma Services is that, overall, the "dedicated severe asthma package" provided at a specialty center leads to significant benefits in hard outcome measures such as the use of health care services and improved quality-of-life measures. As the authors acknowledged, some of these benefits may result from improved treatment adherence, self-management, education, or the effect of seeing many health care professionals regularly in a clinic.

Dr. Matthew Masoli is with Plymouth (England) Hospitals NHS Trust. He made these remarks in an editorial (Chest. 2015;148[4]:843-4) accompanying Dr. Gibeon's report.

No boost to survival

TB meningitis *from page 1*

brain," the investigators noted.

The concentration of rifampin in cerebrospinal fluid reaches only 30% of that in the plasma, so it has been proposed that higher-dose rifampin (15 mg/kg) might be more effective for tuberculous meningitis. Fluoroquinolones such as levofloxacin were proposed because they are active against tuberculosis and achieve good penetration of the blood-brain barrier.

Dr. Heemskerk and her associates tested this hypothesis at two tertiary referral centers for severe cases of tuberculosis or infectious diseases in Vietnam.

All the study participants received standard daily isoniazid (5 mg/kg), rifampin (10 mg/kg), pyrazinamide (25 mg/kg), and ethambutol (20 mg/kg) for 3 months, followed by the same doses of rifampin and isoniazid for an additional 6 months.

Approximately half (408 patients in the intensive-therapy group) received additional rifampin (5 mg/kg) and levofloxacin (20 mg/kg), while the other half (409 patients in the control group) received matching placebos.

The median patient age was 35 years. Approximately 43% of patients were coinfected with HIV.

The primary outcome measure – death at 9-month follow-up – occurred in 113 of the intensive-therapy group and 114 of the control group, a nonsignificant difference (HR, 0.94).

The intensified treatment was no better than was standard treatment in any subgroup of patients or in any secondary outcomes, including neurologic disability and time to a new neurologic event or death, the investigators said (N Engl J Med. 2016 Jan 14. doi:10.1056/NEJMoa1507062).

However, intensive therapy was associated with a higher frequency of seizures (23 vs. 11 patients), visual impairment (14 vs. 4 patients), allergic reactions (30 patients vs. 17 patients), jaundice (19 vs. 7 patients), grade 3 or 4 hyponatremia (112 patients vs. 81 patients), and adverse events leading to treatment interruptions (95 patients vs. 64 patients).

It is possible that raising the dose of rifampin by only 5 mg/kg may not have increased intracerebral drug concentrations "sufficiently to enhance bacterial killing. Recent data suggest that much higher doses (up to 35 mg/kg per day) may have an acceptable side-effect profile and may be necessary to significantly increase the killing of *M. tuberculosis* in pulmonary tuberculosis," Dr. Heemskerk and her associates noted.

"Although the results of our study do not support a change in the currently recommended treatment regimens for tuberculous meningitis, enhanced antituberculosis treatment with higher doses of first-line drugs, including intravenous rifampin, or the newer antituberculosis drugs bedaquiline and delamanid, still require investigation," they added.

Wellcome Trust and the Li Ka Shing Foundation supported the study. Dr. Heemskerk and her associates reported having no relevant financial disclosures.

White House launches MDR-TB action plan

BY ALICIA GALLEGOS
Frontline Medical News

The Obama administration has announced a new action plan to combat the rise of multidrug-resistant tuberculosis (MDR-TB).

The plan outlines three primary goals to accomplish between 2016 and 2020: strengthening domestic capacity to treat the disease, improving international ability and collaboration, and accelerating research and treatment of MDR-TB.

To strengthen state and local capacity to prevent transmission of TB, the action plan proposes improving surge capacity for rapid response to individual patients, patient clusters, and larger outbreaks of drug-resistant TB, as well as advancing the treatment of latent TB infection and disease among vulnerable populations.

The three goals are worthy, but all of this is going to cost money. Where are the dollars that go with that?

DR. OUELLETTE

Surveillance will be upgraded to "gather, store, analyze, and report electronic data on drug-resistant TB," according to the action plan, The Centers for Disease Control and Prevention will increase its capacity to use "whole-genome sequencing to elucidate paths of transmission, identify recent transmission, and identify emerging patterns of resistance."

Taken with other preventive activities, the measures are estimated to reduce by 15% newly-diagnosed MDR-TB cases by 2020, as specified in the National Action Plan for Combating Antibiotic-Resistant Bacteria.

Additionally, the U.S. government will work with partners including the World Health Organization and the Stop TB Partnership to support countries in developing new approaches to MDR-TB. The focus is expected to initiate treatment for an additional 200,000 people with MDR-TB during 2015-2019; an estimated 360,000 people are currently treated under the U.S. government's Global TB Strategy. The plan also aims to improve access to patient-centered diagnostic and treatment services in countries with limited health care resources.

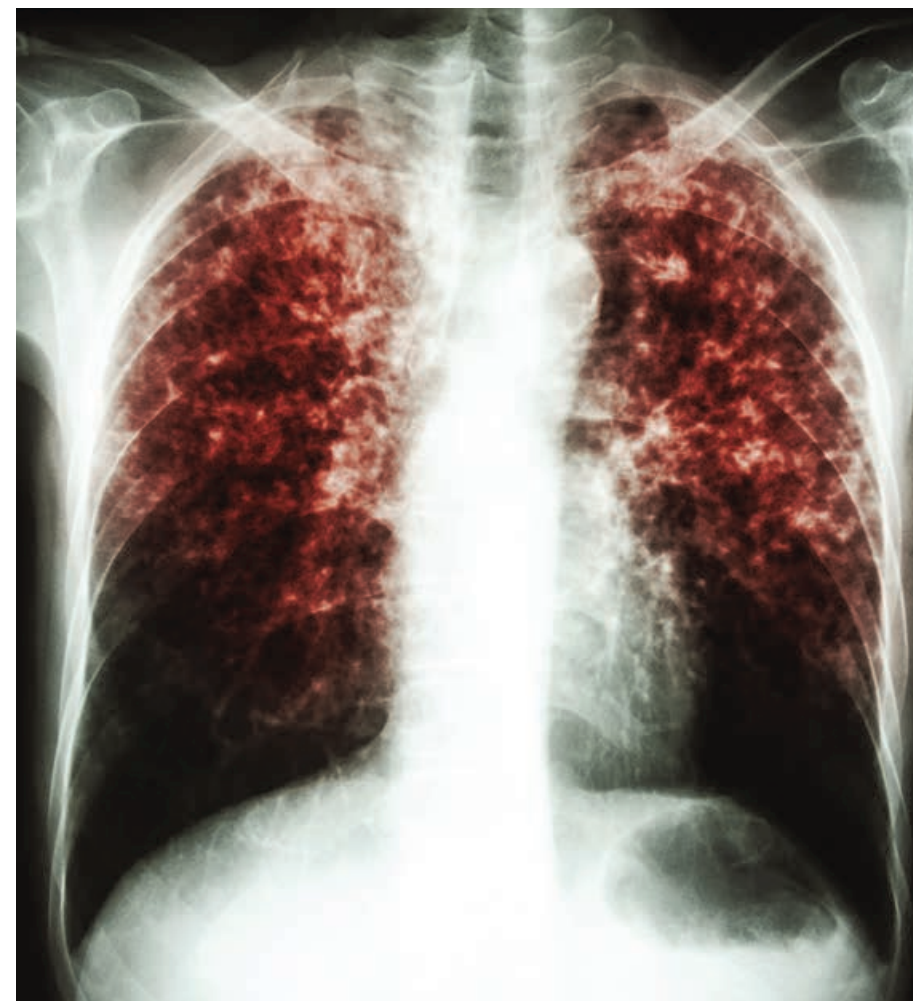
Developing a TB vaccine is a key initiative. The plan details that the National Institutes of Health and the CDC will focus on expanding the dialogue to identify strategies for vaccine development and preventive drugs. The plan also urges research into the discovery of biological markers that indicate early response to therapy or protection against TB.

Pulmonologist Daniel R. Ouellette of Henry Ford Hospital in Detroit, said in an interview that "the three goals are certainly worthy," but the plan does not address the budgetary measures to be taken to increase domestic capacity to combat TB nor does it explain where resources will be found to encourage the development of new medications.

"How much money are we willing to spend in addition to what we spend now in treating general TB? How are we going to incentivize industry to develop new drugs? It all sounds really good, but all of this is going to cost money. Where are the dollars that go with that?" said Dr. Ouellette, who chairs the Guideline Oversight Committee for CHEST.

The action plan states that all activities are subject to budget constraints and approvals, including the "weighing of priorities and available resources by the administration in formulating its annual budget and by Congress in legislating appropriations."

Annually, TB causes more than 1.5 million deaths worldwide, according to White House data. Nearly one-third of the world's population is thought to be infected with *Mycobacterium tuberculosis*; each year, 9.5 million develop active TB and about 480,000 people develop MDR-TB. Fewer than 20% with MDR-TB receive appropriate therapy, and less than half are effectively treated.



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Six-drug therapy boosts multidrug-resistant TB response

BY MARY ANN MOON
Frontline Medical News

Using more than five agents to treat multidrug-resistant tuberculosis markedly increases the cure rate by as much as 65%, according to a report published online Dec. 29 in PLOS Medicine.

At present, the World Health Organization recommends a regimen of pyrazinamide plus at least four second-line drugs that are likely to be effective, based on the patient's previous exposure, background resistance levels in the community, and any drug susceptibility testing results from known cases in contact with the patient. But recent evidence suggested that including even more drugs in the regimen might improve clinical outcomes, said Courtney M. Yuen, Ph.D., of the Centers for Disease Control and Prevention, and her associates.

The researchers performed a secondary analysis of data for 1,137 participants in the Preserving Effective Tuberculosis Treatment Study (PETTS), an international prospective cohort study of patients with multidrug-resistant pulmonary TB. These patients were followed for a median of 20 months, undergoing sputum cultures for TB every month. The researchers used time to sputum culture conversion as the indicator of treatment effectiveness.

Receiving at least six potentially effective drugs per day raised the likelihood of sputum culture conversion by 36%, compared with using the recommended five drugs. In addition, for patients receiving at least one untested drug – any antituberculosis agent given empirically, without susceptibility testing – in their five-drug regimen, adding an extra potentially effective drug raised the likelihood of sputum culture conversion by 65%. Even adding an extra untested drug to a five-drug regimen improved the likelihood of sputum culture conversion by 33%, Dr. Yuen and her associates said (PLOS Med. 2015 Dec 29. doi:10.1371/pmed.1001932).

"We observed a benefit to receiving a greater number of potentially effective drugs ... as well as an interaction in which the presence of more effective drugs enhanced the benefit of untested drugs. Both of these results add to existing evidence that increasing the number of drugs in multidrug-resistant TB regimens is advantageous," they noted.

The WHO initially recommended a regimen of four drugs for these patients in 2006, then raised that number to five in 2011.

"Our results suggest that treatment might be further fortified by adding additional potentially effective drugs," the investigators said.

MYTH OF THE MONTH: Beta-blockers, COPD, and depression

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

A 59-year-old man is admitted to the ICU with a myocardial infarction. He is discharged after 5 days on enalapril, metoprolol, simvastatin, and aspirin. At a 3-month follow-up, he is noted to have marked anhedonia, complaints of insomnia, feelings of worthlessness, and psychomotor retardation.

What would you do?
A) Stop the enalapril.
B) Stop the metoprolol.
C) Stop the simvastatin.
D) Begin a tricyclic antidepressant.
E) Begin an SSRI.


DR. PAAUW

When I was in medical school, the dogma was to never give beta-blockers to patients with systolic heart failure, because it would worsen the heart failure.[1] As we all know, this dogma completely reversed, and beta blockers are a cornerstone of treatment of patients with systolic heart failure, with improvements in morbidity and mortality.[2] Underuse of beta-blockers for indicated conditions is likely due to fear of beta-blocker side effects.[2]

There has long been concern that beta-blockers can cause, or worsen, depression. Reports of possible beta-blocker–induced depression surfaced soon after propranolol became available in the 1960s. A frequently cited reference is a letter to the British Medical Journal in which H.J. Waal reported that 20 of 89 patients on propranolol volunteered or exhibited depressive symptoms.[3] Almost half had grade I depression – symptoms of irritability, insomnia, nightmares, and fatigue. No control group was evaluated to ascertain the prevalence of those symptoms in patients treated with other antihypertensives, or in nonhypertensive patients.

M. H. Pollack and colleagues reported on three patients who developed symptoms of depression after starting propranolol, and the researchers concluded that depression following the administration of propranolol was a real phenomenon.[4]

Many subsequent studies have cast doubt on the association of beta-blockers and depression, which is common following myocardial infarction and in patients with coronary artery disease.

Dr. Steven J. Schleifer and colleagues evaluated 190 MI patients for depression. The patients were interviewed 8-10 days after the infarct and again at 3 months. No antianginal or antihypertensive medications, including beta-blockers, were associated with an increase in depression.[5]

Dr. Joost P. van Melle and colleagues participated in a multicenter study that looked at patients following an MI, assessing for depressive symptoms at baseline and at 3, 6, 9, and 12 months using the Beck depression inventory.[6] A total of 254 patients receiving beta-blockers were matched with 127 control patients post MI not receiving beta-blockers. No significant differences were found in depressive symptoms.

Continued on following page

Continued from previous page

Robert Carney, Ph.D., and colleagues evaluated 75 patients undergoing elective cardiac catheterization with psychiatric interview and psychological assessments.[7] Half were receiving beta-blockers. Thirty-three percent of the patients who were not receiving beta-blockers, and 21% of the beta-blocker–treated patients met DSM-III criteria for depression.

Dr. Linda Battes and colleagues reported that beta-blocker use actually decreased the risk of depression in patients who had undergone a percutaneous intervention, with a risk reduction of 49% for depression in beta-blocker–treated patients.[8]

Dr. Hendrika Luijendijk and colleagues followed 5,104 elderly persons for episodes of incident depression. Beta-blocker use did not increase the risk of depression.[9]

Beta-blockers often have been avoided in patients with asthma and chronic obstructive pulmonary disease because of concern for worsening disease. There is strong evidence now that beta-blocker use is not problematic in patients with COPD.

Dr. Surya Bhatt and colleagues found beta-blocker use decreased COPD exacerbations in a study of almost 3,500 patients.[10] During 2 years of follow-up, beta-blocker use was associated with a lower rate of total exacerbations (incidence risk ratio, 0.73; 95% confidence interval, 0.60-0.90; $P = .003$) and severe exacerbations (IRR, 0.67, 95% CI, 0.48-0.93; $P = .016$).

Dr. Qingxia Du and colleagues found that beta-blocker use in patients with COPD reduced exacerbations and reduced mortality.[11] In another study, the use of beta-blockers reduced mortality in patients hospitalized for acute exacerbations of COPD.[12] Most of the patients receiving beta-blockers in that study had severe cardiovascular disease.

There are far fewer data on beta-blocker use in patients with asthma. In general, beta-blockers are routinely avoided in patients with asthma. In one small study of asthmatic patients receiving propranolol, there was no effect on methacholine challenge response, histamine responsiveness, or asthma control questionnaire results.[13] In a murine model of asthma, long-term administration of beta-blockers resulted in a decrease in airway hyperresponsiveness, suggesting an anti-inflammatory effect.[14] This topic is an area of interest for further study in asthma control.

Much of what we thought we knew about beta-blockers has turned out to not be so. We keep our eyes open and welcome further enlightenment.

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Dr. Paauw is professor of medicine in the department of general internal medicine at the University of Washington, Seattle, and he serves as third-year medical student clerkship director at the University of Washington.

New CHEST guidelines update VTE management

BY MICHELE G. SULLIVAN
Frontline Medical News

FROM CHEST

Updated guidelines regarding the treatment of patients with venous thromboembolism advise abandoning the routine use of compression stockings for prevention of postthrombotic syndrome in patients who have had an acute deep vein thrombosis, according to Dr. Clive Kearon, lead author of the American College of Chest Physicians' 10th edition of "Antithrombotic Therapy for VTE Disease" (Chest. 2015. doi: 10.1016/j.chest.2015.11.026).

The guidelines include 12 recommendations. Two other key changes from the previous guidelines include new recommendations about which patients with isolated subsegmental pulmonary embolism (PE) should, and should not, receive anticoagulant therapy, and a recommendation for the use of non–vitamin K antagonist oral anticoagulants (NOACs) instead of warfarin for initial and long-term treatment of VTE in patients without cancer.

It is another of the group's "living guidelines," intended to be flexible, easy-to-update recommendations … based on the best available evidence, and to identify gaps in our knowledge and areas for future research," Dr. Kearon of McMaster University, Hamilton, Ont., said in an interview.

"Clinicians and guideline developers would like clinician decisions to be supported by very strong, or almost irrefutable, evidence," he said. "It's difficult to do studies that provide irrefutable evidence, however," and most of the updated recommendations are not based on the highest level of study evidence – large, randomized controlled trials.

Nevertheless, "the quality of evidence that supports guidelines and clinical decision making is much better now than it was 20 or 30 years ago," Dr. Kearon said, mainly because more recent studies are considerably larger and involve multiple clinical centers. Plus, "we're continually improving our skills at doing high-quality studies and studies that have a low potential for bias."

The old recommendation to use graduated compression stockings for 2 years after DVT to reduce the risk of postthrombotic syndrome was mainly based on findings of two small single-center randomized trials, published in the Lancet and Annals of Internal Medicine, in which patients and study personnel were not blinded to stocking use. Since then, a much larger multicenter, placebo-controlled trial found that routine use of graduated compression stockings did not reduce postthrombotic syndrome or have other important benefits in 410 patients with a first proximal DVT randomized to receive either active or placebo compression stockings.

The incidence of postthrombotic syndrome was 14% in the active group and 13% in the placebo group – a nonsignificant difference. The same study also found that routine use of graduated compression stockings did not reduce leg pain during the 3 months after a DVT – although the stockings were still able to reduce acute symptoms of DVT, and chronic symptoms in patients with postthrombotic syndrome.

The recommendation to replace warfarin with NOACs is based on new data suggesting that the agents are associated with a lower risk of bleeding, and on observations that NOACs are much easier for patients and clinicians to use. Several of the studies upon which earlier guidelines were based have been reanalyzed, Dr. Kearon and his coauthors wrote. There are also now extensive data on the comparative safety of NOACs and warfarin.

"Based on less bleeding with NOACs and greater convenience for patients and health care providers, we now suggest that a NOAC is used in preference to VKA [vitamin K antagonist] for the initial and long-term treatment of VTE in patients without cancer," they wrote.

The recommendation to employ watchful waiting over anticoagulation in some patients with subsegmental pulmonary embolism is based on a compendium of clinical evidence rather than on large studies. A true subsegmental PE is unlikely to need anticoagulation, because it will have arisen from a small clot and thus carry a small risk of progression or recurrence.

"There is, however, high-quality evidence for the efficacy and safety of anticoagulant therapy in patients with larger PE, and this is expected to apply similarly to patients with subsegmental PE," the authors wrote. "Whether the risk of progressive or recurrent VTE is high enough to justify anticoagulation in patients with subsegmental PE is uncertain."

If clinical assessment suggests that anticoagulation isn't appropriate, these patients should have a confirmatory bilateral ultrasound to rule out proximal DVTs, especially in high-risk locations. If a DVT is detected, clinicians may choose to conduct subsequent ultrasounds to identify and treat any evolving proximal clots.

The guideline has been endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the International Society for Thrombosis and Haemostasis, and the American Society of Health-System Pharmacists.

Dr. Kearon has been compensated for speaking engagements sponsored by Boehringer Ingelheim and Bayer Healthcare related to VTE therapy.

msullivan@frontlinemedcom.com

Andexanet reverses effects of factor Xa inhibitors

BY BIANCA NOGRADY
Frontline Medical News

Andexanet alfa has been found to reverse the anticoagulant effects of factor Xa inhibitors rivaroxaban and apixaban, according to a study presented at the American Heart Association scientific sessions and published simultaneously in the Nov. 11 issue of the New England Journal of Medicine.

In a two-part randomized, placebo-controlled study involving 145 healthy individuals with a mean age of 58 years, patients treated first with apixaban and then given a bolus of andexanet had a 94% reduction in anti-factor Xa activity, compared with a 21% reduction with placebo.

Thrombin generation was restored in 100% of patients within 2-5 minutes.

In the patients treated with rivaroxaban, treatment with andexanet reduced anti-factor Xa activity by 92%, compared with 18% with placebo. Thrombin generation was restored in 96% of participants in the andexanet group, compared with 7% in the placebo group.

Adverse events associated with andexanet were minor, including constipation, feeling hot, or a strange taste in the mouth, and the effects of the andexanet also were sustained over the course of a 2-hour infusion in addition to the bolus (N Engl J Med. 2015 Nov 11. doi: 10.1056/NEJMoa1510991).

"The rapid onset and offset of action of andexanet and the ability to administer it as a bolus or as a bolus plus an infusion may provide flexibility with regard to the restoration of hemostasis when urgent factor Xa inhibitor reversal is required," Dr. Deborah M. Siegal of McMaster University, Hamilton, Ont., and coauthors wrote.

The study was supported by Portola Pharmaceuticals, Bayer, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer.

Several authors are employees of Portola, one with stock options and related patent. Other authors declared grants and personal fees from the pharmaceutical industry, including the study supporters.

VIEW ON THE NEWS

Addresses need for antidotes

Factor Xa inhibitors represent an important advance in anticoagulation therapy, but concern over the lack of antidotes has tempered enthusiasm for their use among patients and physicians. Warfarin is perceived as being safer as a result of the availability of effective reversal strategies.

Although additional studies will be needed to optimize the use of andexanet and to determine its true efficacy and safety, it represents a giant step forward in our ability to control anticoagulation therapy.

Dr. Jean M. Connors is with the hematology division at Brigham and Women's Hospital and Harvard Medical School, both in Boston. These comments are taken from an accompanying editorial (N Engl J Med. 2015 Nov 11. doi: 10.1056/NEJMe1513258). Dr. Connors declared personal fees from Boehringer Ingelheim and Bristol-Myers Squibb outside the submitted work.

Abandon aspirin for stroke prevention in atrial fib

BY BRUCE JANCIN
Frontline Medical News

SNOWMASS, COLO. – It's time to eliminate prescribing aspirin for stroke prevention in patients with atrial fibrillation and a CHA_2DS_2-VASc score of 1, two eminent cardiologists agreed at the Annual Cardiovascular Conference at Snowmass.

"The European guidelines have done away with aspirin for stroke prevention in atrial fibrillation. It barely made it into our current U.S. guidelines. I don't think aspirin should be in there and I don't think it will be there in the next guidelines.

Bruce Jancin/Frontline Medical News

Dr. Gersh: Except in drug-eluting stent patients, there's no role for aspirin.

Dr. Estes: I'm discussing a NOAC with patients with a CHA_2DS_2-VASc of 1.

The role of aspirin will fall away," predicted Dr. Bernard J. Gersh, professor of medicine at the Mayo Clinic in Rochester, Minn.

"It's not that aspirin is less effective than the oral anticoagulants, it's that there's no role for it. There are no good data to support aspirin in the prevention of stroke in atrial fibrillation," he declared.

Dr. N.A. Mark Estes III agreed the aspirin evidence is seriously flawed.

"The use of aspirin has probably been misguided, based upon a single trial that showed a profound effect and was probably just an anomaly," according to Dr. Estes, a past president of the Heart Rhythm Society snf professor of medicine and director of the New England Cardiac Arrhythmia Center at Tufts University, Boston.

The sole positive clinical trial of aspirin versus placebo, the 25-year-old Stroke Prevention in Atrial Fibrillation (SPAF) study (Circulation. 1991; 84[2]:527), found a high stroke protection benefit for aspirin, a result made implausible by multiple other randomized trials showing no benefit.

"In our current guidelines for atrial fibrillation (*Circulation*. 2014; 130[23]:2071), aspirin can be considered as a Class IIb level of evidence C recommendation in patients with

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a CHA_2DS_2-VASc of 1. But I would just take it off of your clinical armamentarium because the best available data indicates that it doesn't prevent strokes. I'm certainly not using it in my patients. Increasingly in my patients with a CHA_2DS_2-VASc of 1, I'm discussing the risks and benefits of a NOAC [novel oral anticoagulant]," Dr. Estes said.

Dr. Gersh was also critical of another common practice in stroke prevention in atrial fibrillation: concomitant use of aspirin with an oral anticoagulant. "We use too much aspirin in patients on oral anticoagulation. Aspirin is perhaps the major cause of bleeding in patients on an oral anticoagulant. Other than in people with a drug-eluting stent, there's no role at all for aspirin in stroke prevention."

He was coauthor of an analysis of 7,347 participants in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) who were on an oral anticoagulant. Fully 35% of them were also on aspirin. In a multivariate analysis, concomitant aspirin and oral anticoagulation was independently associated with a 53% increased risk of major bleeding and a 52% increase in hospitalization for bleeding, com-

pared with atrial fibrillation patients on an oral anticoagulant alone (Circulation. 2013 Aug 13;128[7]:721-8).

Moreover, the widespread use of dual therapy in this real-world registry didn't appear to be rational. Of those on aspirin plus an oral anticoagulant, 39% had no history of atherosclerosis, the presence of which would be an indication for considering aspirin. And 17% of dual therapy patients had an elevated Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) risk score of 5 or more, making dual therapy risky.

This clinically important interaction between aspirin and oral anticoagulation was recently underscored in an analysis of rivaroxaban-treated patients in the ROCKET AF trial, Dr. Gersh observed. Long-term use of aspirin at entry into this pivotal randomized trial of rivaroxaban (Xarelto) versus warfarin in patients with atrial fibrillation proved to be an independent predictor of a 47% increase in the risk of gastrointestinal bleeding, compared with patients on rivaroxaban alone (J Am Coll Cardiol. 2015 Dec 1;66[21]:2271-81).

Dr. Gersh reported serving on the ORBIT-AF Registry, sponsored by Janssen Pharmaceuticals. Dr. Estes had no relevant financial conflicts.

bjancin@frontlinemedcom.com

Pulmonary HT doubles in-hospital deaths in HFpEF

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – The number of Americans hospitalized for acute decompensated heart failure (ADHF) with preserved ejection fraction during 2003-2012 nearly equaled the number hospitalized with ADHF with reduced ejection fraction, in an analysis of more than 5 million hospitalized heart failure patients tracked in a national-sample database.

But the profile of patients hospitalized with ADHF with preserved ejection fraction (HFpEF) differed from patients hospitalized with acute heart failure and reduced ejection fraction (HFrEF), with a substantially higher percentage of women and patients aged 75 years or older, Dr. Parag Goyal said at the American Heart Association scientific sessions.

The analysis also showed the

strongest correlate for in-hospital mortality among HFpEF patients hospitalized with acute decompensation was a pulmonary circulation disorder, such as pulmonary hypertension, which nearly doubled the rate of in-hospital death among HFpEF patients. Other strong correlates of mortality during hospitalization were liver disease, which was linked with about a 50% boost in hospitalized mortality; and chronic renal failure, which was tied to a roughly one-third higher mortality, said Dr. Goyal, a cardiologist at New York–Presbyterian Hospital.

The reduced in-hospital mortality during the study was largely driven by mortality reductions among HFpEF patients aged 65 years or older.

His study used data collected by the Nationwide Inpatient Sample, which included data on more than 388 million hospitalized U.S. patients during 2003-2012, including 5,046,879 hospitalized with acute heart failure. This total included 2,329,391 patients (46%) diagnosed with HFpEF and 2,717,488 patients

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(54%) diagnosed with HFrEF.

The HFpEF patients' average age was 76 years, with 60% at least 75 years old, while the HFrEF patients' average age was 72 years, with 49% age 75 years or older.

Nearly two-thirds of the HFpEF patients were women, compared with 42% in the HFrEF group.

The HFrEF patients also had a substantially higher prevalence of coronary artery disease, 59%, compared with 41% in the HFpEF group.

The prevalence of several comorbidities – including diabetes, hypertension, and chronic renal failure – were each roughly similar in both subgroups, but the obesity rate of 19% in the HFpEF patients substantially exceeded the 12% rate in HFrEF patients.

In-hospital mortality ran 4.3% in the HFpEF patients and 5.1% in the HFrEF patients, a 13% relative-risk reduction that was statistically significant. But average length of stay was similar between the two groups, about 7 days with either type of heart failure.

Dr. Goyal and his associates also examined time trends during 2003-2012. During this period, the percentage of patients with HFpEF aged 75 years or older rose from 57% to 60%. Even more notably, the percentage of men with HFpEF rose from 31% in 2003 to 37% in 2012. Furthermore, the reduced in-hospital mortality during the period was largely driven by mortality reductions among HFpEF patients aged 65 years or older.

A multivariate analysis for significant correlates of in-hospital mortality identified age 75 years or older, male sex, and white race in both the HFpEF subgroup and in those with HFrEF. Older age had the highest impact, linked with about a 60% relatively higher mortality rate in patients with either type of heart failure.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Goyal: The percentage of men with HFpEF rose from 31% to 37%.

The multivariate analysis also identified three comorbidities linked with in-hospital mortality. A pulmonary circulation disorder was associated with a 90% higher mortality rate among HFpEF patients and a 79% higher rate among those with HFrEF. Liver disease and chronic renal disease linked with smaller mortality increases for both heart failure types.

The presence of treatable comorbidities, including hypertension, diabetes, and coronary artery disease, linked with significantly lower in-hospital mortality rates. Dr. Goyal speculated that the reduced mortality resulted from successful treatment of these conditions.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

Hybrid thoracic suite leverages CT imaging

BY MITCHEL L. ZOLER
Frontline Medical News

PHOENIX – Using CT imaging to detect lung cancers in people at high risk for developing it has made it possible to find small tumors with substantially increased sensitivity than is possible with radiography, However, this approach has posed a new challenge to thoracic surgeons: How to visualize these nodules – subcentimeter and nonpalpable – for biopsy or for resection?

The answer may be the hybrid thoracic operating room developed by Dr. Kazuhiro Yasufuku and his associates at Toronto General Hospital, a novel surgical suite that he described at the annual meeting of the Society of Thoracic Surgeons.

Dr. Yasufuku and his team began using the hybrid operating room on an investigational basis in 2013 and have now done about 50 cases as part of several research protocols. The trials address the feasibility of resection, biopsy, and nodule localization, as well as whether the hybrid approach reduces the amount of radiation exposure to both patients and to the surgical team, he said. They plan to report some of their initial results later this year.

The Toronto group assembled the hybrid array of equipment into a single operating room that includes both a dual-source, dual-energy CT scanner and a robotic cone-beam CT scanner, equipment for minimally invasive procedures including video-assisted thoracoscopic and robotic surgery, and advanced endoscopic technology including endobronchial ultrasound and navigational bronchoscopy. "We use innovative methods that we already know about, but bring them all together" within a single space, Dr. Yasufuku explained. "Rather than having patients go to several locations, we can do everything at the same time in one room."

A robotic cone-beam CT scanner with mobile, flat CT-imaging panels overcomes the limitations of a fixed scanner.

DR. YASUFUKU

Perhaps the most novel aspect of this operating room is inclusion of a robotic cone-beam CT scanner, which uses mobile, flat CT-imaging panels that overcome the limitations of a conventional, fixed CT scanner. "They scan the patient and then we can retract them and get them out of the way" to better facilitate surgery, he said in an interview.

"We do not have a culture in thoracic surgery of using imaging during surgery," said Dr. Yasufuku, director of the interventional thoracic surgery program at the University of Toronto. Hybrid operating rooms using noninvasive or minimally invasive equipment and procedures have become commonplace for cardiovascular surgeons and cardiac interventionalists, but this approach has generally not yet been applied to thoracic surgery for cancer, in large part because of the imaging limitations, he said. "It is difficult to perform video-assisted thoracoscopic surgery using fixed CT."

Bronchoscopic technologies provide additional, important tools for minimally invasive thoracic surgery. "We use the hybrid operating room to mark small [nonpalpable] lesions." One approach to marking is to place a microcoil within the nodule with a percutaneous needle. Another approach is to tag the nodule with a fluorescent dye using navigational bronchoscopy.

Dr. Yasufuku also emphasized that the hybrid operating room will also be valuable when new, minimally invasive, nonsurgical therapeutic options for treatment of lung cancer become available in the near future.

Dr. Yasufuku said that he had no relevant disclosures.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

Ischemic mitral regurgitation: Valve repair vs. replacement

BY BRUCE JANCIN
Frontline Medical News

SNOWMASS, COLO. – A clear message from the first-ever randomized trial of surgical mitral valve repair versus replacement for patients with severe ischemic mitral regurgitation is that replacement should be utilized more liberally, Dr. Michael J. Mack said at the Annual Cardiovascular Conference at Snowmass.

The results of prosthetic valve implantation proved far more durable than repair. At 2 years of follow-up in this 251-patient multicenter trial conducted by the Cardiothoracic Surgical Trials Network (CSTN), the incidence of recurrent moderate or severe mitral regurgitation was just 3.8% in the valve replacement group, compared with 58.8% with repair via restrictive annuloplasty.

As a result, the repair group had significantly more heart failure–related adverse events and cardiovascular hospitalizations and a lower rate of clinically meaningful improvement in quality of life scores, noted Dr. Mack, an investigator in the trial and medical director of the Baylor Health Care System in Plano, Tex.

"I think surgical mitral valve replacement has had a bad name over the years, and one of the reasons is because of the worse left ventricular function afterwards. However, that was a casualty of excising the mitral valve and the subvalvular apparatus, causing atrial-ventricular disconnection. We've gotten smarter about this. The techniques we now use are valve sparing," the cardiothoracic surgeon said.

He was quick to add, however, that the CSTN study results are by no means the death knell for restrictive mitral annuloplasty.

Indeed, participants in the mitral valve repair group who didn't develop recurrent regurgitation actually experienced significant positive reverse remodeling as reflected by improvement in their left ventricular end-systolic volume index, the primary endpoint of the study (N Engl J Med. 2016;374:344-35).

The more tethering of the leaflets, the more likely is recurrent mitral regurgitation after annuloplasty.

DR. MACK

The key to successful outcomes in mitral valve repair is to save the procedure for patients who are unlikely to develop recurrent regurgitation. And a substudy of the CTSN trial led by Dr. Irving L. Kron, professor of surgery at the University of Virginia, Charlottesville, provides practical guidance on that score.

The investigators conducted a logistic regression analysis of the mitral valve repair group's baseline echocardiographic and clinical characteristics and identified a collection of strong predictors of recurrent regurgitation within 2 years (J Thorac Cardiovasc Surg. 2015 Mar;149[3]:752-61).

"The bottom line is, the more tethering you have of the mitral valve leaflets, the more likely you are to have recurrent mitral regurgitation after mitral valve annuloplasty," Dr. Mack said.

The predictors of recurrent regurgitation included a coaptation depth greater than 10 mm, a posterior leaflet angle in excess of 45 degrees, a distal anterior leaflet angle greater than 25 degrees, inferior basal aneurysm, mitral annular calcification, and a left ventricular end diastolic diameter greater than 65 mm, as well as other indices of advanced left ventricular remodeling.

No or only mild annular dilation, as occurs, for example, in patients whose mitral regurgitation is caused by atrial fibrillation, is another independent predictor of recurrent regurgitation post repair.

"Shrinking the annulus isn't going to make a difference if the annulus wasn't dilated to begin with," the surgeon observed. "If surgery is performed, we now know those patients who are most likely to recur – and they should have mitral valve replacement. If those factors are not present, then repair is still a viable option," according to Dr. Mack.

That being said, it's still not known whether correcting severe ischemic mitral regurgitation prolongs life or improves quality of life long term, compared with guideline-directed medical therapy, he stressed.

"Secondary mitral regurgitation is a disease of the left ventricle, not the mitral valve. So it's possible that mitral regurgitation reduction has no benefit because the regurgitation is a surrogate marker not causally related to outcome. I don't think so, but it is a possibility," Dr. Mack conceded.

Dr. Mack reported receiving research grants from Abbott Vascular, which is sponsoring the COAPT trial, as well as from Edwards Lifesciences.

bjancin@frontlinemedcom.com

Radiomic features aid diagnostic accuracy of CT screen

BY PATRICE WENDLING
Frontline Medical News

SAN DIEGO – Radiomics-derived imaging features may improve the diagnostic accuracy of low-dose CT lung cancer screening and help predict which nodules are at risk of becoming cancers.

"We are providing pretty compelling evidence that there is utility in this science," Matthew Schabath, Ph.D., said at a conference on lung cancer translational science sponsored by the American Association for Cancer Research and the International Association for the Study of Lung Cancer.

Current practice relies on a single CT feature, nodule size, and clinical guidelines to evaluate and follow-up pulmonary nodules, none of which provides clinicians with the tools to accurately predict the risk or probability of lung cancer development.

Radiomics is an emerging field that uses high-throughput extraction to identify hundreds of quantitative features from computed tomography (CT) images. That data is mined to develop predictive, diagnostic, and prognostic models.

Radiologists first identify a region of interest (ROI) on the CT scan containing either the whole tumor or spatially explicit regions of the tumor called "habitats." These ROIs are then segmented via computer software before being rendered in three dimensions. Quantitative features are extracted from the rendered volumes and entered into the models, along with clinical and patient data.

"Right now our tool box is about 219, but by the end of the year we are hoping to have close to 1,000 radiomic features we can extract from a 3-D rendered nodule or tumor," said Dr. Schabath, of the Moffitt Cancer Center in Tampa, Fla.

Led by Dr. Robert Gillies, often referred to as the father of radiomics, the researchers extracted and analyzed the 219 radiomic features from nodules in 196 lung cancer cases and in 392 controls who had a positive but benign nodule at the baseline scan and

Continued on page 32

COURTESY DR. GILLIES

Robert Gillies, Ph.D., is using radiomic features to improve CT screening to detect lung nodules at risk of becoming cancers.

Targeting high-risk smokers

Adducts *from page 1*

cancer, he explained at a conference on lung cancer translational science sponsored by the American Association for Cancer Research and the International Association for the Study of Lung Cancer.

Biomarkers of tobacco exposure and metabolism are well developed, with blood and urinary biomarker panels applied in many studies and validated by mass spectrometry.

Using the Shanghai cohort study, the researchers identified three urinary biomarkers – PheT (r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene), total NNAL (a metabolite of NNK and its glucuronides), and total cotinine (a surrogate for nicotine that includes cotinine and its glucuronides) – that were significantly associated with lung cancer in 950 smokers, even after adjustment for smoking duration and intensity (Cancer Res. 2011;71:6749).

A more recent, deeper dive of 735 of those urinary samples, still stable about 20 years after they were taken, looked specifically at polymorphisms in cytochrome P450 2A6 (CYP2A6), the primary enzyme responsible for the oxidation of nicotine and cotinine. Data currently in press show that CYP2A6 poor metabolizers had a lower risk of lung cancer than the combined group of normal, intermediate, or slow metabolizers (odds ratio, 0.64; *P* value for trend = .034).

"This is logical because poor metabolizers of nicotine have more unchanged nicotine on board, so they don't need to smoke as intensely in order to get more nicotine because that nicotine is remaining to a greater extent in its natural form, rather than being metabolized into cotinine, which is not addictive," he said.

Recent genomewide-association studies by Dr. Hecht and his colleagues of smokers in the Multiethnic Cohort Study revealed that Japanese Americans had the highest number of low nicotine CYP2A6 metabolizing genotypes of the five ethnic groups analyzed, consistent with their low lung cancer risk.

Levels of total NNAL, 3-hydroxy phenanthrene, a biomarker of polycyclic aromatic hydrocarbon uptake, and S-phenylmercapturic acid (SPMA), a biomarker of benzene exposure, were also significantly higher among African Americans than whites and significantly lower in Japanese Americans than whites.

The findings are consistent with the initial study results published a decade ago (*N Engl J Med.* 2006;354:333) showing that at 10 cigarettes per day, Japanese Americans and Hispanics had one-third the risk of lung cancer of African Americans or Native Hawaiians (*P* less than .001). The differences disappeared at higher levels (30 cigarettes per day).

Urinary levels of 3-hydroxypropylmercapturic acid (3-HPMA), a metabolite of acrolein, were found to be high in Native Hawaiians and relatively low in Hispanics, "which may play into their lung cancer risk because acrolein is a strong toxicant and there is evidence to suggest it is involved in lung cancer," he said.

While tobacco exposure and metabolism biomarkers have hit their stride, less well developed are the DNA adducts and repair biomarkers that can predict lung cancer susceptibility. This is a critical step because of the role DNA adducts play in the formation of lung cancer mutations, Dr. Hecht said.

A smoker may have a high tobacco exposure as indicated by the urinary biomarkers, but have a low metabolism to form DNA adducts or high DNA repair, which would mean their DNA adduct levels would be low. Conversely, another smoker with low exposure and poor DNA repair may have higher DNA adduct levels, and thus, a greater risk for developing lung cancer.

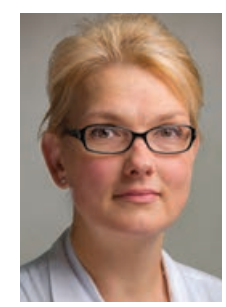
In addition, the exposure biomarkers are not entirely predictive and thus, will need to be combined with multiple DNA adducts and repair if susceptible smokers are to be identified and targeted for state-of-the art cessation approaches and surveillance, he said.

Using high-level mass spectrometry, the researchers have been able to readily measure formaldehyde DNA adducts and tobacco-specific 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB)–releasing DNA adducts in human oral cells. Levels of the HPB adduct were unusually high at 12-45 pmol/mg, which is similar to what is seen in animals when exposed to NNK at a much higher dose than smokers take in.

"So this is a real lead," said Dr. Hecht, who reported having no relevant conflicts of interest.

pwendling@frontlinemedcom.com

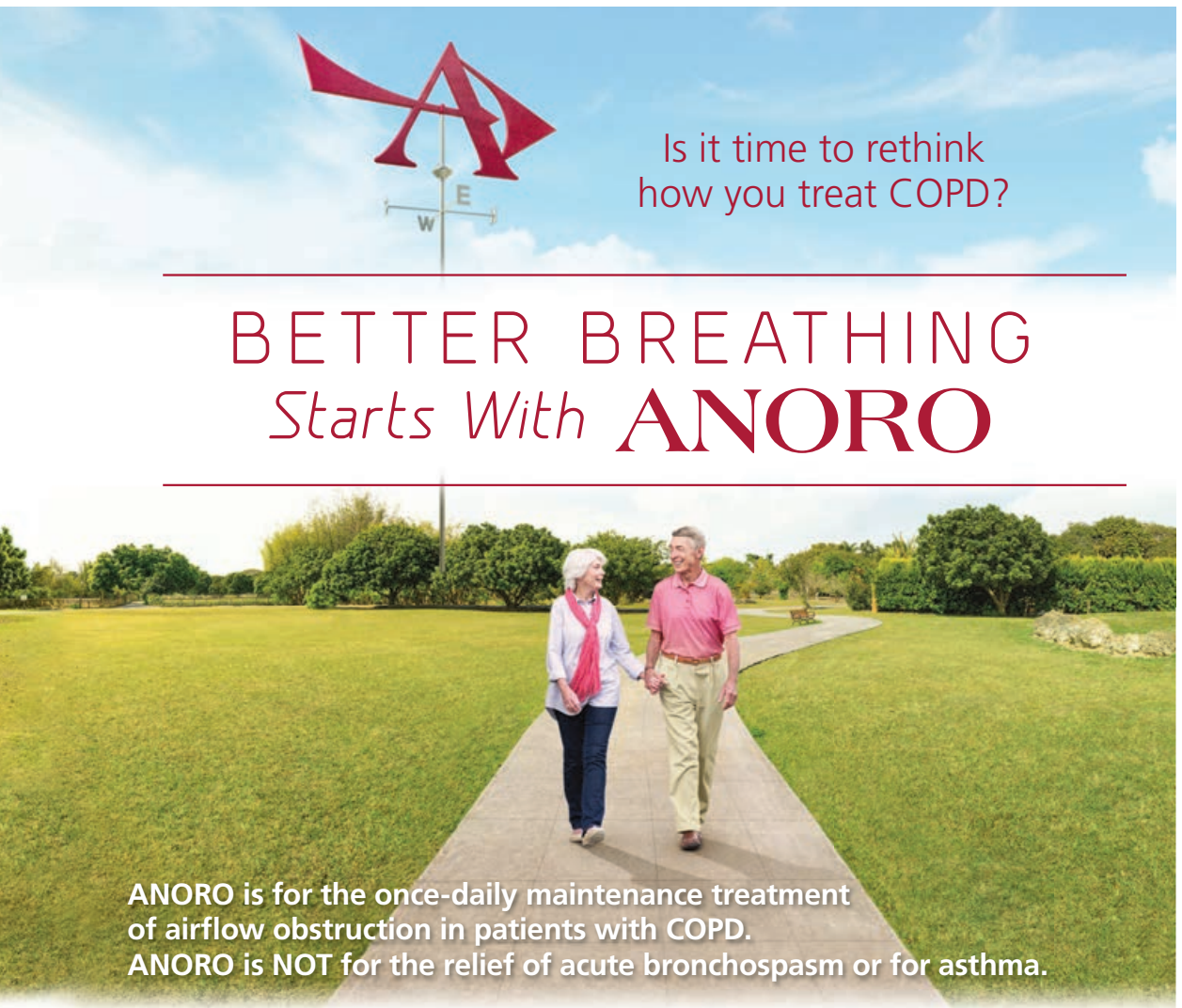
VIEW ON THE NEWS



Dr. Jennifer Cox, FCCP comments: DNA adducts are the result of the metabolism and activation of inhaled carcinogens and the interaction with a patient's DNA. As a result of the miscoding during DNA replication caused by the DNA adducts, we find many of the mutations found in lung cancer. Cytochrome P450 2A6 (CYP2A6) is an enzyme involved in the oxidation of nicotine and cotinine. Four distinct groups of CYP2A6 metabolizers were analyzed. Compared with the combined normal, intermediate, and slow metabolizers, the poor metabolizers had a lower risk of lung cancer. In the future, combining DNA adducts and repair with urinary and blood biomarkers of tobacco exposure may select out a subgroup of smokers who should be more aggressively targeted for efforts at smoking cessation, education and surveillance. However, as physicians, we need to do a better job with all of our smoking patients. We should provide education and a means to be successful at smoking cessation – not just because of the lung cancer risk, but because of all the other devastating tobacco-related diseases.

In a subset (n=366) of a managed care population with a diagnosis of COPD

81% of patients had moderate or worse COPD at spirometry-confirmed diagnosis[1]



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

In the study referenced above, COPD severity was based on GOLD classification at time of study: 50% moderate, 26% severe, 5% very severe.
COPD=chronic obstructive pulmonary disease; GOLD=Global Initiative for Chronic Obstructive Lung Disease.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

gsk | Theravance

ANORO for the maintenance treatment of COPD

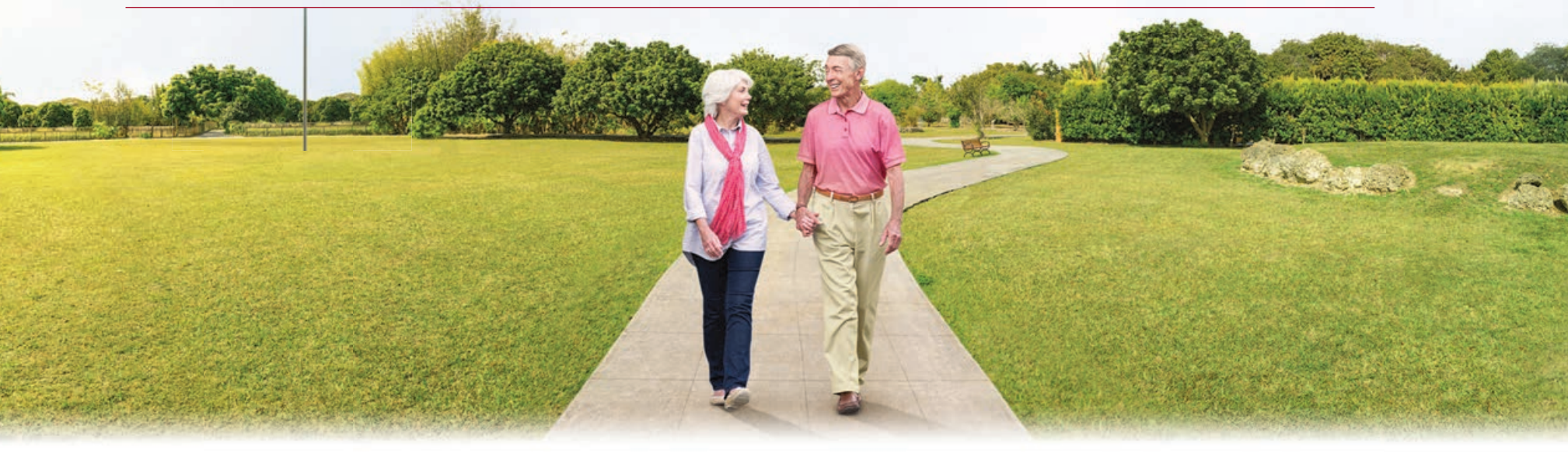
Description of Lung Function Comparison Studies[2-4]

The efficacy and safety of a once-daily dose of ANORO ELLIPTA and SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) were evaluated in 24-week, multicenter, randomized, blinded, active-controlled, double-dummy, parallel-group studies in patients (mean age range: 62 to 65 years) with COPD. At screening, patients had a mean postbronchodilator FEV_1 range of 46.4% to 47.7% predicted (ranges for each study were within GOLD classification 2, 3, or 4). The studies were not powered to compare the safety profile of ANORO ELLIPTA with that of SPIRIVA HandiHaler.

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

FEV_1=forced expiratory volume in 1 second.

SPIRIVA and HandiHaler are registered trademarks owned by Boehringer Ingelheim.



Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

WARNINGS AND PRECAUTIONS (cont'd)

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

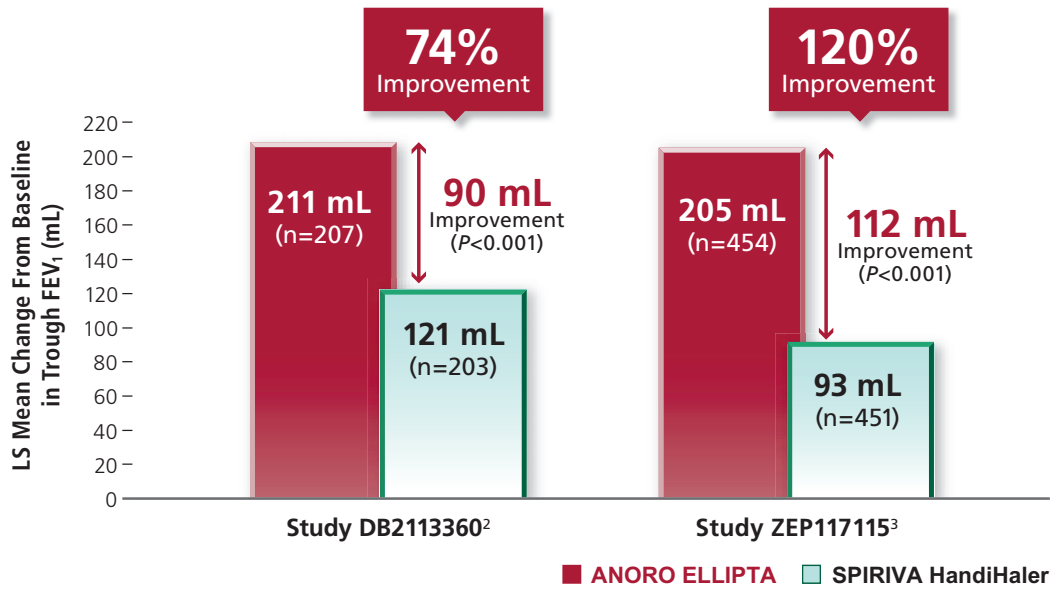
ADVERSE REACTIONS

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

For patients with moderate or worse COPD

Start with ANORO ELLIPTA instead of SPIRIVA HandiHaler for superior improvement in lung function

ANORO ELLIPTA DELIVERED SIGNIFICANT IMPROVEMENT IN TROUGH FEV_1 vs SPIRIVA HandiHaler AT DAY 169 IN 2 STUDIES[2,3]



ANORO ELLIPTA is a combination anticholinergic/LABA for the maintenance treatment of airflow obstruction in patients with COPD.

SPIRIVA HandiHaler is an anticholinergic for the maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.[5]

In a separate study, ANORO ELLIPTA showed a 60-mL difference* compared with SPIRIVA HandiHaler (208 mL and 149 mL, respectively), but due to testing hierarchy, statistical significance cannot be inferred.[2]

LS=least squares.
*Reflects rounding.

Important Safety Information (cont'd)

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO ELLIPTA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.

DRUG INTERACTIONS (cont'd)

- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Learn more at
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Please see additional Important Safety Information for ANORO ELLIPTA on preceding pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA on the following pages.

References: 1. Mapel DW, Dalal AA, Blanchette CM, et al. Severity of COPD at initial spirometry-confirmed diagnosis: data from medical charts and administrative claims. *Int J Chron Obstruct Pulmon Dis*. 2011;6:573-581. **2.** Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med*. 2014;2(6):472-486. **3.** Maleki-Yazdi MR, Kaelin T, Richard N, et al. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med*. 2014;108(12):1752-1760. **4.** Data on file, GSK. **5.** SPIRIVA HandiHaler [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014.

ANORO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

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

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

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

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

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

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

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

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

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

considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

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

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

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

10.2 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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

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

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

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

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

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

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

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

Risks Associated With Beta-Agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a physician immediately should any of these signs or symptoms develops.

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

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

ANORO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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Presurgery radiation shows benefit in mesothelioma

BY RICHARD MARK KIRKNER
Frontline Medical News

The popularity of extrapleural pneumonectomy to treat asbestos-related thoracic mesothelioma has yielded to extended pleurectomy/decortication in recent years, but a study suggests that the extrapleural pneumonectomy procedure can achieve good results in a new protocol that involves administering radiation therapy before surgery as opposed to the more conventional approach of radiation after surgery.

Researchers at the University of Toronto reported on their protocol that uses accelerated intensity modulated radiation therapy (IMRT) for malignant pleural mesothelioma (MPM) (J Thorac Cardiovasc Surg. doi: 10.1016/j.jtcvs.2015.09.129). They call the protocol SMART, for Surgery for Mesothelioma After Radiation Therapy.

"The rationale to develop this protocol was to optimize the delivery of radiation to the whole tumor bed, sterilize the edges of the tumor to limit the risk of spillage at the time of surgery, develop a shorter treatment plan and potentiate the activation of the immune system by using a hypofractionated regimen," wrote Dr. Marc de Perrot and colleagues.

The protocol involves delivering 25 Gy of radiation in five daily fractions over a week to the entire side of the thorax with 5 Gy boosts based on imaging, followed by extrapleural pneumonectomy (EPP) 4-6 days later. Patients with three or more positive lymph notes (ypN2 disease) also are offered adjuvant chemotherapy.

The researchers performed the protocol on 62 patients from November 2008 to October 2014, which represents 24% of all patients with MPM seen at the institution in that period. Fifty-two patients were men and ages ranged from 41 to 75 years. Clinical stage of cancer ranged from T1N0 in 10 patients, to T2N0 in 35 and T3N0 in 13 (two had T4N0 and two had T3N2). Forty-five had right-side cancers. Six patients received an extended protocol for various reasons, including tumor extending to the chest wall.

All 62 patients completed IMRT and EPP. All but one had resection and reconstruction of the diaphragm, and all but four had resection and reconstruction of the pericardium.

Overall death rate was 4.8% (three patients). Results were better in patients with epithelioid tumors, with a median survival of 51 months and disease-free survival of 47 months. Those with biphasic subtypes had median survival of 10 months and disease-free survival of 8 months. Eight patients had ipsilateral chest recurrence. "This analysis demonstrates that the SMART approach is particularly encouraging for patients with epithelial subtype," Dr. de Perrot and coauthors said. They no longer perform the SMART protocol on patients with biphasic subtype.

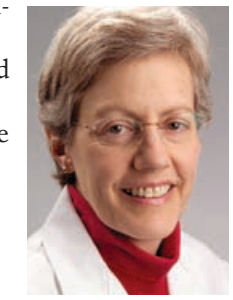
The protocol was not without complications. Twenty-four patients, about 38%, had serious complications that required intervention or worse. Twelve had atrial fibrillation, but none advanced to life-threatening disease. Among other complications, four had empyema – one resulting in death – and three had pulmonary emboli. One other patient in the complications group died from pneumonia, and another died from a heart attack at home.

This is the Toronto researchers' second attempt at studying the three-modality approach. In their first attempt, only half the patients who started with preoperative chemotherapy went onto complete the radiation after surgery because of difficulties administering it (J Thorac Cardiovasc Surg. 2007;133:111-6; J Clin Oncol. 2009;27:1413-8). Also, about 25% of patients had disease progression during induction chemotherapy and could not go onto surgery.

The study authors had no conflicts to disclose.

VIEW ON THE NEWS

Results hard to reproduce



Implementing the treatment regimen for malignant pleural mesothelioma (MPM) that the Toronto researchers studied poses several high stakes challenges and will be difficult to replicate. The study results are among the best reported for MPM to date, but are they solely related to patient selection or do they reflect the true impact of a novel approach to treatment?

Patients selected for the treatment need to be able to undergo the extrapleural pneumonectomy and the surgeon has to be able to predict the resectability of the tumor. But limitations in existing staging methods for MPM make it difficult to predict tumor resectability. To avoid bronchial stump leaks and other serious complications requires experience along with meticulous surgical technique and postoperative care. Only high-volume centers of excellence could potentially reproduce these results.

Despite the waning in popularity of EPP, the study results underscore its effectiveness in carefully selected patients – those with epithelioid tumor histology and no tumor metastases.

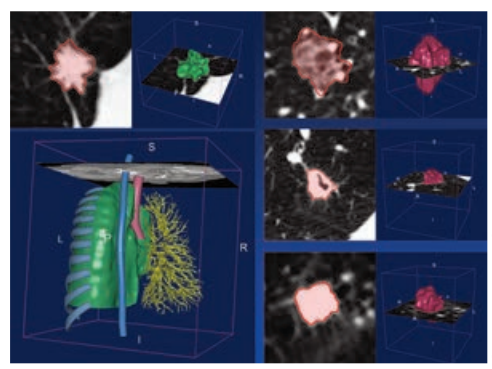
Dr. Valerie Rusch and coauthors at Memorial Sloan-Kettering Cancer Center, New York, made these remarks in a commentary (J Thorac Cardiovasc Surg. doi: 10.1016/j.jtcvs.2015.10.038) accompanying the editorial.

Continued from page 26

were matched for age, sex, smoking status, and race. The post hoc, nested case-control study used images and data from the pivotal National Lung Screening Trial.

Two classes of features were extracted from the images: semantic features and agnostic features. Sematic features are commonly used in radiology to describe ROIs, and agnostic features are mathematically extracted quantitative descriptors that capture lesion heterogeneity.

In the risk prediction model, eight "highly informative features" were identified, Dr. Schabath said. Five were agnostic and three were semantic – circularity of the nodule, volume, and distance from or pleural attachment. The receiver operating characteristic (ROC) area under the curve for the model was 0.92, with 75% sensitivity and 89% specificity.



COURTESY DAVID GERING, PHD, HEALTH MYNE INC.

Automated segmentations of a lung nodule created from a CT lung scan.

Six highly informative features were identified in the diagnostic model, which extracted features from the nodules found at the first and second follow-up interval, Dr. Schabath said. Three were agnostic and three semantic – longest diameter, olume, and distance from or pleural attachment. The ROC for the diagnostic model was 0.89, with 74% sensitivity and 89% specificity.

The overlap of volume and distance from or pleural attachment in both the diagnostic and predictive models suggests "there might be something very important about these two features," he added.

Dr. Schabath stressed that the findings are preliminary. Long-term goals are to implement radiomic-based decision support tools and models into radiology reading rooms.

"In the future, we envision that all medical images will be converted to mineable data with the process of radiomics as part of standard of care," Dr. Gillies said in an interview. "Such data have already shown promise to increase the precision and accuracy of diagnostic images, and hence, will increasingly be used in therapy decision support."

Among the many challenges that first need to be resolved are that images are often captured with settings and filters that can be different even within a single institution. The inconsistency adds noise to the data that are extracted by computers.

"Hence, the most robust data we have today are generated by radiologists themselves, although this has its own challenges of being time-consuming with inter-reader variability," Dr. Gillies noted.

Another major challenge is sharing of the image data. Right now, radiomics is practiced at only a few research hospitals and thus, building large cohort studies requires that the images be moved across site. In the future, the researchers anticipate that software can be deployed across sites to enable radiomic feature extraction, which would mean that only the extracted data will have to be shared, he said.

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David Bowie's 'good death,' and advance care planning

BY THERESE BORDEN
Frontline Medical News

The death of David Bowie, iconic musician and artist, on Jan. 10 inspired palliative care specialist Dr. Mark Taubert to write a blog about end-of-life scenarios and the importance of advance care planning. The blog, which begins by thanking Mr. Bowie for his many artistic contributions, continues by suggesting that his planned death at home will inspire many people in similar health crises to consider palliative care.

KymiWikimedia Commons/CC BY-SA 3.0

David Bowie's final music project and his death at home have inspired palliative care discussions.

The palliative care conversation between a doctor and a patient facing death can be challenging but can lead to what Dr. Taubert called "a good death" at home with symptoms managed and loved ones nearby. Mr. Bowie's son, Duncan Jones, tweeted a link to the blog in the days after his father's death.

Dr. Taubert found himself speaking with a patient who was facing probable death in the near future, and both doctor and patient found inspiration in Mr. Bowie's final music project and his death at home with his family.

Dr. Taubert and his patient were able to have the conversation about palliative care at end-of-life in part because they were both impressed with what Mr. Bowie was able to achieve in his last months. "Your story became a way for us to communicate very openly about death, something many doctors and nurses struggle to introduce as a topic of conversation," he wrote.

Dr. Taubert of the Velindre NHS Trust in Cardiff, Wales, noted that, palliative care is a highly developed skill with many resources to help patients at the end of life, but "training is not always available for junior healthcare professionals, including doctors and nurses, and is sometimes overlooked or under-prioritized by those who plan their education. I think if you [David Bowie] were ever to return (as Lazarus did), you would be a firm advocate for good palliative care training." The blog is available at http://blogs.bmj.com/spcare/2016/01/15/a-thank-you-letter-to-david-bowie-from-a-palliative-care-doctor/

Families reported few benefits from aggressive end-of-life cancer care

BY AMY KARON
Frontline Medical News

Bereaved families were substantially more satisfied with end-of-life cancer care when patients did not die in hospital, received more than 3 days of hospice care, and did not enter the ICU within 30 days of dying, according to a multicenter, prospective study published online Jan. 19 in JAMA.

The analysis is one of the first of its type to assess these end-of-life care indicators, said Dr. Alexi Wright of Harvard Medical School, Boston, and her associates.

The findings could affect health policy as electronic health records expand under the Health Information Technology for Economic and Clinical Health Act, they said.

End-of-life cancer care has become increasingly aggressive, belying evidence that this approach does not improve patient outcomes, quality of life, or caregiver bereavement.

To explore alternatives, the researchers analyzed 1,146 interviews of family members of Medicare patients who died of lung or colorectal cancer by 2011. Their data source was the multiregional, prospective, observational Cancer Care Outcomes Research and Surveillance (CanCORS) study (*JAMA* 2016;315:284).

Family members described end-of-life care as "excellent" 59% of the time when hospice care lasted more 3 days, but 43% of the time otherwise (95% confidence interval for adjusted difference, 11% to 22%).

Notably, 73% of patients who received more than 3 days of hospice care died in their preferred location, compared with 40% of patients who received less or no hospice care.

Care was rated as excellent 52% of the time when ICU admission was avoided within 30 days of death, and 57% of the time when patients died outside the hospital, compared with 45% and 42% of the time otherwise.

The results support "advance care planning consistent with the preferences of patients," said the investigators.

They recommended more extensive counseling of cancer patients and families, earlier palliative care referrals, and an audit and feedback system to monitor the use of aggressive end-of-life care.

The National Cancer Institute and the Cancer Care Outcomes Research and Surveillance Consortium funded the study.

One coinvestigator reported financial relationships with the American Academy of Hospice and Palliative Medicine, National Institute of Nursing Research, National Institute on Aging, Retirement Research Retirement Foundation, California Healthcare Foundation, Commonwealth Fund, West Health Institute, University of Wisconsin, and UpToDate.com.

Senior author Dr. Mary Landrum, also of Harvard Medical School, reported grant funding from Pfizer and personal fees from McKinsey and Company and Greylock McKinnon Associates. The other authors had no disclosures.

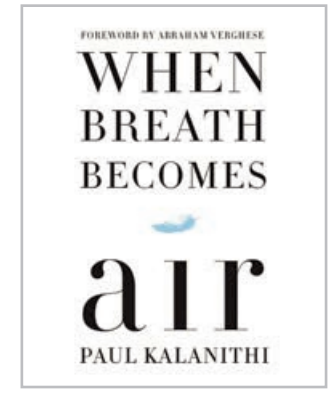
Neurosurgeon's memoir examines 'learning how to die'

BY THERESE BORDEN
Frontline Medical News

Dr. Paul Kalanithi, a neurosurgeon who had just completed his residency at the Stanford (Calif.) University, died of metastatic lung cancer last year, but he left a memoir of his experiences as a physician, a patient, and a dying man that was published on Jan. 12. His book, "When Breath Becomes Air" (New York: Random House, 2016), recounts the many years of working to exhaustion and deferring of life experiences and pleasures that are necessary to complete medical training.

Dr. Kalanithi reflected on the profound grief and sense of loss that comes with a diagnosis that he knew meant imminent death. The memoir also reveals his search for meaning and joy, and finally, his acceptance of mortality. He opted for palliative care and his memoir, along with the epilogue written by his wife, Dr. Lucy Kalanithi, gives insight into the value of the palliative path to patients and their families in dire medical crises.

In her New York Times review of the book, Janet Maslin wrote, "One of the most poignant things about Dr. Kalanithi's story is that he had postponed learning how to live while pursuing his career in neurosurgery. By the time he was ready to enjoy a life outside the operating room, what he needed to learn was how to die."



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Short sleep duration in hypertensives ups mortality

BY BRUCE JANCIN
Frontline Medical News

ORLANDO – Hypertensive persons who sleep 5 hours or less per night have a significantly higher all-cause mortality rate than those who get more shut-eye, according to an analysis from the Penn State Adult Cohort Study.

"We found that the odds of all-cause mortality associated with hypertension increased in a dose-response manner as a function of the degree of objective short sleep duration, even after adjusting for a multitude of factors," Julio Fernandez-Mendoza, Ph.D., reported at the American Heart Association scientific sessions.

The Penn State Adult Cohort consists of a random, general population sample of 1,741 men and women who enrolled in the study back in the 1990s, at a mean age of 48.7 years. As part of their comprehensive evaluation they were studied in the overnight sleep laboratory. The cohort has been followed for 15.5 years, during which 20% of subjects died.

As expected, hypertension was associated with increased risk of all-cause mortality in the Penn State Adult Cohort. But Dr. Fernandez-Mendoza and coinvestigators further dissected this association by incorporating the subjects' objective sleep lab data, something that hadn't been done in other studies. They found that while as a group the roughly 35% of study participants with hypertension had an adjusted 2.54-fold increased risk of all-cause mortality, compared with normotensive subjects, those who slept 6 or more hours at night – placing them at or above the 50th percentile for sleep duration – had a 1.75-fold increased risk, which just barely reached statistical significance.

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Short sleep duration in hypertensive patients may be a marker of the severity of autonomic dysfunction, said Dr. Julio Fernandez-Mendoza.

In contrast, those who slept 5-6 hours per night were at 2.36-fold increased risk of all-cause mortality, while hypertensives in the bottom quartile for sleep duration with 5 hours or less of sleep had an even more robust 4.04-fold increased risk. All risk figures were determined in a multivariate logistic regression analysis extensively adjusted for age, gender, race, diabetes, obesity, smoking, depression, insomnia, sleep apnea, and history of heart disease or stroke.

This finding of an inverse association between sleep duration and all-cause mortality was consistent with the investigators' study hypothesis that short sleep duration in hypertensive patients may be a marker of the severity of autonomic dysfunction. After all, it is known that the autonomic nervous system not only controls cardiovascular function, it also regulates sleep, explained Dr. Fernandez-Mendoza, a behavioral psychologist at Pennsylvania State University in Hershey.

Other possible explanations for the findings are that short sleep duration in hypertensive patients might be genetically driven or behaviorally induced, but he considers these less plausible.

In an interview, Dr. Fernandez-Mendoza said he and his coinvestigators have found the same relationship between short sleep duration and increased all-cause mortality in Penn State Adult Cohort members with diabetes or dyslipidemia, although he didn't present those data at the AHA meeting.

If indeed short sleep duration is a marker of autonomic dysfunction, it would have important clinical implications: "Objective sleep duration may allow for refinement of estimates of mortality risk. I predict that someday cardiovascular risk calculators will incorporate sleep duration," he said.

The Penn State Adult Cohort findings bring a measure of clarity to what has been a somewhat cloudy area, Dr. Fernandez-Mendoza said. Most prior epidemiologic studies of sleep's impact on health have relied upon self-reported sleep duration, which is considerably less reliable than objectively measured sleep lab data. And many studies have looked at sleep duration as an isolated variable in relation to morbidity and mortality risk. This, he said, has contributed to public misunderstanding.

"We have people coming into the sleep lab thinking, 'If I don't get 7 hours of sleep I'm going to die,'" according to the sleep scientist. "But the paradigm we've developed, tied to what we know about autonomic control, is that the cardiovascular system and the sleep system are connected to each other. It doesn't mean that short sleep kills you, it's that the combination of the traditional cardiometabolic risk factors and short sleep increases risk of morbidity and mortality."

Dr. Fernandez-Mendoza reported having no conflicts of interest.

bjancin@frontlinemedcom.com

Statins might prevent vascular inflammation in sleep apnea

BY AMY KARON
Frontline Medical News

Statins reduced complement-related vascular inflammation in patients with obstructive sleep apnea, according to research published online in Science Translational Medicine.

The "unexpected" finding suggests that statins might offer a targeted therapy for the significant vascular manifestations of OSA, wrote Dr. Memet Emin and Dr. Gang Wang of Columbia University College of Physicians and Surgeons, New York, together with their associates. "Statins also have antioxidant effects, which may be particularly beneficial in conditions associated with oxidative stress, such as OSA," the investigators added.

Obstructive sleep apnea affects one in four Western adults and triples the risk of cardiovascular diseases. The disorder is uniquely characterized by intermittent hypoxia, which the researchers hypothesized might lead to a distinct pattern of endothelial cell (EC) activation.

To test this theory, they used a phage display peptide library to analyze protein expression in vascular ECs from 76 patients with OSA and 52 OSA-free controls. They also modeled intermittent hypoxia by exposing cultured ECs to alternating periods of normal and low (2%) oxygen levels (*Sci Transl Med.* 2016 Jan 6. doi: 10.1126/scitranslmed.aad0634).

Patients with OSA who were receiving statins had EC surface levels of the CD59 complement inhibitor similar to those of controls, and significantly greater levels compared with patients with OSA who were not receiving statins ($P = .05$). The CD59 protein is a major complement regulator that inhibits the formation of the terminal membrane attack complex, and thereby protects cells from complement-mediated injury, the researchers noted. In addition, intermittent hypoxia induced the internalization of CD59 in cultured ECs, leading to MAC deposition and endothelial inflammation, they said.

Most notably, patients with OSA who were taking statins had normal EC surface levels of CD59, and cultured ECs that were treated with atorvastatin were better protected from complement activity in a cholesterol-dependent manner, the investigators reported. By reducing cholesterol biosynthesis, statins might decrease the formation of cholesterol-enriched plasma membrane and CD59 endocytosis, which would reduce its internalization and preserve its ability to protect cells against complement activity, they said.

The National Heart, Lung, and Blood Institute of the National Institutes of Health funded the study. The investigators had no disclosures.

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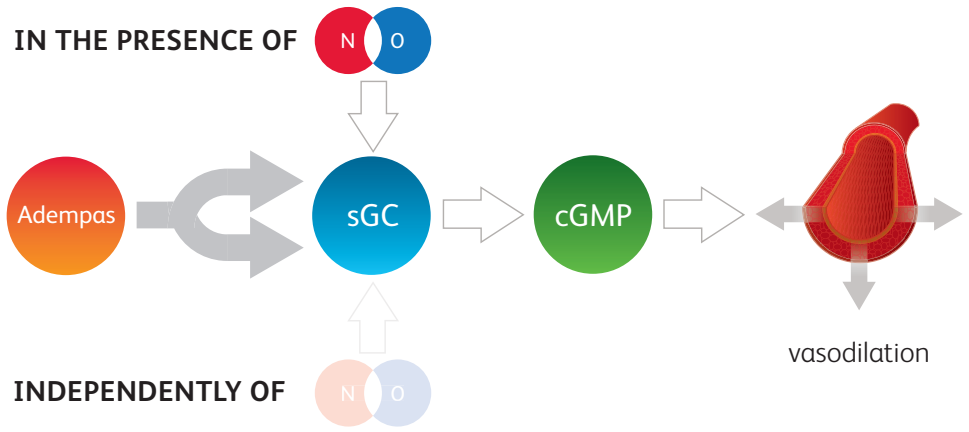

INDICATIONS

- Adempas (riociguat) tablets are 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.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

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In pulmonary arterial hypertension (PAH), (WHO Group 1)

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 443 adult PAH patients with predominantly WHO Functional Class II-III. The primary endpoint was change from baseline in 6MWD at 12 weeks.

In inoperable and persistent/recurrent chronic thromboembolic hypertension (CTEPH), (WHO Group 4)

46m improvement (mean) in 6MWD over placebo at Week 16 (95% CI: 25m-67m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 261 adult patients with persistent/recurrent CTEPH after surgery or who were inoperable. The primary endpoint was change from baseline in 6MWD at 16 weeks.

CONTRAINDICATIONS (continued)

- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

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 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.

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 next page.

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WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)**
- **For females, Adempas is available only through a restricted program called the Adempas REMS Program. (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 Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

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 hypotension *[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 *[see Contraindications (4.3) and Clinical Pharmacology (12.2)]*. 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 50-60% 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

See 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). Patients should 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)]*. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

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CRITICAL CARE COMMENTARY: Does corticosteroid therapy improve community-acquired pneumonia outcomes? YES!

BY DR. MUTHIAH P. MUTHIAH, FCCP

Community-acquired pneumonia (CAP) is a significant public health problem worldwide. In the United States, pneumonia causes more disease and death than any other infection. In 2002, there were over 1.3 million hospital admissions due to pneumonia. With about 55,000 deaths per year in the United States, pneumonia ranks eighth among the leading causes of death (www.cdc.gov/nchs/fastats/leading-causes-of-death.htm). While physicians have diligently used antimicrobials to control the pathogens, very little effort has been expended investigating strategies to modulate the inflammation initiated by CAP pathogens.

The two major components of any infection include the pathogen and the host's inflammatory response. When CAP pathogens invade the sterile lower respiratory tract, the innate immune response produces local and systemic inflammation. Irrespective of the microbiological etiology, the host's inability to adequately down-regulate systemic inflammation is the dominant process contributing to acute and long-term morbidity and mortality in CAP. The primary manifestations of pneumonia (fever, tachycardia, tachypnea, and hypoxemia) are due to local and systemic inflammation accompanied by significant increases in pro-inflammatory cytokine levels.


DR. MUTHIAH

Systemic manifestations of dysregulated inflammation in CAP include hypotension due to inflammation-induced vasodilatation, capillary leak with acute respiratory distress syndrome (ARDS), and remote organ (kidney and central nervous system) dysfunction and/or failure. Such systemic effects of pneumonia are driven more by host response-generated inflammation rather than microbial propagation and invasion.

In CAP, most hospital and post-discharge mortality occur after eradication of bacteria from tracheal secretions and bloodstream (Corrales-Medina et al. *J Infect.* 2011;63[3]:187). This implies that factors other than antimicrobials need to be considered in order to achieve further reductions in morbidity and mortality; one such strategy is modulating inflammation. Studies have shown that disease severity and clinical outcomes parallel the extent of elevation in inflammatory cytokine levels in patients with severe CAP.

The most robust contribution to this body of knowledge originates from analysis of the GenIMS data set (1,886 CAP patients), which included daily measurements of cytokines until day seven and once weekly thereafter in patients with pneumonia and sepsis. These data indicate that inflammatory cytokine concentrations have generally reached their peak at the time patients with CAP present to the hospital. Higher levels of inflammatory cytokines at hospital admission correlated with worsened short- and long-term morbidity and mortality (Kellum. *Arch Intern Med*. 2007;167[15]:1655; Yende et al. *Am J Respir Crit Care Med.* 2008;177[11]:1242). Interleukin (IL)-6 levels obtained at hospital discharge in clinically stable patients strongly correlate with subsequent 1-year mortality after adjusting for age, race, gender, comorbidity score, and APACHE III scores. Interestingly, high IL-6 concentrations were associated with death due to cardiovascular disease, cancer, infections, and

Leukocytosis that starts beyond 72 h after initiating steroids and/or presence of bandemia should prompt the search for intercurrent infections.

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renal failure (Yende et al. *Am J Respir Crit Care Med*. 2008;177[11]:1242).

It is clear that biological resolution of CAP lags behind clinical resolution. Inflammatory cytokines such as tumor necrosis factor alpha and IL-6 remain elevated for days or weeks after the clinical resolution of CAP (Kellum. *Arch Intern Med*. 2007;167[15]:1655) . These findings support the belief that the inflammatory response to infection persists at hospital discharge, despite resolution of clinical signs and symptoms and likely contribute to delayed adverse outcomes.

While antibiotics are effective in eradicating the pathogens, they generally do not significantly modulate the inflammatory cascade triggered by acute infection. For this reason, a strategy directed against both the causative organism and the inflammatory response may be more efficacious rather than traditional stand-alone antimicrobial therapy. Evidence-based current best practices include adjunct corticosteroids in patients with *Pneumocystis jiroveci* pneumonia or select cases of bacterial meningitis.

Glucocorticoids work by genomic and nongenomic mechanisms to provide anti-inflammatory and immunosuppressive effects. Glucocorticoids readily cross the cell membranes to enter the cytoplasm where they bind the glucocorticoid receptor. The resulting complex translocates into the nucleus, binds to glucocorticoid responsive elements, and down-regulates pro-inflammatory transcription factors including activator protein-1 and nuclear factor kappa B.

Several animal studies, as well as pneumonia and nonpneumonia-related human trials, have shown rapid, significant, and consistent reduction in pro-inflammatory cytokine levels following administration of glucocorticoids.

A randomized, double-blind, placebo-controlled, proof-of-concept trial by Confalonieri and colleagues consisting of 46 CAP patients showed improvements in organ function and radiograph scores, increases in ventilator-free days and the Pao_2:FIO_2 ratio, decreased length of stay, and reduced C-reactive protein (CRP) levels (Confalonieri et al. *Am J Respir Crit Care Med*. 2005;171[3]: 242). A recent meta-analysis takes us to the brink of accepting steroid adjunctive therapy for severe CAP. Among 13 randomized controlled trials, including 2,005 patients, there was a 2.6% absolute reduction in mortality (7.9% mortality in the control groups vs 5.3% in the corticosteroid group, RR 0.67 (95% CI, 0.45-1.01), $P = .01$). Additional benefits included decreased need for mechanical ventilation [RR 0.45 (0.26-0.79)], less development of ARDS [RR 0.24 (0.10-0.56)], and a 1-day reduction in duration of hospitalization [RR -2.96 (-5.18 to -0.75)]. Corticosteroid use increased the incidence of hyperglycemia [RR 1.49 (CI 1.01-2.19)] but did not increase GI hemorrhage or neuropsychiatric complication rates (Siemieniuk et al. *Ann Intern Med*. 2015;163[7]:519).

When should steroids be used in CAP? It is presently reasonable to conclude that steroids can be used in patients with severe CAP. While there is no clear consensus on what constitutes severe pneumonia, accepted standards such as the Pneumonia Severity Index, CURB-65, or major society guidelines (American Thoracic Society, British Thoracic Society) seem prudent.

In CAP, most hospital and postdischarge mortality occur after eradication of bacteria, implying that factors other than antimicrobials need to be considered in order to achieve further reductions in morbidity and mortality.

The Extended Steroid in CAP (ESCAPe) investigators have adopted a scheme to defining severe pneumonia as greater than or equal to one major criteria (need for invasive or noninvasive mechanical ventilation, vasopressor requirement, pH <7.30) or greater than or equal to three minor criteria (new-onset confusion, hypothermia, hypotension requiring fluid resuscitation, Pao_2:FIO_2 <250, WBC <4,000, platelet count <100,000 or >400,000, multilobar pneumonia) (ClinicalTrials.gov: NCT01283009). While utilizing biomarkers seems reasonable—elevated CRP levels are associated with increased mortality and treatment failures—there are no accepted values for CRP or IL-6 to establish severe CAP (Torres. *JAMA*. 2015;313[7]:677).

Several key questions remain. Which is the glucocorticoid of choice? What should be the dose? How long should patients be treated? When and how should the steroid be tapered? How do you monitor efficacy? These questions – and likely others – will have to be answered in future clinical trials.

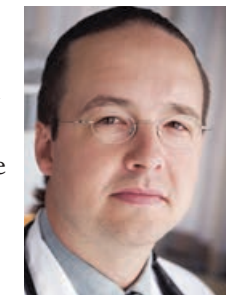
Monitoring for superinfections in steroid-treated patients is a challenge. Steroid therapy usually causes a brisk leukocytosis, due to demargination, which can be difficult to differentiate from leukocytosis due to intercurrent infection. In general, steroid-associated leukocytosis almost always occurs within 12 to 24 h of initiation and seldom beyond 72 h. It is usually associated with a profound eosinopenia, most times close to 0%. Leukocytosis that starts beyond 72 h after initiating steroids and/or presence of bandemia should prompt the search for intercurrent infections.

Our group has also adopted an infection surveillance system in ICU patients receiving systemic corticosteroid therapy for any indication. We obtain routine blood, urine, and lower respiratory tract cultures every 5 to 7 days. Prior clinical trials have shown that a vast majority of infections occurring in patients receiving systemic steroids are likely to be asymptomatic and, if left untreated, can have adverse consequences.

In severe CAP, the pathogenesis, clinical manifestations, and adverse consequences (organ dysfunction, treatment failures, short- and long-term mortality) are closely related to the degree of systemic inflammation. As such, it makes physiologic sense that controlling inflammation is likely to decrease some of these adverse events. There is mounting evidence supporting the use of glucocorticoids as adjunct therapy for severe CAP. The time has come for guidelines to reflect the positive impact of steroids in treating these patients. The economic and biologic impact on CAP could be significant, including faster recovery, shorter length of stay, and reduced mortality.

Dr. Muthiah is Associate Professor of Medicine; Director, Pulmonary & Critical Care Medicine Fellowship Program; and Director, MICU, VAMC, Memphis; Division of Pulmonary, Critical Care, and Sleep Medicine; University of Tennessee, Memphis.

EDITOR'S COMMENTS



In the current Critical Care Commentary, Dr. Muthiah shares his wealth of experience and insight regarding the evolving and controversial topic of adjunctive steroids in patients with severe CAP. This summary calls to mind the Albert Einstein quip, "The more I learn—the more I realize how much I don't know." Unfortunately, and as is often the case, much of our present confusion regarding CAP and steroids is self-inflicted. Existing studies have variably defined "severe" pneumonia, used different steroid dosing regimens, and assessed outcomes that, at best, appear to overlap more by chance than by design. Given the magnitude of the consequences of severe CAP—coupled with the potential untapped benefits of steroids seen with other severe infections causing critical illness—the importance of Dr. Muthiah's call for ongoing collaborative research cannot be overstated. Hopefully, such investigations will do more than help us to realize how much we still don't know.

Dr. Lee Morrow, FCCP

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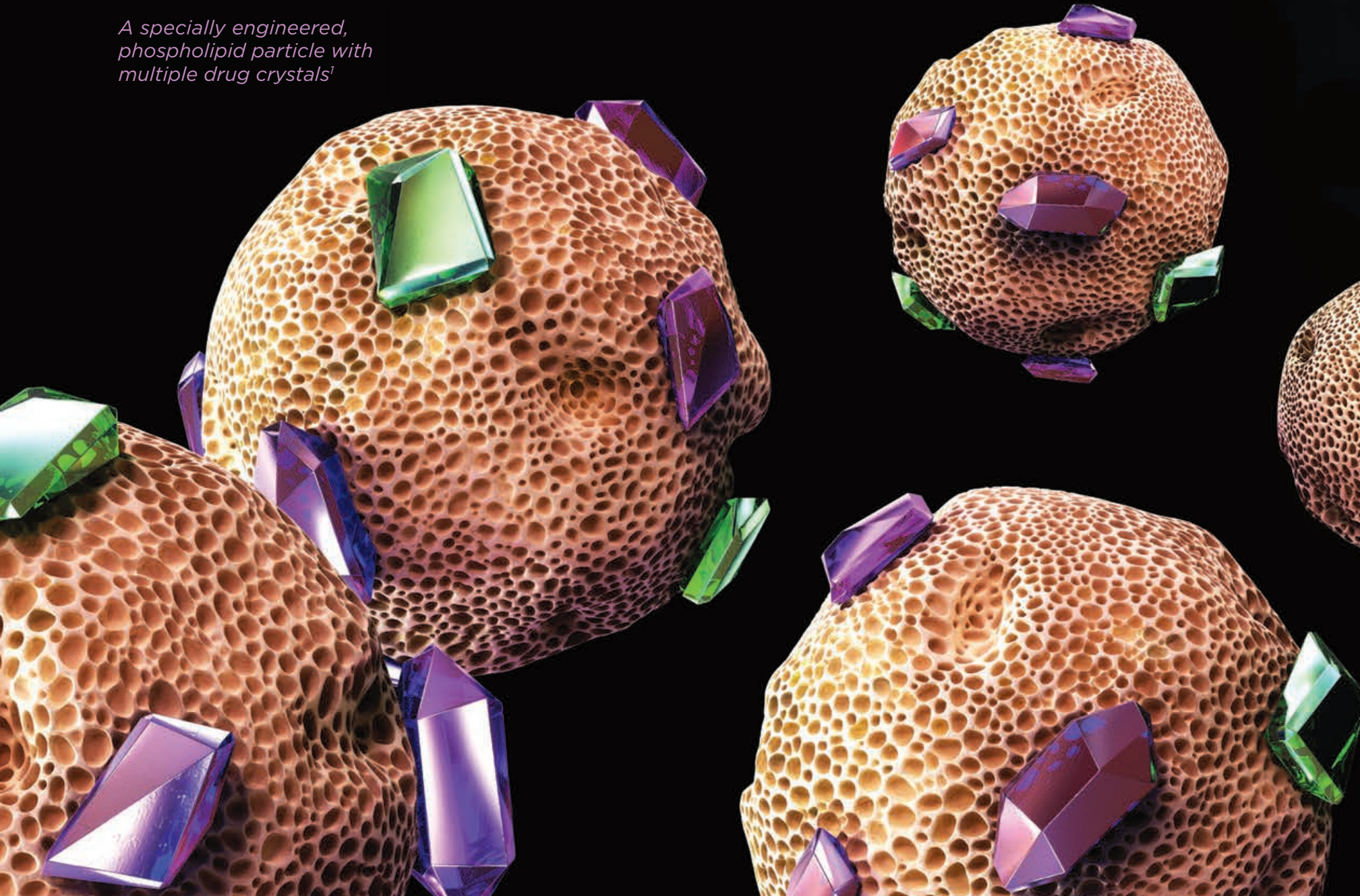

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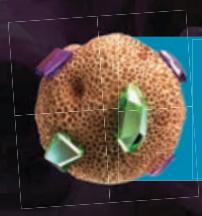

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AstraZeneca

Gene signatures tag cause of respiratory infection

BY SHARON WORCESTER
Frontline Medical News

Pathogen-specific host gene expression patterns accurately discriminated most noninfectious from infectious illnesses, and bacterial from viral causes of acute respiratory infection (ARI) in an observational study conducted in acute care settings.

The findings could have important implications for combating inappropriate antibiotic use and emerging antibiotic resistance, Dr. Ephraim L. Tsalik of the department of medicine at Duke University, Durham, N.C., and his colleagues reported online Jan. 20 in Science Translational Medicine.

The investigators analyzed peripheral whole-blood gene expression from 273 subjects with community-onset viral ARI (115 subjects), bacterial ARI (70 subjects), or noninfectious illness (88 subjects) who were seen in an emergency department, and from 44 healthy control subjects.

Classifiers for bacterial ARI, viral ARI, and noninfectious causes of illness were developed, and were 87% accurate overall (Sci Transl Med. 2016;8[322]:322ra11. doi/10.1126/scitranslmed.aad6873).

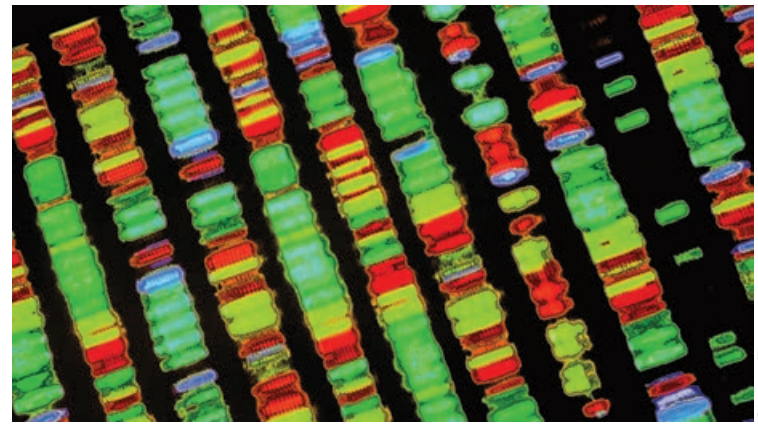
"Bacterial ARI was identified in 83% of patients and excluded in 94% without bacterial infection. Viral ARI was identified in 90% and excluded in 92% of cases. Using the noninfectious illness classifier, infection was excluded in 86% of cases," they wrote.

The classifiers were more accurate than procalcitonin – a widely used biomarker with some specificity for bacterial infection (86% vs. 78% accuracy in 238 available samples), and three published classifiers of bacterial vs. viral infection, and were validated in five publicly available data sets, they noted.

The gene signature patterns identified in the course of this study mark an important step toward development of a rapid blood test that could be used in clinics to guide appropriate treatment for ARIs, the investigators said.

Precision treatment of viruses

More precise ways to distinguish infections could reduce unnecessary antibiotic use and lead to more precise treatment of viruses, senior author Dr. Geoffrey S. Ginsburg, director of Duke's Center for Applied Genomics & Precision Medicine, said in a press statement.


GIO_TTO/THINKSTOCK

"Right now, we can give patients [oseltamivir] Tamiflu to help them recover from an influenza infection, but for most viral infections, the treatment is fluids and rest until it resolves. In the next 5-10 years, we will likely see new antiviral medications for common bugs like respiratory syncytial virus and even rhinovirus, and guiding treatment choices will be even more important," he added.

Senior author Dr. Christopher W. Woods, also of Duke University, further explained in an interview that the findings are particularly exciting because "there isn't much out there that accomplishes what we've done. So just about any level of accuracy is an improvement."

Further, he said the test is "a tool to aid in diagnosis, used in conjunction with the patient's symptoms, examination, and other testing. So an imperfect test is okay, because it does not stand alone."

Next steps include putting the assay on a testing platform that can be used at the point of care, and validating the findings in all populations, including infants, the elderly, and across ethnic groups, he said.

"The work is ongoing, and we expect to have results available within the course of an outpatient visit in the near future," Dr. Woods, also a professor of medicine and global health, added, noting that efforts also are underway to "expand the repertoire of this approach to many different types of viral and bacterial infections and also to fungal infections, and to address the challenges of critically ill patients in intensive care units."

This study was supported by the U.S. Defense Advanced Research Projects Agency, the National Institutes of Health, the Agency for Healthcare Research and Quality, the U.S. Department of Veterans Affairs Office of Research and Development, and an in-kind contribution from bioMérieux. The authors reported having no relevant competing interests.

sworcester@frontlinemedcom.com

Hospital-acquired pneumonia in 20% with spinal injury

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – The overall rate of hospital-acquired pneumonia following cervical spinal cord injury is about 20%, results from a study of national data demonstrated.

"Cervical spinal cord injury patients are at an increased risk for the development of hospital-acquired pneumonia," lead study author Dr. Pablo J. Diaz-Collado said in an interview after the annual meeting of the Cervical Spine Research Society.

"Complete cord injuries, longer length of stay, ICU stay and ventilation time lead to significantly increased risk of HAP, which then leads to poor inpatient outcomes," he said. "It is of crucial importance to keep these risk factors in mind. There is a need to optimize the management protocols for these patients to help prevent the development of HAPs."

Dr. Diaz-Collado, an orthopedic surgery resident at Yale–New Haven (Conn.) Hospital, and his associates identified 5,198 cervical spinal cord injury patients in the 2011 and 2012 National Trauma Data Bank (NTDB) to analyze risk factors for the development of HAP and inpatient outcomes in this population. They used multivariate logistic regression to identify independent associations of various risk factors with the occurrence of HAP.

HAP was linked to more deaths, inpatient adverse events, and discharges to extended care.

DR. DIAZ-COLLADO

The researchers found that the overall incidence of HAP among cervical spinal cord injury patients was 20.5%, which amounted to 1,065 patients. Factors independently associated with HAP were complete spinal cord injuries (compared to central cord injuries; OR 1.44; $P = .009$); longer inpatient length of stay (OR 3.08 for a stay that lasted 7-13 days, OR 10.21 for 21-27 days, and OR 14.89 for 35 days or more; $P = .001$ or less for all associations); longer ICU stay (OR 2.86 for a stay that lasted 9-11 days, OR 3.05 for 12-14 days, and OR 2.94 for 15 days or more; P less than .001 for all associations), and longer time on mechanical ventilation (OR 2.68 for ventilation that lasted 3-6 days, OR 3.76 for 7-13 days, OR 3.98 for 14-20 days, and OR 3.99 for 21 days or more; P less than .001 for all associations).

After the researchers controlled for all other risk factors, including patient comorbidities, Injury Severity Score, and other inpatient complications, HAP was associated with increased odds of death (OR 1.60; $P = .005$), inpatient adverse events (OR 1.65; P less than .001), discharge to an extended-care facility (OR 1.93; $P = .001$), and longer length of stay (a mean of an additional 10.93 days; P less than .001).

Dr. Diaz-Collado acknowledged that the study is "limited by the quality of the data entry. In addition, the database does not include classifications of fractures, and thus stratification of the analysis in terms of the different kinds of fractures in the cervical spine is not possible. Finally, procedural codes are less accurate and thus including whether or not patients underwent a surgical intervention is less reliable."

Dr. Diaz-Collado reported having no financial disclosures.

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Introducing CHEST's President-Designate

CHEST's President-Designate is Dr. John Studdard, FCCP, a pulmonary and critical care physician in private practice with Jackson Pulmonary Associates in Jackson, Mississippi.

Dr. Studdard completed his fellowship training at the Mayo Graduate School of Medicine. He has served in numerous leadership roles with the American College of Chest Physicians (CHEST), including President and Chair of the CHEST Foundation, the philanthropic arm of CHEST; chair of the Government Relations Committee; member of the Marketing Committee; and Ex Officio member of the Diversity Committee, Scientific Program Committee, and Financial Oversight Committee.

His dedication to reducing the number of patients he treats for tobacco-related diseases, and his leadership qualities, led him to serve as a representative for CHEST in the negotiations with the tobacco industry, leading to the Attorneys General Master Settlement Agreement of

Dr. John Studdard, FCCP

1998. More recently, in his roles with the CHEST Foundation, Dr. Studdard served as a vice chair of the Beyond Our Walls capital campaign and as a member of the CHEST Foundation Nominating Committee and several foundation work groups.

Dr. Studdard's term as CHEST President will be 2017-2018.

This month in *CHEST:* Editor's picks

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

Loss of Vascular Distensibility During Exercise Is an Early Hemodynamic Marker of Pulmonary Vascular Disease. *By Dr. E. M. T. Lau et al.*

Assessing Differences in Mortality Rates and Risk Factors Between Hispanic and Non-Hispanic Patients With Cystic Fibrosis in California. *By Dr. M. C. Buu et al.*

Clinical Characteristics and Outcomes in Extreme Elderly (Age ≥85 Years) Japanese Patients With Atrial Fibrillation: The Fushimi AF Registry. *By Dr. Y. Yamashita et al.*

Update of Antithrombotic Guidelines: Medical Professionalism and the Funnel of Knowledge. *By Dr. J. E. Heffner (Editorial and Podcast)*

Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report (10th edition). *By Dr. C. Kearon et al.*

Impact of Tobacco Smoke and Nicotine Exposure on Lung Development. *By Dr. K. Gibbs et al.*

CHEST Foundation grant portal opens

Every year, the CHEST Foundation awards grants to members of our community who are passionate about championing lung health. These funds are used to advance projects and research of innovative investigators and physicians and also support critical programs in patient education.

Our grants are wide-reaching, crossing multiple disciplines and areas of focus.

Dr. Tetyana Kendzerska, recipient of the 2015 CHEST Foundation Research Grant in Women's Lung Health, focused her project on the development and evaluation of cardiovascular consequences of obstructive sleep apnea in women.

"The proposed project will allow me to study gender-specific aspects of the relationship between obstructive sleep apnea and cardiovascular events development that may have direct implications for risk stratification and treatment of patients with sleep apnea. This award will support the development of the research platform that will be the foundation for my future research career."

Our past grant winners' accomplishments have made a worldwide impact, from Tanzania to San Antonio.

The awards empower our winners to focus on critical research that can sometimes lead to federal funding.

Dr. Tetyana Kendzerska received the 2015 CHEST Foundation Research Grant in Women's Lung Health, presented by Dr. John Howington, Foundation President.

This year, we offered the following awards:

- GlaxoSmithKline Distinguished Scholar in Respiratory Health
- CHEST Foundation Research Grant in Lung Cancer
- CHEST Foundation Research Grant in Pulmonary Arterial Hypertension
- CHEST Foundation and Alpha 1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
- CHEST Foundation Research Grant in Pulmonary Fibrosis
- CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
- CHEST Foundation Research Grant in Venous Thromboembolism
- CHEST Foundation Research Grant in Nontuberculous Mycobacteria
- CHEST Foundation Research Grant in Women's Lung Health
- Community Service Grant Honoring Dr. D. Robert McCaffree, Master FCCP

What will you do to help champion lung health?

Visit chestnet.org/grants to learn more about how you and your team could be one of the next grant recipients.

Unique inspiration at CHEST World Congress 2016

When you travel to Shanghai, China, to attend CHEST World Congress 2016, you won't want to miss a minute of the cutting-edge education sessions and simulation training. Yet, you can't send a postcard home if you haven't witnessed first-hand the beauty, culture, and uniqueness of the city's sites featured on your postcard. We've got you covered. If you want to see the famous, "must see" sites of Shanghai, follow our list below, and you will not be disappointed.

The most famous and iconic location in Shanghai is a street called The Bund. The street is located just west of the Huangpu River, and it features international architecture with building styles from art deco and gothic to late renaissance and classic European. You can also find ritzy shopping and high-end restaurants and bars at this swanky attraction.

If you are interested in history, you'll want to visit the Shanghai Museum and the Old Town neighborhood. The Shanghai Museum has a large collection of historical artifacts, and you can rent an audio phone with narratives of the major exhibits. Old Town is the center of the old Chinese city and the first part of Shanghai to be settled. Today, you'll find souvenirs and antiques, a Daoist Temple, and Huxinting Teahouse in this neighborhood.

As for entertainment, Shanghai offers several compelling options. Take in the bustling city and the local architecture from an enjoyable vantage point - the Huangpu River.

There are boat tours available ranging from a quick ferry ride to 3-hour cruises. Or, you can sit back and be entertained by the world famous Shanghai Acrobatic Troupe. Performances are available at the Shanghai Center Theatre.

Here are some other interesting tourist destinations:

• Nanjing Road – A shopper's paradise, this road is walkable in 20 to 30 minutes (if you don't stop to shop!)

• French Concession Area – This neighborhood is full of mansions and beautiful parks. Take a walk and enjoy the area on foot!

• Jade Buddha Temple – This unique temple features two beautiful white jade Buddhas.

• Yu Garden – Enjoy the beauty of this classic Chinese garden situated in urban Shanghai.

If you're planning to extend your stay and experience all that China has to offer, find more information and suggested itineraries at meet-in-shanghai.net/ or frommers.com.

Shanghai will captivate you with its culture and beauty, and CHEST World Congress 2016 will inspire and energize your patient care. We'll keep you busy with many different learning formats and sessions. You won't want to miss CHEST World Congress, April 15 - 17, 2016. Learn more at chestworldcongress2016.org.

Jens Fersterra/Thinkstock

A shopper's paradise, Nanjing Road is walkable in 20 to 30 minutes.

New HIPAA guidance on patient record requests

BY ALICIA GALLEGOS
Frontline Medical News

The age of the information-empowered patient means patients don't just bring the results of their Internet research when they come to the office, they also want to take a record of the clinical encounter with them when they leave.

New HIPAA guidance issued in January by the Health & Human Services Department's Office of Civil Rights (OCR) aims to guide the response to those requests and what information can be provided; it also addresses when patients can be charged for the information.

In the past, physicians had to "wing it" when it came to unclear rules about patient's data requests, said Dianne J. Bourque, a Boston health law and HIPAA compliance attorney. "Prior to this, there may not have been readily available guidance that would drill down" to address specific concerns.

When it comes to systems security, physicians and other health providers do not have to put their health IT systems at risk in an effort to meet a request for patient records. For example, Mrs. Smith requests that her protected health information (PHI) be copied onto a thumb drive that she has provided.

In most cases, a covered entity must provide data access in the manner requested by the patient.

If maintained electronically, HIPAA-covered entities must be able provide PHI to patients electronically.

MS. BOURQUE

But the updated guidance states that health providers are not expected to tolerate "unacceptable levels of risk to the security of the PHI on its systems" in responding to requests.

Unlike system security, patient security does not trump patient access. If Mr. Black requests that his records be emailed to him, but a connection cannot be made secure, physicians are still required to send the data.

While OCR requires HIPAA-covered entities to implement reasonable safeguards to protect PHI while in transit, patients have a right to receive a copy of records by unencrypted email if they so wish.

To comply with the new rules, be sure to warn patients of the risks, and confirm that they still want their PHI by unencrypted email. If confirmed, you must comply with the request. This clarification relieves doctors of potential breach notification and liability if the data is intercepted in transit.

The guidance also clarifies how to deliver patients' data. If PHI is maintained electronically, physicians and other HIPAA-covered entities must be able provide it to patients electronically.

"Because you hold it electronically, you can't say, 'Forget it, you have to have paper,'" Ms. Bourque said. "You lose that option when you keep [data] electronically. Maybe you have to go buy a scanner and scan [the document] and email it, but you can't charge [patients] for the scanner."

The new guidance also allows patients to get results directly from a clinical laboratory; however, labs are not required to interpret test results. Rather, patients are encouraged to reach out to their physician for such insights.

Overall, the access guidelines

I routinely send my patients home with at least their lab tests and copies of their radiology reports.

DR. SLISHMAN

appear reasonable and hopefully will relieve hassles for patients in obtaining their health information, said Dr. Sam Slishman, an emergency physician for Sierra Vista Hospital in San Luis Obispo, Calif., and co-founder of Pre-R, a service that provides in-home visits.

Dr. Slishman does not foresee the guidance having much impact on his practices.

"It's crazy to me that patients have to struggle to retrieve their records at all," he said in an interview. "I routinely send my patients home with at least their lab tests and copies of their radiology reports so they have something to bring to their [primary care physicians]. If they want more, I hand it to them."

Dr. Rocky D. Bilhartz, an interventional cardiologist in private practice in College Station, Tex., said that he has concerns about the guidelines. Specifically, that doctors may charge a fee to cover the cost of copying records, but that they cannot charge for the cost of searching and retrieving data, said Dr. Bilhartz, who is founder of ECGsource, an online cardiovascular medical education resource.

Record requests can take significant time to filter through and gather. That time should be reimbursable.

DR. BILHARTZ

"Record requests can take significant time for staff to filter through and gather," he said in an interview. "That time should be reimbursable ... If updated provisions prohibit charging for time spent compiling records, it seems those provisions are a bit out of touch with understanding what those of us on the ground floor must do when a request is received."

But Dr. Bilhartz acknowledged that he would be unlikely to charge patients for "reasonable" data requests.

"I'm in private practice ... and because of that, I have more market-driven accountability to all my patients," he said.

"Why would I nickel and dime people who I would want to be satisfied patients? For reasonable requests, I would just provide records for free," he said.

Ms. Bourque notes that while the clarifications are primarily positive for health providers, they present a double-edged sword.

"The good side is that, it has all this detail and it's really helpful and makes things easier when you have a tricky access request and don't know what to do," she said.

"The flip side is that once it's out there, they expect you to read it and pay attention. You start running out of excuses for why you didn't comply with the access right or why you got it wrong."

agallegos@frontlinemedcom.com
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Prior authorization regs might up the 'hassle factor'

BY ALICIA GALLEGOS
Frontline Medical News

Starting February 29, Medicare won't pay for certain durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) without prior authorization. The regulation could mean headaches for doctors in the form of extra paperwork and frustrated patients.

Under the new requirement – effective Feb. 29 – prior CMS authorization will be required for certain DMEPOS items that are frequently subject to "unnecessary utilization," according to a Dec. 29 announcement. The prior authorization process requires the same information currently necessary for Medicare payment, but will happen earlier in the process.

The early evaluation will assure that all relevant coverage, coding, and clinical documentation is provided before the equipment is furnished to the patient and before the claim is submitted for payment. CMS hopes the prior review will reduce improper payments for DMEPOS.

Not every piece of durable medical equipment will be subject to prior authorization; instead, CMS will prescreen items from its master list of 135 costly and overprescribed items, especially those with an average purchase price of more than $1,000 or rental fee of $100. The complete master list was published within CMS' final rule in the Federal Register. CMS published a "required prior authorization list" 60 days before implementation.

The final rule primarily impacts vendors paid by Medicare to supply durable medical equipment to patients, said Dr. Yul D. Ejnes, an internist in private practice and a past chair of the American College of Physicians Board of Regents.

The prescriber is responsible for meeting all Medicare coverage, coding, and payment rules. However, doctors will likely be indirectly affected because of the clinical documentation required for CMS approval, Dr. Ejnes said.

"The documentation requirement could be burdensome depending on how DME vendors interpret the regulations, and then the whole issue of increasing the amount of chart documentation that's going out to various places raises some concern," Dr. Ejnes said in an interview. "Even though it may all be covered under HIPAA, [there's] the issue of content in the notes that's irrelevant to the DME request and how we handle that. Do we need to start redacting notes to meet the documentation requirements for prior authorization?"

The new requirements also may mean that patients wait longer for needed equipment, Dr. Ejnes added. "Oftentimes, there's the finger-pointing exercise that occurs when things don't happen quickly enough and patients are unhappy. "It just adds to the temperature of the environment, which is already pretty high because of patients unhappy about increasing copays and deductibles and everything else."

To prepare for the rule, physicians should identify the DMEPOS items they order or prescribe most often and engage with suppliers early to ensure they understand what kind of documentation will be needed.

If the physician understands upfront what Medicare requires and is able to provide it to the DMEPOS supplier at the time the DMEPOS items are ordered/prescribed, that may save time on the back-end preventing or otherwise dealing with additional documentation requests from the DMEPOS supplier in support of prior authorization requests.

Be extremely thoughtful about prescribing durable medical equipment and make sure that equipment orders are placed that meet the patient's needs rather than their desires, Dr. Ejnes recommended.

In addition, it's helpful for practices to consider work flow and how to efficiently respond to document requests. In some cases, office staff can locate records or precomplete basic information on forms, he said.

"Figure out a way to respond to these in terms of who in the office will take the first pass if there's a form to fill out," he said. "Be aware that there may be some delays in getting patients what they need. Some of these items are not emergency items. Educate patients to the fact that there's a couple steps between writing the prescription and them picking up the item."

agallegos@frontlinemedcom.com
On Twitter @legal_med

CMS: IT changes are coming to meaningful use

BY WHITNEY MCKNIGHT
Frontline Medical News

Don't walk away from meaningful use quite yet. That's the message from CMS leaders Andy Slavitt and Dr. Karen DeSalvo.

Mr. Slavitt, acting administrator of the Centers for Medicare & Medicaid Services, announced on Jan. 11 that change would be coming to health care IT. "The meaningful use program as it has existed will now be effectively over and replaced with something better," he said at the annual J.P. Morgan Healthcare Conference.

In a blog post intended to elaborate on those statements, Mr. Slavitt and Dr. DeSalvo, National Coordinator for Health IT, wrote that "the approach to meaningful use under the [Medicare Access & CHIP Reauthorization Act of 2015 (MACRA)] won't happen overnight. Our goal in communicating our principles now is to give everyone time to plan for what's next and to continue to give us input. We encourage you to look for the MACRA regulations this year; in the meantime, our existing regulations – including meaningful use stage 3 – are still in effect."

Although CMS had been hinting since late in 2015 that it was considering dropping or modifying the meaningful use program, Mr. Slavitt made it official during the J.P. Morgan conference. The latest announcement asks providers to have patience with this process. "We will continue to listen and learn and make improvements based on what happens on the front line," Mr. Slavitt and Dr. DeSalvo wrote. "The process will be ongoing, not an instant fix and we must all commit to learning and improving and collaborating on the best solutions."

Allowing groups of providers to receive hardship exemptions under meaningful use should make the process simpler.

MR. SLAVITT

Since health IT changes under MACRA apply only to Medicare, the CMS leaders pointed out that electronic health record incentives for Medicaid and Medicare hospitals are unchanged; however, they noted that the agency would seek ways to help health care institutions streamline their IT needs as well.

The blog post also pointed out that late last year, CMS was given the authority to allow groups of providers – rather than individuals – to receive hardship exemptions under meaningful use. "This should make the process much simpler for physicians and their practice managers in the future. We will be releasing guidance on this new process soon," Mr. Slavitt and Dr. DeSalvo noted.

But as CMS forges ahead with new tech mandates, others advised the agency not to throw away the good with the bad.

"We are heartened that CMS has its ears to the ground and is trying to shape the program in a way that will be genuinely beneficial for providers and patients," Ed Park, chief operating officer at AthenaHealth, a Boston-based health IT solutions firm, said in an interview. "With that said, just because providers found meaningful use stage 2 hard doesn't by itself make it a bad program."

This latest information out of CMS would seem to reinforce Mr. Slavitt's promise to the investors at the J.P. Morgan conference that the move away from meaningful use would be to "start small and leave a lot of tool-building opportunities for the private sector." He told attendees that CMS would level the playing field for start-ups and new entrants into the health IT space who can help providers securely transfer patient data and close the loops on referrals and other essentials of continuous care.

Some are not so optimistic about the private sector's ability to help make MACRA a sustained reality, however. "As to whether the systems will be ready for the new payment regime, I am not holding my breath," Johnathan Graham, a health economist and senior fellow at the National Center for Policy Analysis, Washington, D.C., said in an interview.

Even with updated technologies, physician satisfaction will not rise overall, he predicted, because of what he referred to as a too-slow rate of growth in Medicare's Part B budget.

He also called out MACRA payment adjustments as onerous to physicians: The implementation of MACRA's range of positive or negative payment adjustments in the MIPS program of minus 3.5% to plus 4.5% in 2019, plus or minus 5% in 2020, plus or minus 7% in 2021, and plus or minus 9% after that, meaning that the more providers who score above the threshold for the positive payment update, the narrower the update will be to each practice.

CMS shouldn't water down incentives so that the definition of success is that everyone succeeds.

"I think MACRA will fall apart within 2 or 3 years as practicing physicians learn they are in a dog-eat-dog environment, or zero-sum game. The can will get kicked down the road just like meaningful use was," Mr. Graham said.

But forcing doctors to face off is the point, according to Mr. Park: "Our health care system is on a transformational journey and we should all expect it to be hard. We want to encourage CMS to continue to keep the bar high on the right things and we hope that CMS doesn't water down merit-based incentive pay so that the definition of success is that everyone succeeds."

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EOE

NETWORKS: Airways disorders, clinical research, critical care, home-based mechanical ventilation, interstitial lung disease

Airways Disorders

Bronchial thermoplasty studies

In 2010, bronchial thermoplasty (BT) was approved by the FDA to treat severe asthma not controlled with inhaled corticosteroids and bronchodilators. The AIR2 trial, a sham-controlled study, showed improved quality of life, with fewer ED visits and hospitalizations in those who received treatment (Castro. *Am J Respir Crit Care Med*. 2010;181[2]:116). There has been considerable debate about the significant placebo effect observed in the sham group regarding quality-of-life markers. It is plausible that this was a consequence of increased interaction between the investigators and the sham subjects, coupled with the enthusiasm of a new therapy. This trial was also limited by excluding subjects with chronic sinus disease, frequent chest infections, or FEV_1 <60% predicted.

DR. MASELLI

What have we learned over the past 5 years? Longitudinal data showed that patients from the AIR2 trial had lasting beneficial effects after 5 years without side effects (Wechsler. *J Allergy Clin Immunol*. 2013;132[6]:1295). The data are reassuring, but the control group was not followed during this period. Additional studies are warranted to reach firmer conclusions regarding safety.

Patient selection has also been an area of controversy. BT is not the only alternative for patients with uncontrolled asthma. For patients who have uncontrolled allergic asthma, eosinophilic asthma, or both, how do we decide between omalizumab, mepolizumab, and BT? While some experts argue that there is more experience and research in the biological arena with proven efficacy, others favor BT because it is a finite series of treatments (eg, three bronchoscopies) with lasting effects. Additionally, it has been suggested that BT is potentially cost-effective. (Cangelosi et al. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15[2]:357; Zein et al. *J Asthma*. 2015;17:1[Epub ahead of print]). Guidelines advocate the use of this therapy with caution based on the current limited evidence and in the setting of research protocols (Chung et al. *Eur Respir J*. 2014;43[2]:343; www.ginasthma.org). Future, "real-life" studies are urgently needed to explore better patient selection algorithms and to evaluate cost, safety, and long-term asthma outcomes.

Longitudinal data showed that patients from the AIR2 trial had lasting beneficial effects after 5 years without side effects.

Dr. Diego Maselli, FCCP
Steering Committee Member

Clinical Research

Trends and challenges for academic medical centers in the 21st century

Biomedical research leads to the discovery and development of new medications and medical devices that improve public health by providing means for management of health problems. While research partnership among academic institutes, government agencies, and industry is essential, federal government had historically taken the lead in supporting research. However, since the mid-1980s, research funding by pharmaceutical, biotechnology, and medical device firms has surpassed that of the government. At the same time, the growth of clinical revenues slowed down to contain health-care costs, and health-care centers responded by increasing clinical activities and reducing time spent on research.

DR. ADRISH

"Given the difficulties of increasing other revenue sources, US academic health-care centers responded by having their faculty further increase their clinical activities." said Dr. Kimford J. Meador (*Neurology*. 2015;85[13]:1171).

Dr. Meador mentioned a study comparing academic physician activities from 1984 to 2001, which noted that patient care activities doubled while research activities reduced by half. Failure

Continued on following page

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to adequately train physicians in clinical and basic sciences research resulting in poor quality research application to NIH by physicians was also identified. Not surprising as the author mentioned that PhDs were three times more likely to be NIH funded than physicians.

"The declining support for clinical research and the inadequate training of MDs in clinical research methodology will become increasingly impactful because the effect of scientific discovery is cumulative over time. Ultimately, the present course will threaten the predominance of the United States in biomedical research," he wrote.

No funding was reported for the article.

Dr. Muhammad Adrish
Steering Committee Member

Critical Care

Is SIRS criteria useful?

A recent retrospective study found that 88% of patients admitted with severe sepsis had two or more criteria for systemic inflammatory response syndrome (SIRS) within the first 24 hours of ICU admission (Kaukonen. *NEJM*. 2015;372[17]:1629). Data from 172 ICUs collected over 14 years were analyzed. The diagnosis of severe sepsis was determined by a diagnosis code of infection and organ failure based on SOFA[MZ1] score, both obtained at the time of ICU admission. SIRS criteria before ICU admission or subsequent diagnosis code of infection (after the first day in the ICU) were not studied. SIRS-positive patients had higher mortality (24.5% vs 16.1%, *P*<.001), acute renal failure (18.9% vs 11.7%, *P*<.001), and septic shock (58% vs 42.4%, *P*<.001). There was a greater proportion of SIRS-negative patients admitted postoperatively (38.3% vs 19%).


DR. TAMAE KAKAZU

When SIRS criteria were used in ProCESS, ARISE, and ProMISe trials to screen for sepsis in the ED, it led to the earlier start of antibiotics and fluids, mostly before randomization. Organ failure and need for ICU admission were not present in all patients, and the average mortality was lower than expected. A prospective study will help determine whether use of SIRS criteria really helps to identify and treat patients with early sepsis, or if a newer definition with better sensitivity may lead to earlier intervention and a consequent reduction in mortality. As SIRS is not only caused by infection, gene expression may help to distinguish infectious from noninfectious inflammation in the future (Sweeney. *Sci Transl Med*. 2015;7[287]:287ra71).

Dr. Maximiliano Tamae Kakazu
Steering Committee Member
Dr. Keith Wille, FCCP
Steering Committee Member

Home-Based Mechanical Ventilation and Neuromuscular Disease

Management of pulmonary complications in patients with ALS

Amyotrophic lateral sclerosis (ALS) is a progressive debilitating disorder that affects both upper and lower motor neurons. As such, patients tend to have bulbar and pseudobulbar symptoms, muscular weakness, diminished cough, and weakness of the diaphragm. These can lead to significant pulmonary complications. Some of our main concerns include sleep-disordered breathing, a poor cough leading to pulmonary secretion buildup, and progressive dyspnea leading to respiratory failure.


DR. ELSAYEGH

Many patients with ALS develop obstructive sleep apnea, which is usually treated with BiPAP. It is not widely discussed because most patients with ALS are already supported by noninvasive ventilation. However, it is important for the physician to keep this in the back of their mind in order to encourage use of such devices at night.

Poor airway clearance secondary to a diminished cough is another important problem. Patients with ALS have an insufficient expiratory force secondary to respiratory muscle weakness, resulting in a weakened cough. Coughing has two main features, breaking down secretions in smaller airways and moving secretions out to the larger airways. These can be managed with two distinct sets of devices. First, an airway clearance device needs to be used to break down secretions. Second, a cough assistive device is used to move secretions to larger airways and out of the mouth.

The most devastating complication is respiratory failure secondary to muscle weakness. This is usually monitored using serial measurements of forced vital capacity (FVC) and negative inspiratory force (NIF). As the FVC and NIF begin to decline significantly or if the patient begins to feel symptoms of dyspnea, noninvasive ventilation must be considered.

A more recent device being used for respiratory support in patients with ALS is a diaphragm pacemaker. Since this is a very new device, we are still obtaining data on outcomes. At this point, we are mainly inserting the device for improvement of quality of life. We are currently evaluating data on prolongation of life. The device is recommended to be used in conjunction with noninvasive ventilation.

It is important to note that each patient must be treated on an individual basis, some requiring all of the above, while others require different combinations of these devices.

For more information:

1. NeuRx DPS by Synapse Biomedical www.synapsebiomedical.com/ (actual device)

Ongoing studies:

2. Multicenter Randomized Trial of DPS in ALS (Several centers are participating; the one I am involved in is the one at Cedars Sinai Medical Center in Los Angeles.)
3. DPS in ALS (ClinicalTrials.gov)

Dr. Ashraf Elsayegh, FCCP
Steering Committee Member

Interstitial and Diffuse Lung Disease

New findings in IPF

Advances in idiopathic pulmonary fibrosis (IPF) have recently brought about treatment choices that are mainly guided by side effect profile, along with patient and physician preferences. Exciting new work by the IPFnet Investigators may offer a glimpse into the possible future of therapy. In a recent article (Oldam. *Am J Respir Crit Care Med*. 2015;192[12]:1475), the investigators studied the effect of single-peptide polymorphisms (SNPs) within two genes associated with IPF susceptibility and survival (TOLLIP and MUC5B), on a composite endpoint of death, transplantation, hospitalization, or a decline in FVC ≥10%. Initially, they performed a post-hoc genetic analysis on subjects enrolled in the PANTHER-IPF trial in which patients with IPF were treated with combination prednisone, azathioprine, and n-acetyl cysteine (NAC) vs NAC alone vs placebo. They found that specific SNPs within TOLLIP were associated with significant treatment response to NAC therapy, whereas others showed a trend toward harm with the same drug. They subsequently replicated these results in an independent cohort of patients enrolled in the INSPIRE trial. Although the initial trial (PANTHER-IPF) did not show any benefit of NAC in IPF, the authors show that genetic predisposition may make certain IPF subjects respond to this therapy, while warning against the indiscriminate use of NAC given the harm signal observed with a different allele profile. These novel findings still need to be replicated in large randomized clinical trials and could signal the start of a new era of personalized medicine for patients with IPF.


DR. ALLAM

Dr. J. Shirine Allam, FCCP
Steering Committee Member

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BTG