Celebrating 10 Years
VOL. 11 • NO. 8 • AUGUST 2016

CHEST® Physician

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Courtesy University of Miami

Dr. Marilyn K. Glassberg, FCCP, (at right) with the multidisciplinary team at the University of Miami Health System. From left to right, Dr. David De La Zerda, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine; Dr. Dana Ascherman, Department of Rheumatology & Immunology; Dr. Nilesh Kashikar, Department of Pathology; and Dr. Joel Fishman, Professor of Diagnostic Radiology.

Opioid overdose epidemic is being felt in the ICU

Admissions are up 150% since 2009.

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – The opioid overdose crisis in the United States is now plainly evident in intensive care units (ICUs), finds a study conducted from 2009-2015 in hospitals in 44 states.

During the study period, ICU admissions for opioid overdoses increased nearly 150%, investigators reported in a session and a related press briefing at an international conference of the American Thoracic Society. Further, ICU deaths from opioid overdoses have roughly doubled.

"This means the opioid use epidemic has probably reached a new level of crisis," said lead investigator Jennifer P. Stevens, MD, an instructor in medicine at Harvard Medical School, and an adult intensive care physician at Beth Israel Deaconess Medical Center, both in Boston. "In spite of everything that we can do in the ICU – keeping them alive on ventilators, doing life support, doing acute dialysis, doing round-the-clock care and round-the-clock board-certified intensivist care – we are still not able to make a difference in that mortality."

Dr. Stevens added that

See **Opioids** • *page 6*

INSIDE

Teams boost accuracy of IPF diagnoses

BY KATIE WAGNER LENNON
Frontline Medical News

The accuracy of idiopathic pulmonary fibrosis (IPF) diagnoses is improving with the use of multidisciplinary team meetings and updated guidelines, based on the findings of a study that compared the diagnostic agreement of individual clinicians and teams evaluating patients with interstitial lung disease.

Pulmonologists who participate in multidisciplinary team meetings said the findings validate the approach.

"The [study's] data confirm what we see in clinical practice ... it takes a multidisciplinary team – and perhaps often multiple pulmonologists – to review these cases," Marilyn K. Glassberg, MD, FCCP, Professor of Medicine, Surgery, and Pediatrics; Division of Pulmonary, Allergy, Critical Care and Sleep Medicine; and Director of the Rare and Interstitial Lung Disease Program at the University of Miami Health System, said in an interview."This study

See **Teams** • *page 7*

Apnea device effective at 42 months

BY BRUCE JANCIN
Frontline Medical News

DENVER – The surgically implanted Inspire system for controlled upper airway stimulation as therapy for moderate to severe obstructive sleep apnea demonstrated sustained benefit at 42 months of prospective follow-up in the STAR trial, Patrick J. Strollo Jr., MD, FCCP, reported at the annual meeting of the Associated Professional Sleep Societies.

STAR was the pivotal trial whose previously reported 12-month outcomes led to Food and Drug Administration clearance of the device. Dr. Strollo was first author of that paper (N Engl J Med. 2014 Jan 9;370:139-49). At SLEEP 2016, he presented patient- and partner-reported outcomes at 42 months. Bottom line: The device had continued safety and no loss in efficacy.

"So far it seems to be a useful option for people who frequently didn't have an option. And the technology is improving and will

See **Apnea** • *page 4*

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  - —**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[2,3]**
- **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006[2,4]**
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)[2]

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  - —eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash

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

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter 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 $\%DL_{co}$ (percent predicted diffusing capacity of lung for carbon monoxide) between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. The primary endpoint was change in %FVC from baseline to week 72.

†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.

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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.

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.

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

References: 1. Data on file. Genentech, Inc. 2015. **2.** Esbriet Prescribing Information. Genentech, Inc. September 2015. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083-2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760-1769. **5.** 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 [published correction appears in *Am J Respir Crit Care Med.* 2015;192(5):644]. *Am J Respir Crit Care Med.* 2015;192(2):e3-e19.

Esbriet®
(pirfenidone) capsules 267 mg

Device stimulates upper airway

Apnea *from page 1*

only get better," said Dr. Strollo, professor of medicine and clinical and translational science, director of the Sleep Medicine Center, and codirector of the Sleep Medicine Institute at the University of Pittsburgh.

The Inspire system consists of three parts implanted by an otolaryngologist in an outpatient procedure: a small impulse generator, a breathing sensor lead inserted in the intercostal muscle, and a stimulator lead attached to the distal branch of the 10th cranial nerve, the hypoglossal nerve controlling the tongue muscles.

The device is programmed to discharge at the end of expiration and continue through the inspiratory phase, causing the tongue to move forward and the retrolingual and retropalatal airways to open.

Upper airway stimulation is approved for commercial use in patients such as those enrolled in the STAR trial on the basis of pilot studies that identified most likely responders. The key selection criteria include moderate to severe obstructive sleep

apnea as defined by an apnea-hypopnea index of 20-50, nonadherence to continuous positive airway pressure (CPAP), a body mass index of 32 kg/m^2 or less, and absence of concentric collapse of the airway at the level of the palate during sedated endoscopy.

STAR included 126 participants who received the upper airway stimulation device. There have been two explants: one from septic arthritis, the other elective.

A total of 97 STAR participants had 42-month follow-up data available. Among the key findings were that:

• Mean scores on the Epworth Sleepiness Scale were 11.6 at baseline, 7 at 12 months, and 7.1 at 42 months.

• Scores on the Functional Outcomes of Sleep Questionnaire improved from 14.3 at baseline to 17.3 at 12 months and 17.5 at 42 months.

• Scores on the Epworth Sleepiness Scale and Functional Outcomes of Sleep Questionnaire were abnormal at baseline and converted to normal range at 12 and 42 months.

• At baseline, 29% of the patients' sleeping partners characterized the snoring as loud, 24% rated it 'very intense,' and 30% left the bedroom. At 32 months, 11% of partners called the snoring loud, 3% deemed it very intense, and 4% left the room.

• At 42 months, 81% of patients reported using the device nightly. That's consistent with the objective evidence of adherence Dr. Strollo and his coinvestigators obtained in a study of postmarketing device implants in which they found device usage averaged about 7 hours per night.

DR. STROLLO

The 5-year follow-up of STAR will include a full lab polysomnography study to obtain objective apnea-hypopnea index figures.

Given that only about 50% of patients with moderate to severe sleep apnea are able to tolerate CPAP long term, where does the Inspire system fit into today's practice of sleep medicine?

"In my practice, normally I'd let patients try positive pressure first. I want to make sure they've tried CPAP, and they've tried more advanced therapy like autotitrating bilevel positive airway pressure ... I also offer an oral appliance," Dr. Strollo said.

The STAR trial is supported by Inspire Medical Systems. Dr. Strollo receives a grant from the company.

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VIEW ON THE NEWS

Krishna M. Sundar, MD, FCCP, comments: For 97 out of the 126 participants with moderate to severe OSA who received the upper airway stimulation device, investigators provide compelling data at 42 months of follow-up for efficacy and high rate of compliance with the hypoglossal nerve stimulator as the only therapy for OSA. Further refinements in hypoglossal nerve stimulation technologies and better understanding of upper airway properties in individuals with OSA will result in better patient selection for upper airway stimulation therapy.

Rise in ICU deaths

Opioids *from page 1*

any ICU admission for overdose from opioids is a preventable admission. "So if we have an increase in mortality of this population, we have a number of patients who have preventable deaths in our ICU," she said.

Efforts to track this epidemic on a national level are important, she said, and the U.S. Centers for Disease Control and Prevention has been investigating opioid overdoses in some cities, including Boston, as they would any epidemic.

The factors driving the observed trends could not be determined from the study data, Dr. Stevens said. But state-specific patterns that show, for example, higher baseline rates and greater increases over time in ICU admissions for opioid overdose in Massachusetts and Indiana may be a starting point for investigation.

Certain practices in the ICU may also be inadvertently contributing. "I imagine that a patient who comes in with an opioid overdose can cause harm to themselves in a number of ways, and the things that we try to do to help them might cause harm in other ways as well," she said. "So in an effort to try to maintain them in a safe, ventilated state, we might give them a ton of sedation that then prolongs their time on the ventilator. That's sort of a simple example of how the two could intersect to have a multiplicative effect of harm."

The idea for the study arose because ICU staff anecdotally noticed an uptick in admissions for opioid use disorder. "Not only were we seeing more people coming in, but we were seeing sicker people coming in, and with the associated tragedy that comes with a lot of young people coming in with opioid use disorder," Dr. Stevens said. "We wanted to see if this was happening nationally... We asked, is this epidemic now reaching the most technologically advanced parts of our health care system?"

SUSAN LONDON/FRONTLINE MEDICAL NEWS

ICU deaths due to opioid overdoses rose 87%, Dr. Jennifer P. Stevens said.

The investigators studied hospitals providing data to Vizient (formerly the University HealthSystem Consortium) between 2009 and 2015. The included hospitals – about 200 for each study year – were predominantly urban and university affiliated, but representation of community hospitals increased during the study period.

Analyses were based on a total of 28.2 million hospital discharges of patients aged 18 years or older, which included 4.9 million ICU admissions.

Based on billing codes, 27,325 patients were admitted to the study hospitals' ICUs with opioid overdose. Opioid overdose was seen in 45 patients per 10,000 ICU admissions in 2009 but rose to 65 patients per 10,000 ICU admissions in 2015, a 46% increase.

Furthermore, ICU deaths due to opioid overdose rose by 87% during the same time period, and mortality among patients admitted to the unit with overdose rose at a pace of 0.5% per month.

"This is somewhat unusual because a lot of times, when we are admitting more people to our ICUs or examining [a trend] further, mortality actually goes down. This is partly because maybe we are doing more for them and we are taking care of them in an aggressive way. But it's also because we are admitting less sick people because we are more aware of the issue," Dr. Stevens said. "And we saw the opposite of this – we saw that the mortality was going up."

The use of billing data was a specific means but not a sensitive means of identifying opioid overdoses, she noted. Therefore, the observed values are likely underestimates of these outcomes.

Addressing the opioid overdose epidemic will require a multifaceted approach, according to Dr. Stevens, who disclosed that she had no relevant conflicts of interest.

"Folks are doing very impressive work in the community trying to make sure EMTs and other first responders have access to the tools that they need," she said. "But one thing we haven't approached before is the care that we provide in the ICU, and maybe that's a space that we need to think more prospectively about."

IN THIS ISSUE

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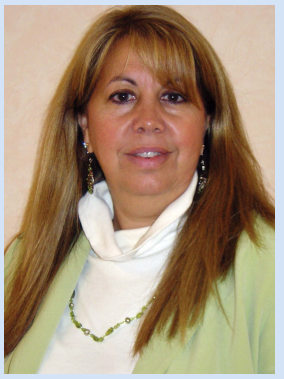

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CHEST Physician (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $230.00 per year. Phone 973-206-3434, fax 973-206-9378.

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Accuracy of IPF diagnoses

Teams *from page 1*

demonstrates the importance of multiple perspectives when evaluating a patient and coming to a diagnosis at a time when reliable biomarkers are not available."

The study, published in The Lancet Respiratory Medicine (2016;4[7]:557-65), is the first evaluation of multidisciplinary team agreement on diagnosis of interstitial lung disease since updated guidelines were published, according to Simon L. F. Walsh, MD, of Kings College Hospital NHS Foundation Trust, London, and his colleagues.

In 2015, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALTA) adopted joint guidelines for treating IPF. In 2013, the ATS and ERS updated guidelines for the classification and terminology for idiopathic interstitial pneumonias.

"Our study shows ... in [IPF], MDTMs (multidisciplinary team meetings) have a higher level of agreement on diagnoses, assign diagnoses with higher confidence more frequently, and provide diagnoses that have non-significant greater prognostic separation than do clinicians or radiologists in most cases," the researchers wrote.

Before MDTMs were initiated, the clinicians, radiologists, and pathologists who would be participating in them independently reviewed each patient's case without consulting other specialists and provided up to five diagnoses with diagnostic likelihoods for each patient.

For the study, 70 patients were evaluated and the level of diagnostic agreement was assessed at seven international centers for the diagnosis of interstitial lung disease (diffuse parenchymal lung disease). Following independent reviews of the 70 cases, the clinician, radiologist, and pathologist from each center met as a team to review the same cases together and give up to five diagnoses with diagnostic likelihoods.

VIEW ON THE NEWS

Daniel R. Ouellette, MD, FCCP, comments: "Recommendations have been that multidisciplinary teams add to the accuracy of the diagnosis of IPF. The value of this study is that it provides objective data that this is so."

All clinical information supplied in the first stage of the study, including pulmonary function test results, high-resolution CT at presentation, and digitalized surgical lung biopsy slides, were available to the multidisciplinary team. The patients' outcomes were used to validate the diagnoses.

The inter-MDTM agreement was better than interobserver agreement for all diagnoses (unweighted kappa value (K) = 0.50). The inter-MDTM agreement was highest for IPF (K = 0.60) and connective tissue disease-related interstitial lung disease (K = 0.64).

"We have shown an acceptable level [based on a K of greater than 0.40 being deemed clinically acceptable] of diagnostic agreement exists between multidisciplinary teams in the setting of diffuse parenchymal lung disease. Additionally, we showed that this agreement was validated by the non-significant increases toward greater prognostic separation of an IPF diagnosis made by multidisciplinary teams than by individual clinicians or radiologists," the researchers wrote.

The weighted kappa (KW) values for estimation of diagnostic likelihood for diagnoses of IPF were 0.72 (0.67-0.76) for clinicians, 0.60 (0.46-0.66) for radiologists, 0.58 (0.45-0.66) for pathologists and 0.71 (0.64-0.77) for MDTMs.

For connective tissue disease–related interstitial lung diseases, the KW for estimation of diagnostic likelihood for diagnoses for MDTMs were 0.73 (0.68-0.78), compared with 0.76 (0.70-0.78) for clinicians, 0.17 (0.08-0.31) for radiologists, and 0.21 (0.06-0.36) for pathologists.

Krishna Thavarajah, MD,, who sees patients with interstitial lung disease within the Henry Ford Health System in Detroit, has been participating in MDTMs for nearly 6 years.

"The accuracies of diagnoses for patients with IPF are much better than even 10 years ago," she said in an interview. "I think this is because of the improvement in consistency in diagnostic criteria based on the updated guidelines in IPF. Among the MDTMs that participated in the study, the agreement about diagnoses was highest for IPF. The interobserver agreement for clinicians was also pretty high for IPF."

In her work within an academic center, Dr. Glassberg sees patients in an IPF clinic and in a separate autoimmune disorders clinic. For each clinic, there is a multidisciplinary team. In the IPF clinic, there are three pulmonologists and a radiologist, and when there is a biopsy, there are two pathologists. Dr. Glassberg's IPF team also includes four pulmonary radiologists.

During her MDTMs, Dr. Thavarajah, a radiologist, and a pathologist will examine a patient's chest imaging and pathology slides. They sit together until they become confident of their diagnosis in the absence of a biopsy.

There are times when the team tells a patient the probable diagnosis and acknowledges the small chance of an alternative diagnosis. "It was comforting to me that, in the Lancet study, there was a good level of agreement in diagnosis of IPF among multidisciplinary teams, whether the patients had undergone a biopsy or not," said Dr. Thavarajah. "The mortality of patients given a diagnosis of IPF was worse than those given a diagnosis of non-IPF to validate the IPF diagnosis."

Establishing and implementing MDTMs is challenging, though, said Dr. Glassberg.

"[We] need to address how multidisciplinary teams could work for doctors who are in smaller cities or who are not in academic centers. We need to utilize existing channels to create new avenues for these colleagues to present their cases – particularly challenging ones or patients who need to be referred – to be evaluated by an interdisciplinary team. The Internet may offer these opportunities for networking and decision making, said Dr. Glassberg.

The study was funded by the National Institute of Health Research, Imperial College London. Several of the study's authors declared receiving personal fees, grants, or research support from a variety of sources, but had no financial disclosures relevant to this study.

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Diffuse alveolar damage boosts death risk in ARDS

BY KATIE WAGNER LENNON
Frontline Medical News

FROM CHEST

Among patients with acute respiratory distress syndrome (ARDS), those who are also diagnosed with diffuse alveolar damage (DAD) via an open lung biopsy face nearly twice as high a mortality risk as do those without DAD, based on a meta-analysis by Pablo Cardinal-Fernandez, MD, PhD, and his colleagues.

ARDS with DAD appears to be a specific clinicopathological entity different from ARDS without DAD," said Dr. Cardinal-Fernandez of the department of genetic medicine, Cornell University, New York, and his colleagues (CHEST 2016 149:1155-64.). The pooled odds ratio for death in patients who had ARDS with DAD, compared with patients with ARDs who did not have DAD was 1.81.

"Our meta-analysis underscores the need for less-invasive approaches to individualize therapy for patients with ARDS, including the development of biomarkers for predicting responses to treatments," they wrote.

The researchers analyzed studies from Jan. 1, 1967, to Sept. 1, 2015. Eight studies involving 350 patients satisfied the researchers' criteria of patients who received an open lung biopsy after being diagnosed with ARDS, histologic results indicating the presence or absence of DAD based on the open lung biopsy, and the mortalities of both a group of patients diagnosed with DAD and a group of patients not diagnosed with DAD.

At the time of ARDS diagnosis, the meta-differences for sequential organ failure assessment scores and the index of hypoxemia (PaO_2/FiO_2) ratio between the patients who had DAD and those who did not were 0.26 and 4.36, respectively.

On the day of open lung biopsy, the meta-differences for the sequential organ failure assessment score and the PaO_2/FiO_2 ratio between the two patient groups were also small; the meta-difference for sequential organ failure was 0.45 and the meta-difference for the PaO_2/FiO_2 ratio was –8.63.

"The mortality heterogeneity of this meta-analysis was low, suggesting that no other variables affect the results (that is, the observed effect depends mainly on the presence of DAD). Patients without DAD may have more favorable responses to specific treatments, the researchers said. Lower tidal volume appeared to be beneficial in all subgroups.

The researchers had no relevant financial disclosures.

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A MACRA primer

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

Most physicians realize that the specter of the Sustainable Growth Rate (SGR) has been replaced by a "new plan" enacted by Congress under the guise of the Medicare Access and CHIP Reauthorization Act (MACRA) of 2015. A major goal of the programs defined by MACRA is to provide quality care while improving value, the Quality Payment Program (QPP).

There are currently two paths for reimbursement from which physicians may choose defined by QPP: the Merit-based Incentive Payment System (MIPS) or the Advanced Alternative Payment Models (APMs). These will be explained in general terms but it would benefit all health-care professionals to visit the CMS website for additional details on the program.

Most physicians will initially choose MIPS by default as most do not currently participate in programs that qualify as APMs. MIPS will eventually result in the demise of the multiple reporting systems presently used by CMS to include the Physician Quality Reporting System (PQRS), the Value-Based Modifier (VBM) Program, and the Medicare Electronic Health Record (EHR) Incentive Program (Meaningful Use). These will be streamlined into a single program, although many of the components are carried through to MIPS (Fig. 1).

Data from health-care providers will be collected through a variety of sources beginning in January 2017 and this will be used to determine the MIPS score as briefly outlined by the colored text in Figure 1. The 2017 data will determine the MIPS Composite Performance Score (CPS).

From 2017 through 2019, CMS will provide a 0.5% increase in payment for services. Between 2020 and 2025, no increase is planned, but starting in 2026, a yearly 0.25% increase in reimbursement is planned. In 2019, physician payment will be adjusted positively or negatively by 4% based upon their MIPS CPS and a threshold CPS determined for all participants. This adjustment will be revenue-neutral, so for every winner there will be a corresponding loser based upon one's MIPS score.

However, there is a scaling factor built into the system for years 2019 to 2024, using up to $500 million to reward those whose CPS are at the highest levels. This adjustment will increase to 5% in 2020, 7% in 2021, and 9% from 2022 onward. Eligible providers can participate as an individual or as a group.

The Advanced Alternative Payment Model, as defined by MACRA, may include a CMS Innovation Center model, MSSP (Medicare Shared Savings Program), Demonstration under the Health Care Quality Demonstration Program, or Demonstration required by federal law.

To be an eligible APM requires that these entities: require participants to use certified EHR technology; base payment on quality measures comparable to those in the MIPS quality performance category; either require APM entities to bear more than nominal financial risk for monetary losses; or be a Medical Home Model expanded under Center for Medicare and Medicaid Innovation authority.

To become a qualifying participant (QP) one must have either a percentage of payments or a percentage of patients through an eligible APM. CMS will calculate a threshold score using Medicare Part B data for professional services and payments in that APM. The percentage of each is illustrated in Figure 2 and will increase from 2019 to 2024. 2017 will be the first year eligible participants will be assessed to determine whether they qualify. If an eligible participant qualifies, year 2018 base payments will be used to determine year 2019 lump sum payment. This is set at 5%.

Physicians will be required to participate in either the MIPS or APM programs unless they are in their first year of Part B participation or have a low volume of patients.

This cycle will continue each year to determine if the participant qualifies for the lump sum distribution. Qualified APMs will receive a yearly 0.75% increase in base payments starting in year 2026.

If one participates in an APM but does not meet the threshold for QP set by CMS, one receives either no payment adjustment or may opt to participate in MIPS. Beginning in 2021, CMS may count data from other non-Medicare payers to determine eligibility as a QP.

The goal of the Quality Payment Program is to change the way Medicare pays clinicians and to offer financial incentives for providing high value care. Physicians will be required to participate in either the MIPS or APM programs unless they are in their first year of Part B participation or have a low volume of patients. The program will almost certainly continue to change as input is received from many stakeholders, most importantly health-care professionals and patients. Physicians are, therefore, encouraged to learn more about the program to maximize reimbursement.

For more on MACRA, see p 29.

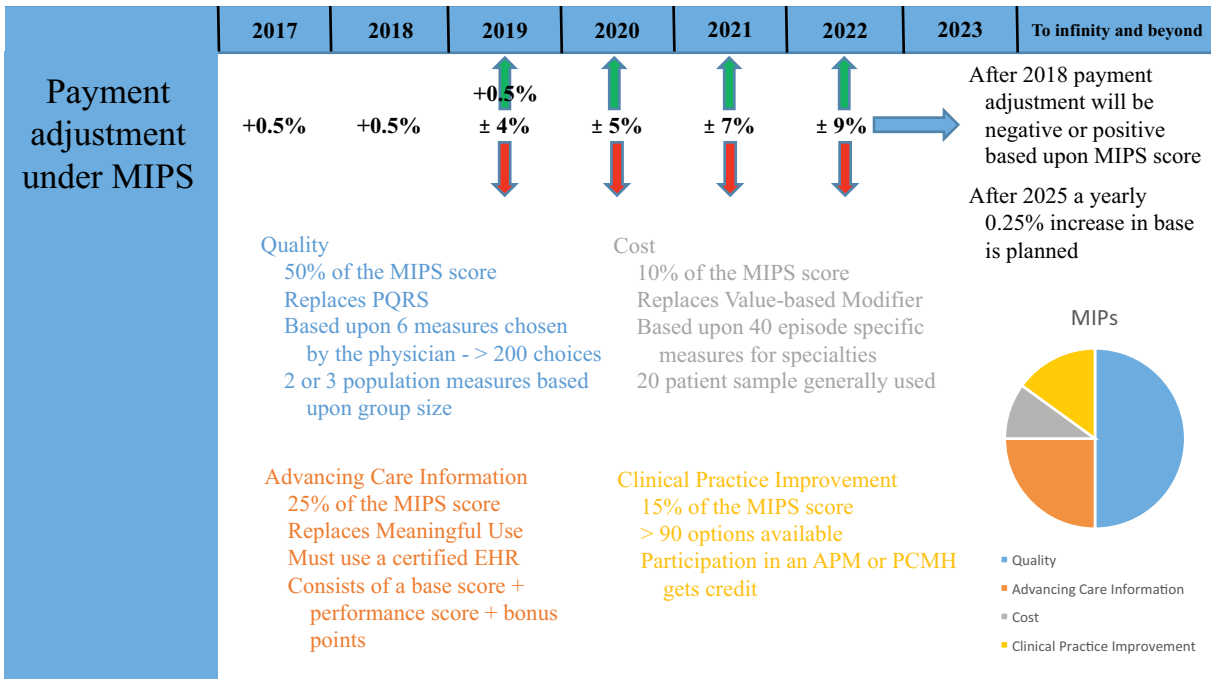

Fig. 1

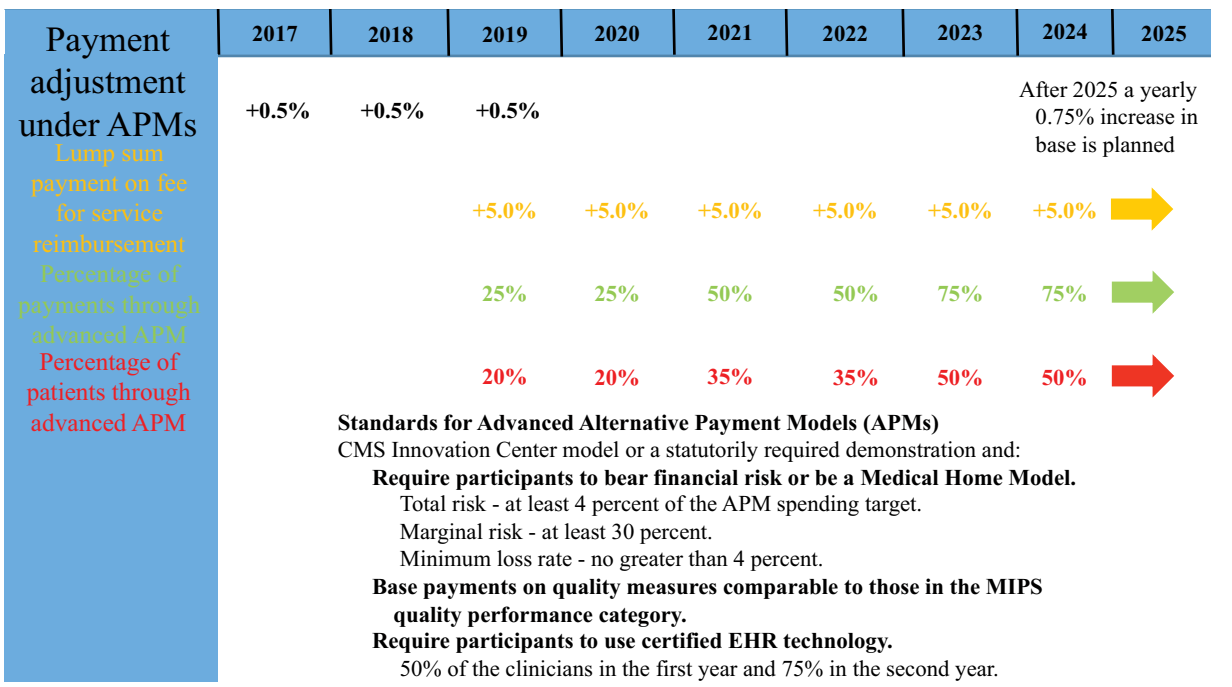

Fig. 2

The power of flexibility is yours with **REVATIO Oral Suspension**

Adjust your dosing to each patient's needs.

With REVATIO you have 3 dosage forms to treat pulmonary arterial hypertension (PAH): oral suspension, tablet, and injection.

To learn more, please visit REVATIOHCP.com

Revatio®
sildenafil

Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α–blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

REVATIO is available in the following dosage forms:

- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)

The Revatio® Family

Available in OS, tablet, and injection forms.

Please see brief summary of Full Prescribing Information on following pages.

Revatio®
sildenafil

Revatio® sildenafil 20 mg tablets

Brief Summary of Prescribing Information. Consult Full Prescribing Information at REVATIOHCP.com

INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension *[see Warnings and Precautions]*, Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations]*.

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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.

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications]*.

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only Rev. June 2015

Pulmonologists unsure about using handheld small-volume nebulizers

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Pulmonologists are knowledgeable about inhalational devices used in the treatment of chronic obstructive pulmonary disease (COPD), but there are areas where more education would be welcomed, based on a survey conducted by Harris Poll on behalf of the American Thoracic Society and sponsored by Sunovion Pharmaceuticals.

More than half of respondents believed that they were at least very knowledgeable about medications used to treat COPD and the devices as a whole, Sidney S. Braman, MD, FCCP, professor of medicine; pulmonary, critical care, and sleep medicine at the Icahn School of Medicine at Mount Sinai in New York, reported in a press conference and poster session at an international conference of the American Thoracic Society.

But only a third knew what handheld small-volume nebulizers were intended for or how to use them, and respondents varied in their views regarding which patients are candidates for use.

The survey assessed knowledge, attitudes, and practices regarding the management of COPD, including the use of metered-dose inhalers, dry powder inhalers, and handheld small-volume nebulizers. In all, 205 U.S. pulmonologists and pulmonology fellows participated.

During an interview, press conference moderator David Mannino, MD, FCCP, professor and chair of preventive medicine and environmental health at the University of Kentucky College of Public Health in Lexington, said he was not surprised by the survey's results.

"Years ago and certainly when I was going through training as a resident, there was this body of literature being developed showing that respiratory therapists working with patients in hospitals with the use of metered-dose inhalers and spacers got results that equaled that of the nebulizer, which I frankly never bought because although the data may have supported that, people don't take respiratory therapists home with them. ... I know my sick patients cling to their nebulized therapies very stringently.

"Ultimately, we have patients who very much would benefit by having a truly very small nebulizer that they could take with them because the problem with inhaled therapies in COPD – your metered-dose inhalers, your dry powder inhalers, and all these other devices – is that you basically get one opportunity in some-

Dr. Sidney S. Braman

Dr. David Mannino

where between about half a second and 2 seconds to get your dose of medication in," Dr. Mannino said.

"Even when you throw a spacer on, it does not pass what I would call the 'my mom test,'" meaning that use would be difficult for an older adult with suboptimal hand-eye-breathing coordination and comorbidities such as arthritis and cognitive impairment, he added.

In contrast, nebulizers deliver medication during a full 2-3 minutes of tidal breathing. Patients "have more of an opportunity to get the medication," Dr. Mannino maintained.

"Ultimately, what I'd love to see is a nebulizer that is truly the size of a little metered-dose inhaler. That will then be the game changer, I think," he said.

PULMONARY PERSPECTIVES® Enhanced ENB Technology

BY ERIC L. FLENAUGH, MD, FCCP; AND MARILYN G. FOREMAN, MD, FCCP

Following the National Lung Screening Trial (NLST), which showed at-risk patients screened with CT scans had reduced lung cancer-specific mortality, many institutions have incorporated lung cancer screening protocols into clinical practice (Aberle et al. *N Engl J Med*. 2011;365[5]:395). These protocols, along with new generation, high resolution multidetector CT scans, have increased the number of detected peripheral lung nodules, many smaller in size. It is estimated that over 150,000 solitary nodules are diagnosed each year in the United States (Herth et al. *Expert Rev Respir Med*. 2016; 0[8]:901) and, in keeping with the NLST, greater than 25% of subjects screened have lung nodules suspicious for lung cancer. As a result, many leading health practices have created specific lung nodule programs to handle the volume in an effort to deliver timely care in the evaluation of lung cancer.

Pulmonary specialists managing patients with lung nodules are faced with the difficult challenge of deciding if a patient with a nodule is a candidate for serial surveillance, tissue biopsy (transthoracic needle aspiration [TTNA] vs bronchoscopic biopsy [TBX]), or surgical resection.

Calculation of the probability of a nodule being malignant is most helpful in making these decisions for patients with low and high malignancy risk factors, as surveillance and resection are appropriate steps, respectively. However, for those with an intermediate (5%-65%) probability of having a malignant nodule, the diagnostic procedure risks, yields, and timing have to be considered because delayed sampling or false-negative results may negatively impact survival.

Kanashiki et al (*Oncol Rep*. 2003;10[3]:649) showed that worse survival is associated with patients with imaging-to-diagnosis times of greater than 4 months. Over the past decade, image-guided bronchoscopy has been used to improve the yield for tissue sampling of smaller peripheral nodules in a timely fashion. The most common method of image-guided bronchoscopy today is electromagnetic navigation bronchoscopy (ENB).

Electromagnetic navigation bronchoscopy has shown promise for increasing diagnostic yields for peripheral nodules (PN) over conventional bronchoscopy. Over time, the improved yields have plateaued as ENB use in clinical practice increased and limitations of the early generation technology became apparent.

Earlier ENB technology uses a single inspiratory CT scan of the chest to reconstruct a 3D virtual model of the airways and parenchyma. A tracked sensor is then used to navigate through the imaging reconstructed airways toward the targeted lesion, the sensor is then removed, and through a dedicated catheter instruments are used to obtain samples from the lesion.

In a meta-analysis using this technology, lesions greater than 2 cm

had a diagnostic yield ranging from 66.7% to 94.7%. However, as the PN size decreased to less than or equal to 2 cm, the diagnostic yield range dropped significantly with some yields reported as low as 18.2% (van 't Westeinde et al. *Chest*. 2012;142[2]:377).

More recently, Ost and colleagues performed a multicenter study of consecutive patients undergoing bronchoscopic sampling of PN (Ost et al. *Am J Respir Crit Care Med*. 2016;193[1]:68).

Although it was not a randomized trial and each bronchoscopist influenced the selection of the sampling technique, the authors reported that the diagnostic yields for navigation-guided bronchoscopy were lower than conventional bronchoscopy, 38.5% and 63.7%, respectively.

Taken on face value alone, one might conclude that ENB not be used to biopsy PNs. However, deeper analysis of the data showed that 97% of the ENB procedures were performed using the earlier technology described above, suggesting that the single inspiratory imaging CT scan and navigation procedure technique, which differs significantly from conventional bronchoscopy, may have some influence on the lower than expected yields.

Despite increasing use and experience with ENB, diagnostic yields remain static. Chen and colleagues hypothesized that using a single inspiratory CT scan may not allow the endoscopist to make adjustments for PN movement as the lung moves during the respiratory cycle.

Using different imaging protocol, the investigators assessed movement of 85 lung nodules during the respiratory cycle with paired-full inspiration and tidal-volume expiration, thin sliced (0.5-1.0 mm) CT scans. They found that the average motion of all lesions during respiration was 17.6 mm, 12.2 mm in the right-upper lobe, 10.6 mm in the left-upper lobe, and 25.3 mm and 23.8 mm in the right- and left- lower lobes, respectively (Chen et al. *Chest*. 2015;147[5];1275). (Fig. 1)

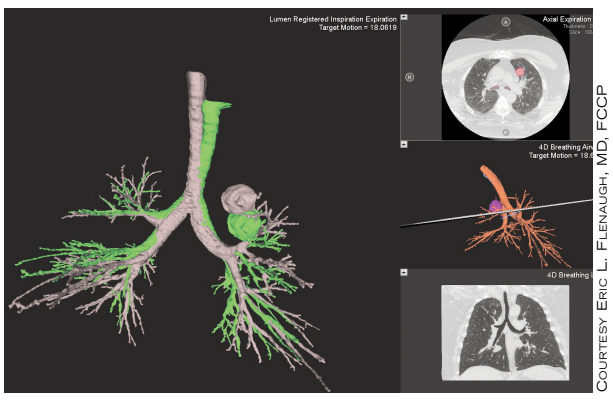

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Fig 1. 3-D reconstruction of the bronchial tree made from paired full-inspiration (grey) & tidal volume-expiration (green) CT images. The left upper lobe nodule migrates 18 mm during the respiratory cycle.

They concluded that the location of targeted lesions on a single inspiration planning CT scan alone does not accurately represent the position of the lesion during bronchoscopy.

Although being able to correct for nodule movement throughout the respiratory cycle during the procedure is a significant improvement, it doesn't guarantee that the tissue sample is obtained from the targeted lesion. To accomplish that, the system would have to be able to determine when the instrument being used to sample is in the target.

The earlier ENB systems allowed for navigation to the target with a separate sensor through a steerable catheter. However, when the target was reached, the sensor had to be removed so that sampling instruments could be introduced into the catheter. Since the instruments are not tracked and the movement of the nodule is occurring, there is no guarantee that the instrument is in the target at the time of sampling.

Advanced technology now allows for the tracking sensor to be placed in the tip of standard bronchoscopy instruments, making them "tip-tracked" and able to be used with standard bronchoscopes and equipment; thus, making the new ENB procedure similar to conventional bronchoscopy that was shown to have higher diagnostic yields (Figs. 2 and 3).

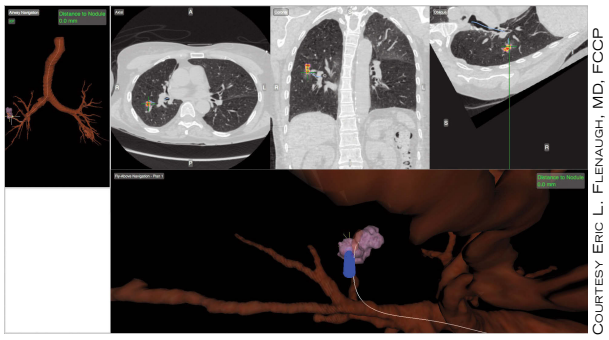

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Fig 2. A tip-tracked biopsy forceps (blue marker) inside the targeted lesion during the expiratory phase of the respiratory cycle during a bronchoscopy procedure.

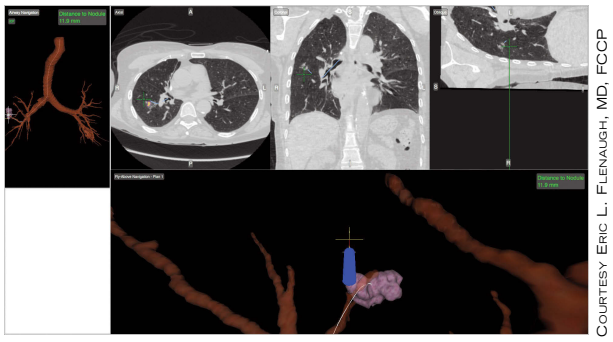

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Fig 3. Targeted lesion from Fig 2 moved 12 mm away from the tip-tracked biopsy forceps (blue marker) during the inspiratory phase of the respiratory cycle during a bronchoscopy procedure.

Our institution incorporated this technology (Veran Medical) into our advanced diagnostic and interventional pulmonary program for lung nodules and published our initial experience and results.

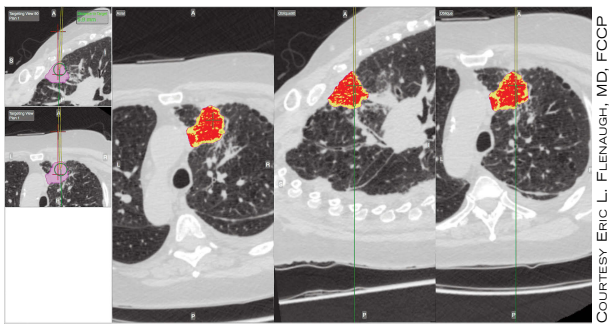
During the initial 8 months of screening for lung cancer, we performed procedures on 44 patients with PNs suspicious for lung cancer.

The rate for successful target sampling was 90.2% with a cancer diagnosis rate of 39%, which is similar to that found in the NLST. Those patients who had nonmalignant but abnormal pathologic findings (inflammation, granuloma, fibrosis, and so on) were monitored for a minimum of 12 months. Most of the lesions either remained stable or disappeared on follow-up imaging (Flenaugh et al. *The Internet Journal of Pulmonary Medicine*. 2016;18[1]).

We concluded that (1) the combination of paired inspiratory and expiratory CT scan imaging accounts for nodule movement and (2) using tip-tracked conventional instruments to enter into the lesion at the time of biopsy contributes to improved yields.

Newer ENB technology is not limited to transbronchial sampling. For PNs less than 2 cm and deep in the lung periphery, current recommendations prefer TTNA over bronchoscopic biopsy because of yield rates of 90% (*Chest*. 2007; 132(suppl 3):131S).

Using the same paired CT scanning and tip-tracking method on transthoracic needles, the new systems allow pulmonologists to perform electromagnetic transthoracic needle aspiration (ETTNA) of PNs using the same basic equipment and during the same procedure visit (Fig. 4).



COURTESY ERIC L. FLENAUGH, MD, FCCP

Fig 4. The real-time use of a tip-tracked percutaneous needle to perform ETTNA of a peripherally based lung nodule.

This "one stop shopping" approach of bronchoscopy with the option of converting to ETTNA if the PN is not reachable endoscopically has proven to be cost efficient and allows for timely diagnosis and focused care (Yarmus et al. *J Thorac Dis*. 2016;8(1):186).

In a prospective study designed specifically to assess feasibility, safety, and diagnostic yield of ETTNA in a single procedure, Yarmus and colleagues enrolled 24 patients to undergo endobronchial ultrasound for lung cancer staging followed by ENB and ETTNA. Ninety-six percent of the patients were candidates for ETTNA.

The authors reported the yield for ETTNA was 83%, ETTNA plus ENB 87%, and ETTNA plus ENB plus endobronchial ultrasound for complete staging was 92%. Five pneumothoraces were reported; however, only two (8%) required a drainage intervention.

This protocol is unique because it makes use of several advanced diagnostic procedures, including tip-tracked navigation technology, to localize, sample, diagnose, and stage during one patient procedure visit.

As lung cancer screening becomes commonplace in clinical practice and imaging technology improves, pulmonary specialists can expect to encounter and manage a greater number of pulmonary nodules.

Advancements in technology now offer options for improving diagnostic accuracy while providing timely, safe, and cost effective care. While not all new technology will prove beneficial in disease management, those that improve the deficiencies of earlier technology offer us the best chance to improve practice. This perspective highlights such technology.

Dr. Flenaugh is Associate Professor, Director of Advanced Diagnostic & Interventional Pulmonary Service, Morehouse School of Medicine and Grady Hospital; Dr. Foreman is Professor of Medicine, Associate Chair for Research, Pulmonary & Critical Care Medicine, Morehouse School of Medicine, Atlanta.

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.

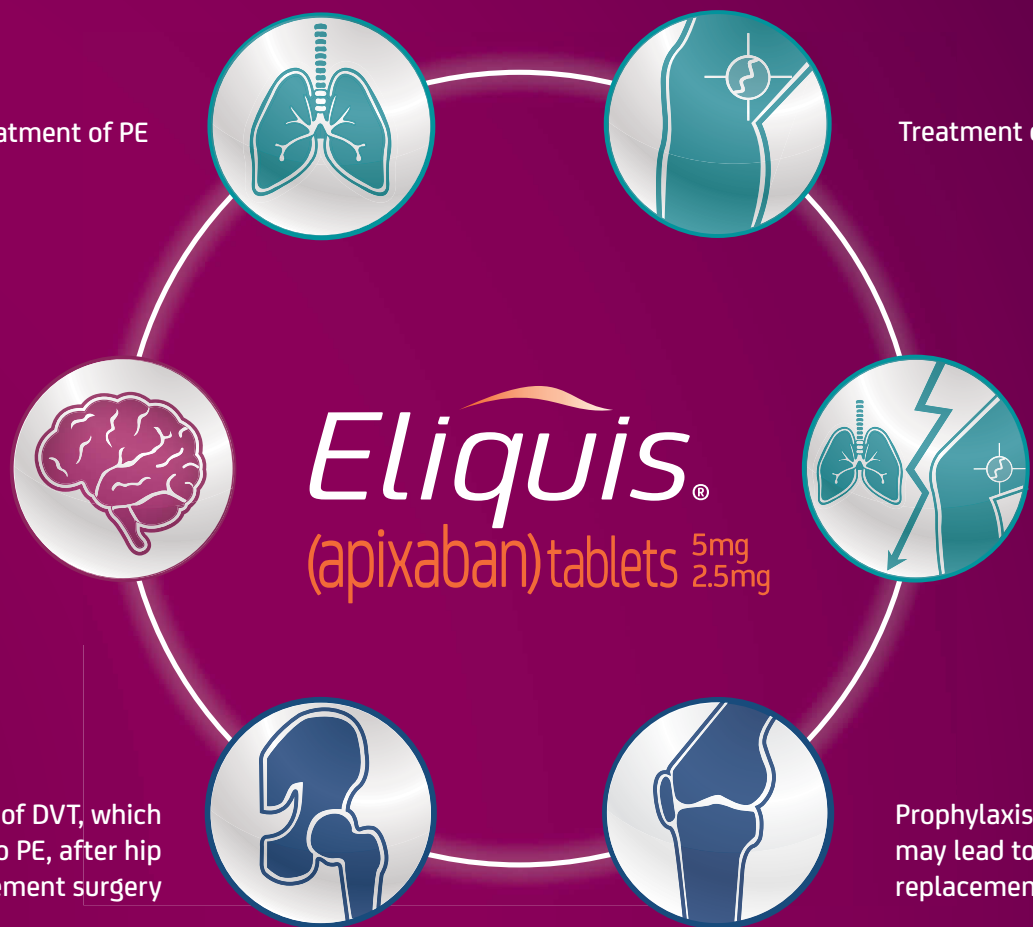
DRUG INTERACTIONS

- **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.

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

1356615A0 / 1356514A0 Rev September 2015

432US1501679-06-01

Aspergillosis guidelines endorse galactomannan

BY M. ALEXANDER OTTO
Frontline Medical News

New aspergillosis guidelines from the Infectious Diseases Society of America recommend serum and bronchoalveolar lavage galactomannan as a marker for the diagnosis of invasive *Aspergillus* in adult and pediatric patients who have hematologic malignancies or have undergone hematopoietic stem cell transplants.

Serial monitoring of serum galactomannan (GM) is also useful to monitor disease progression, therapeutic response, and prognosis in hematologic malignancy and hematopoietic stem cell transplant (HSCT) patients who have elevated baseline GM (Clin Infect Dis. 2016 Jun 29. doi: 10.1093/cid/ciw326).

Although not very specific for infection, serum beta-D-glucan assays also are recommended for diagnosing invasive *Aspergillus* in these high-risk patients.

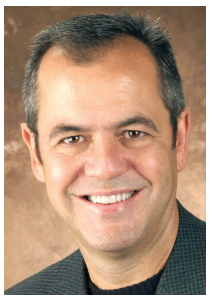
The advice illustrates the Society's emphasis on early diagnosis in its new guidelines, which supplant the group's 2008 guidance. There are almost 100 recommendations covering the management of invasive, allergic, and chronic *Aspergillus* infections in all their manifestations.

"Aspergillosis mortality rates have decreased significantly in recent years, but there is still significant mortality from the infection, and we have a ways to go. We felt that early diagnosis was key, which is why it's such an important part of these guidelines," lead author Thomas Patterson, MD, chief of the division of infectious diseases at the University of Texas Health Science Center, San Antonio, said in an interview.

"We know a lot more since 2008 about the benefits of using biomarkers like GM in bronchoalveolar lavage samples, which could be highly useful for diagnosis. However, biomarkers have not been as well validated for biologic response and are not recommended" in most cases for monitoring how well patients are doing. Also, "biomarkers are not as useful in solid organ transplants; we discuss that" in the guidelines, Dr. Patterson said.

Although there has been a lot of work on polymerase chain reaction (PCR) testing of blood samples for diagnosis, the evidence isn't strong enough yet to establish overall clinical benefit. There is emerging evidence for the diagnostic use of PCR in conjunction with radiologic findings, the guideline writers concluded.

For treatment, voriconazole remains the go-to drug, but the guidelines make room for more recently approved therapies. "We now have isavuconazole, which may be better tolerated," but it's recommended only as an alternative to voriconazole because evidence comes mostly from a single clinical trial, he said.



We felt that early diagnosis was key, which is why it's such an important part of these guidelines.

DR. PATTERSON

Posaconazole extended-release tablets are strongly recommended as prophylaxis based on high-quality evidence from studies in neutropenic patients. Posaconazole extended-release tablets result in significantly higher antifungal blood levels than those seen with voriconazole, and "it certainly has been useful in some patients"; however, posaconazole is not approved for primary therapy in the United States, Dr. Patterson said.

A large clinical trial that tested voriconazole plus an echinocandin against voriconazole alone found that in patients diagnosed using serum galactomannan – especially those with hematologic malignancies – outcomes were better with the combination. "The panel felt combinations could be considered in some patients" but didn't recommend them for routine use because [again,] there's not strong evidence," he said.

For now, it seems that higher-risk patients might be the ones who benefit most from combination therapy. "We also discussed allergic and saprophytic diseases. We know that some patients with allergic bronchopulmonary aspergillosis will respond to antifungal therapy, and perhaps reduce their need for steroids, so that's now part of the suggestions, as well," he said.

The IDSA funded the work. Dr. Patterson has been an adviser to numerous drug companies.

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Blood *Aspergillus* RNA may mark invasive disease

BY M. ALEXANDER OTTO
Frontline Medical News

Elevated *Aspergillus* RNA blood levels after 4-6 weeks of antifungal treatment predict poor response at week 12 in patients with proven or probable invasive aspergillosis, according to results of a small observational study of 41 evaluable patients.

The study attempted to address the need for reliable biomarkers of early invasive aspergillosis treatment response. Standard clinical and radiological criteria are somewhat subjective, and serial biopsies and bronchoalveolar lavage are often impractical, reported Yanan Zhao, PhD, of the New Jersey Medical School–Rutgers Biomedical and Health Sciences, Newark, and her associates.

NASBA has been used before to diagnose invasive aspergillosis, but using it to monitor treatment "is still in its infancy."

Study participants' blood was checked for serum galactomannan (GM), 1, 3-beta-D-glucan (BG), and *Aspergillus* RNA within 24 hours of starting antifungal therapy, then twice per week during the first 2 weeks, then once during weeks 4, 6, and 12, the investigators reported (Med Mycol. 2016 Jun 22. pii: myw043).

Ribosomal *Aspergillus* RNA – like GM and BG, a marker of fungal load – was measured by nucleic acid sequence-based amplification (NASBA), a robust isothermal amplification technique more sensitive than polymerase chain reaction due largely "to increased starting target numbers (RNA versus DNA) and more robust amplification." NASBA has been used before to diagnose invasive aspergillosis, but using it to monitor treatment "is still in its infancy," the authors noted.

Eleven of 14 patients who did not respond to treatment at 12 weeks (79%) had *Aspergillus* RNA in their blood after 4 weeks of treatment, and 12 (86%) were positive at 6 weeks.

Among patients who did respond at 12 weeks, 11 of 27 (41%) had RNA in their blood at 4 weeks, and 14 (52%) at 6 weeks. The findings were statistically significant.

There was no correlation between *Aspergillus* RNA and serum GM levels in terms of outcomes, but the kinetics of circulating *Aspergillus* RNA correlated with BG in some patients, with an excellent match in three.

Serum GM responds fairly soon if treatment is working. *Aspergillus* RNA, however, responds more slowly, like BG. "This may explain ... the correlation between *Aspergillus* RNA and BG ... Therefore, the combination of *Aspergillus* RNA and BG might be useful to assess therapeutic response, particularly in GM negative cases," the investigators said.

This work was funded by Merck. Four investigators are current or former employees of Merck.

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ICU-based therapy fails to shorten hospital stay

BY HEIDI SPLETE
Frontline Medical News

Standardized rehabilitation therapy did not reduce hospital length of stay in patients with acute respiratory failure, based on data from a randomized trial of 300 adults published online in JAMA.

Hospital length of stay averaged 10 days for patients in the standardized rehabilitation therapy group (SRT) and 10 days in the control group that received usual ICU care, wrote Peter E. Morris, MD, of the University of Kentucky, Lexington, and his colleagues (JAMA. 2016 Jun;315:2694-702. doi: 10.1001/jama.2016.7201).

The patients were followed for 6 months; 84 patients in the SRT group and 81 in the usual care group completed the study. Patients in the SRT group received daily therapy including passive range of motion, physical

therapy, and progressive-resistance exercises. The usual care group received weekday physical therapy as determined by the clinical team.

The researchers also assessed secondary outcomes related to physical function and quality of life, including ventilator days, Short Physical Performance Battery (SPPB) score, handgrip, Mini-Mental State Examination, and Functional Performance Inventory (FPI).

Overall, there was no difference in duration of ventilation or ICU care, and scores of handgrip strength and mental health also were similar at 6 months' follow up. However, the SF-36 physical function scores were significantly higher in the SRT group (difference, 12.2; 95% confidence interval, 3.8-20.7; $P = .001$), and the FPI scores and SPPB scores were higher, compared with the usual care group at 6 months.

"In view of the SPPB, SF-36 PFS, and FPI data at 6 months, the SRT group demonstrated a potential signal of improvement compared with the usual care group that was not evident at hospital discharge," they wrote.

The study was supported by the National Institutes of Health, National Institute of Nursing Research, and the National Heart, Lung, and Blood Institute. Dr. Morris had no financial conflicts.

Staffing, work environment drive VAP risk in the ICU

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – The work environment for nurses and the physician staffing model in the intensive care unit influence patients' likelihood of acquiring ventilator-associated pneumonia (VAP), based on a cohort study of 25 ICUs.

Overall, each 1-point increase in the score for the nurse work environment – indicating that nurses had a greater sense of playing an important role in patient care – was unexpectedly associated with a roughly sixfold higher rate of VAP among the ICU's patients, according to data reported in a session and press briefing at an international conference of the American Thoracic Society. However, additional analyses showed that the rate of VAP was higher in closed units where a board-certified critical

care physician (intensivist) managed and led care rather than an open unit where care is shared.

"We think that the organization of the ICU is actually influencing nursing practice, which is a really novel finding," commented first author Deena Kelly Costa, PhD, RN, of the University of Michigan School of Nursing in Ann Arbor. "In closed ICUs, when you have a board-certified physician and an ICU team managing and leading care, even if the work environment is better, nurses may not feel as empowered to standardize their care or practice."

"ICU nurses are the ones who are primarily responsible for VAP preventive practices: they keep the head of the bed higher than 45 degrees, they conduct oral care, they conduct (patient) surveillance. ICU physicians are involved with writing the orders and ventilator setting management. So how these providers work together could influence the risk for patients developing VAP," Dr. Costa said.

"We need to be thinking a little bit more critically about not only the care that's happening at the bedside... but also at an organizational level. How are these providers organized, and can we work together to improve patient outcomes?"

"I'm not suggesting that we get

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rid of all closed ICUs because I don't think that's the solution," Dr. Costa maintained. "I think from an administrative perspective, we need to be considering what's the organization of these clinicians and this unit, and [in a context-specific manner], how can we improve it for better patient outcomes? That may be both working on improving the work environment and making the nurses feel more empowered, or it could be considering other staffing models."

Some data have already linked a more favorable nurse work environment and the presence of a board-certified critical care physician independently with better patient outcomes in the ICU. But studies of their joint impact are lacking.

The investigators performed a secondary, unit-level analysis of nurse survey data collected during 2005 and 2006 in ICUs in southern Michigan.

In all, 462 nurses working in 25 ICUs completed the Practice Environment Scale of the Nursing Work Index, on which averaged summary scores range between 1 (unfavorable) and 4 (favorable). The scale captures environmental factors such as the adequacy of resources for nurses, support from their managers, and their level of involvement in hospital policy decisions.

The rate of VAP in the same period was assessed using data from more than 1,000 patients in each ICU.

In open ICUs, as the score rose, the rate of VAP fell (from about 16% to 5%), whereas in closed ICUs, as the score rose, so did the rate of VAP (from about 3% to 14%).

The summary nurse work environment score averaged 2.69 points in the 21 ICUs that had a closed physician staffing model and 2.62 points in the 4 ICUs that had an open physician staffing model. The respective rates of VAP were 7.5% and 2.5%.

In adjusted analysis among all 25 ICUs, each 1-point increase in an ICU's Practice Environment Scale score was associated with a sharply higher rate of VAP on the unit (adjusted incidence rate ratio, 5.76; $P = .02$).

However, there was a strong interaction between the score and physician staffing model (P less than .001). In open ICUs, as the score rose, the rate of VAP fell (from about 16% to 5%), whereas in closed ICUs, as the score rose, so did the rate of VAP (from about 3% to 14%).

Dr. Costa had no relevant conflicts of interest. The parent survey was funded by the Blue Cross Blue Shield Foundation of Michigan.

This Month in *CHEST*: Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP
EDITOR IN CHIEF, CHEST

COMMENTARY
Establishing Pulmonary and Critical Care Medicine in China: 2016 Report on Implementation and Government Recognition: Joint Statement of the Chinese Association of Chest Physicians and the American College of Chest Physicians. *By Dr. Renli Qiao et al, on behalf of the China-CHEST PCCM Program Steering Committee.*

CONTEMPORARY REVIEWS IN SLEEP MEDICINE
Cancer and OSA: Current Evidence From Human Studies. *By Dr. M. A. Martinez-Garcia et al.*

ORIGINAL RESEARCH
Association Between Occupational Exposures and Sarcoidosis: An Analysis From Death Certificates in the United States, 1988-1999. *By Dr. H. Liu et al.*

Nonlinear Imputation of Pao_2/Fio_2 From Spo_2/Fio_2 Among Patients With Acute Respiratory Distress Syndrome. *By Dr. S. M. Brown et al.*

Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD. *By Dr. M. Bafadhel et al.*

A Randomized Controlled Trial of a Novel Sheath Cryoprobe for Bronchoscopic Lung Biopsy in a Porcine Model. *By Dr. L. B. Yarmus et al.*

Catching up with our Past Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to give us a look at what's new.

Dr. Little and wife Louise in Vienna 2015.

Alex G. Little, MD, FCCP
President 1990-1991

Being President of the American College of Chest Physicians was a remarkable and exhilarating experience beginning with my inauguration in 1990. Although I had been active with the College for several years, the responsibility of the presidency entailed a much closer relationship with the organization, the excellent staff, the physician leaders, the greater membership, and notably, Dr. Al Soffer. As the Executive Director, Al was my go to advisor and guide for questions and advice. He and his wife Izzy became good personal friends and that relationship is one of the major benefits of my presidency (although it never resulted in him showing any mercy on the tennis courts).

For me, as a surgeon, one of the appealing aspects of the College, and, in particular, its annual meeting, was its interdisciplinary nature with pulmonologists, surgeons, and cardiologists interacting in a way that more

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Updated patient education guides available

The CHEST Foundation continues to look for new ways to expand our patient education offerings. With the collaboration of the CHEST Foundation's Patient Education Work Group, the Allergy & Asthma NetWork, and CHEST's NetWorks, we have completely revamped Living Well With COPD and Living Well With Asthma (previously titled Controlling Your Asthma). At less than 30 pages each, the guides are more user-friendly, featuring multiple diagrams to supplement instructions, take-away glossaries, easy-to-read infographics, and new FAQs.

The guides are available to order in packs of 25 in the CHEST store. Packs are $50 for members and $62.50 for nonmembers. The new guides are available for viewing online at chestnet.org/asthmainfo and chestnet.org/copdinfo.

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narrowly focused specialty societies rarely provide. Learning alternative perspectives and hearing from other disciplines is always interesting and occasionally critically important for progress toward maximal patient care.

During my tenure, there were several noteworthy events. The College continued to exhibit robust growth

Alex G. Little, MD, FCCP
Convocation 1990

in membership, strengthening its role in supporting chest physicians. We opened the new (amazingly, now the old) headquarters building in Northbrook, signaling a commitment to remain state of the art and joined the challenge of providing continuing medical education for our members.

I retired from clinical practice and as Chair of Surgery at Wright State in 2010 when my wife Louise and I settled in Tucson. I am involved with teaching and mentoring general and cardiothoracic residents at the University of Arizona and also keep active with ongoing clinical research projects. With my leisure time, I play tennis, read books I should have gotten to in earlier years, look for a publisher for a book I have written on the evolution of thoracic surgery (for the general reader), and admire my wife's expertise in making glass beads and jewelry.

LA cuisine, clinical education at CHEST 2016

Los Angeles is famous for its eclectic mix of palate-pleasing dining options. Chic cafes; international flavors; vegan eateries; and local, coastal cuisine are all readily available. When CHEST 2016 travels to Los Angeles in October, we know you'll satisfy your taste buds and your educational needs.

With so many options, here are some recommendations from our favorite Los Angeles locals – CHEST members – to plan your menu:

• **LA Prime**, 35th floor of the Westin Bonaventure Hotel (6-minute drive): Famous for prime beef steaks, seafood, and panoramic city views. *Located at 404 S. Figueroa St, Los Angeles, CA 90071*

• **Water Grill** (6-minute drive): This restaurant is sustainably minded and provides delicately prepared seafood in an elegant space. *Located at 544 S. Grand Ave, Los Angeles, CA 90071*

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• **Pacific Dining Car** (7-minute drive): Dine on steak in a railway dining car atmosphere at this iconic restaurant open 24 hours a day every day of the year. *Located at 1310 W. 6th St, Los Angeles, CA 90017*

• **Sticky Rice** (7-minute drive): Inside Grand Central Market, enjoy Thai "comfort food" with an emphasis on organic, free-range, and locally sourced seasonal ingredients. *Located at 317 S. Broadway, Los Angeles, CA 90013*

• **Mexicali Taco & Co** (9-minute drive): Enjoy mouthwatering Baja style Mexican food, reasonable prices, and a casual dining experience. *Located at 702 N. Figueroa St, Los Angeles, CA 90012*

• **Crossroads Kitchen** (22-minute drive): Courtesy of Oprah's former chef Tal Ronnen, this upscale eatery provides an elegant backdrop for refined vegan dishes. *Located at 8284 Melrose Ave, Los Angeles, CA 90046*

• **The Sky Room in Long Beach** (33-minute drive): This hotel bar/eatery offers New American fare and city views, plus music and dancing on weekends. *Located at 40 S. Locust Ave, Long Beach, CA 90802*

Looking for a quick bite? Here are some options within walking distance to the convention center:

• **Yardhouse** (5-minute walk): Find the craft beer you're looking for and select from a diverse menu. *Located at 800 W. Olympic Blvd, Los Angeles, CA 90015*

• **Tom's Urban** (1-minute walk): Enjoy a sprawling gastropub featuring an all-day American menu, large draft beers, and sports on big screens. *Located at 1011 S. Figueroa St, Los Angeles, CA 90015*

• **TASTE Food Hall FIGat7th** (4-minute walk): Walk to Figueroa and 7th, and you'll find a food court complete with unique flavor profiles. *Located at 735 S. Figueroa St, Los Angeles, CA 90017*

Los Angeles is sure to satisfy your inner foodie. From October 22 to 26, CHEST 2016 will also offer you postgraduate courses, simulation and interactive learning, interdisciplinary programs, problem-based learning sessions, keynotes and honor lectures, and more.

CHEST 2016 delivers the latest information in pulmonary, critical care, and sleep medicine, ensuring you make the best decisions with your patients.

Register by August 31 to pay the lowest fees. Visit chestmeeting.chestnet.org.

CHEST Clinical Trials Registry

A new clinical trial is now available in the CHEST Clinical Trials Registry.

SENSCIS™ (Safety and Efficacy of Nintedanib in Systemic SClerosIS) is a double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

The CHEST Clinical Trials Registry is a free service that connects physicians to information about clinical trials in respiratory disease, conducted by participating pharmaceutical companies.

To learn more about the registry and how to participate in the SENSCIS™ clinical trial, please visit www.chestnet.org/Guidelines-and-Resources/Clinical-Trials/Clinical-Trials-Registry.

NETWORKS: Disaster preparedness, New MACRA acronyms, ECS in transplantation, Electronic cigarettes

Disaster Response

Lessons from Orlando

The recent nightclub shootings in Orlando have forced me and my colleagues at our Level I Trauma Center to reexamine the way we do

Evolution of trauma care has "followed the money" but not necessarily the need.

business. Our typical approach to injury involves resource-intense therapy with a gang of clinicians, while anticipating no more than one or two patients at a time. While this model is excellent for training, we would struggle with the scale of casualties seen in Orlando.

Several observations may be made internally and have been made in the press. Triage should take place prior to the emergency department so that patients are appropriately prioritized to high-intensity support. Fundamental high-impact interventions requiring simple application, such as tourniquets, should be part of the training for all medical and nonmedical first responders. Perhaps most importantly, we need to reexamine the concept that health care is provided by competing geographic and economic entities. Evolution of trauma care has "followed the money" but not necessarily the need. An approach viewing trauma care as a right and acute response as a community resource may be necessary.

In 2008, the Republican Party held its convention in St. Paul, Minn. Reports indicated that 20,000-50,000 individuals were expected to enter the city, including protesters and anarchist groups. We prepared together for events ranging from vehicular crashes to biologic agents or explosive events (Dries et al. *J Trauma*. 2012; 73[6]:1614). Since then, however, there has been little community-wide planning.

Orlando reminds us that we dare not leave these plans on the shelf.

David Dries, MD, FCCP
Steering Committee Member

Practice Operations

MACRA, QPP, MIPS, APM: Know these acronyms

In October 2015, Congress passed the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA).

DR. BASSILY-MARCUS

A bipartisan legislation, it replaces the flawed Sustainable Growth Rate (SGR) formula that would have forced a 21% cut in Medicare payments to clinicians. MACRA established Quality Payment Program (QPP) that has two paths that link quality to payments: the Merit-Based Incentive Payment System (MIPS) or Advanced Alternative Payment Models (APMs).

MIPS streamlines three currently independent programs – (Physician Quality Reporting Program [PQRS], Value-Based Payment Modifier [VM], and Medicare Electronic Health Records Incentive Program) – into a single program in which eligible professions (EPs) will be measured on quality (50%), resource use/cost (10%), clinical practice improvement activities (15%), and advancing care information (25%).

The resulting composite performance score (CPS, scale 0-100) is used to determine and apply a +/- or neutral payment adjustment based on a performance threshold. Payment adjustments will begin in 2019 (based on 2017 performance period).

Most physicians will be subject to MIPS, which does not apply to hospitals or facilities.

APMs are new approaches to paying for medical care incentivizing quality and value. As defined by MACRA, APMs include CMS Innovation Center models, the Medicare Shared Saving program, and certain demonstration programs.

To qualify for payments, the APMs must also use certified EHR technol-

Continued on page 32

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Indications ProAir RespiClick® (albuterol sulfate) Inhalation Powder is indicated in patients 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

Important Safety Information

- ProAir RespiClick® (albuterol sulfate) Inhalation Powder is contraindicated in patients with hypersensitivity to albuterol or patients with a severe hypersensitivity to milk proteins. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate. There have been reports of anaphylactic reactions in patients using inhalation therapies containing lactose
- ProAir RespiClick® can produce paradoxical bronchospasm that may be life-threatening. Discontinue ProAir RespiClick® and institute alternative therapy if paradoxical bronchospasm occurs
- Need for more doses of ProAir RespiClick® than usual may be a marker of acute or chronic deterioration of asthma and requires reevaluation of treatment
- ProAir RespiClick® alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids
- ProAir RespiClick®, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and/or symptoms. If such effects occur, the drug may need to be discontinued
- ProAir RespiClick®, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension), convulsive disorders, hyperthyroidism, and diabetes
- Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. Do not exceed the recommended dose

References: 1. ProAir RespiClick Prescribing Information. Horsham, PA: Teva Respiratory, LLC; April 2016. **2.** ProAir RespiClick Patient Information Leaflet. Horsham, PA: Teva Respiratory, LLC; April 2016.

TEVA Respiratory

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ProAir RespiClick®

(albuterol sulfate) Inhalation Powder

Important Safety Information (continued)

- Immediate hypersensitivity reactions may occur. Discontinue ProAir RespiClick® immediately
- ProAir RespiClick® may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation
- Potential drug interactions can occur with beta-blockers, diuretics, digoxin, or monoamine oxidase inhibitors, and tricyclic antidepressants
- In controlled studies of ProAir RespiClick® in patients 12 years of age and older, adverse events that occurred at an incidence rate of at least 1% and greater than placebo included back pain (2% vs 1%), pain (2% vs <1%), gastroenteritis viral (1% vs <1%), sinus headache (1% vs <1%), and urinary tract infection (1% vs <1%)
- In controlled studies of ProAir RespiClick® in patients 4 to 11 years of age, adverse events that occurred at an incidence rate of at least 2% and greater than placebo included nasopharyngitis (2% vs 1%), oropharyngeal pain (2% vs 1%), and vomiting (3% vs 1%)

Please see brief summary of full Prescribing Information on following pages.

For more information visit **ProAir.com**

Continued from page 29

ogy, report on certain quality measures, and bear more than nominal financial risk.

Both MIPS and APMs are value-based payment models that incentivize providers on quality, outcomes, and cost containment.

Most physicians who see Medicare patients will be required to report either the MIPS or Advanced APM track starting in January 2017.

Editor's Note – See additional article on MACRA on page 8.

Adel Bassily-Marcus, MD, FCCP
Vice-Chair

Transplant

Extracorporeal circulatory support in thoracic medicine and surgery – evolving technology and expanding role

There is growing interest in the use of extracorporeal support (ECS) beyond intraoperative and perioperative utility. This has been driven by improvements in safety and efficacy resulting from corresponding technological advances and enhanced user ability. The paucity of donors, however, remains a significant limiting factor in lung transplantation (LT), and there is a growing number of recipients on the waiting list getting too sick for transplantation. ECS is

now commonly used to bridge recipients to LT, and reported outcomes show great promise. Indeed, there is even a growing interest in combining ECS with the ex vivo reconditioning of lungs in a further attempt to broaden the donor pool.

This newly developing paradigm constitutes a confluence of contemporary technologies that should allow more marginal or previously unacceptable donor lungs to be procured and also for the use of cardiopulmonary support to bridge sicker recipients safely. As with most technologies, the prerequisite capital outlay, training, and logistical resources will be required to allow for the acquisition of skill and safety. Furthermore, these trends will likely stimulate development of standards and guidelines to ensure a continuing quest for excellence.


DR. HAYANGA

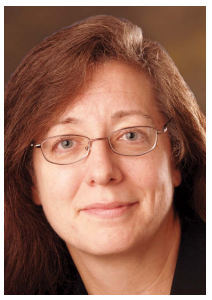

DR. SHIGEMURA

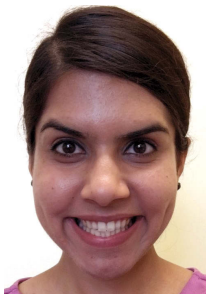
The ongoing use of ECS in transplantation has a ripple effect that may prompt its use in other clinical scenarios, such as a rescue therapy in acute exacerbations of COPD, an alternative to mechanical ventilation following complex thoracic pulmonary or esophageal resections, and in cases of unexpected intraoperative cardiopulmonary collapse. One thing remains likely, however, ECS is here to stay.

Jeremiah Hayanga, MD
Steering Committee Member
Norihisa Shigemura, MD
Steering Committee Member

Women's Health

Exposure of adolescents to electronic cigarettes: still a cause for alarm despite recent FDA ruling


DR. EFFEREN


DR. KAUR

Developed in 2003, electronic cigarettes (e-cigarettes) have been available in the United States since 2007. Between 2010 and 2013, adult use doubled. By 2013, the major tobacco companies had entered the market, and e-cigarettes were marketed widely (television, Internet, and print) as healthier alternatives to tobacco, useful for quitting smoking, and a way to circumvent smoke-free laws by allowing smokers to "smoke

Continued on page 35

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Continued from page 33

anywhere" (Grana et al. *Circulation*. 2014;129[19]:1972).

For adolescents, e-cigarette use tripled between 2013 and 2014, from 4.5% (660,000) to 13.4% (2 million) for high school students and from 1.1% (120,000) to 3.9% (450,000) for middle school students (CDC Press Release. http://www.cdc.gov/media/releases/2015/p0416-e-cigarette-use.html).

ENDS as a smoking cessation tool, a "safer" alternative to combustible tobacco, is much debated.

Teenage experimentation, in conjunction with susceptibility to brain-modifying effects of nicotine, places this population at risk for lifelong nicotine addiction. Teenagers who use e-cigarettes are more likely to become regular cigarette smokers than nonusers (Dutra et al. *JAMA Pediatr.* 2014;168[7]:610Levanthal et al. *JAMA*. 2015;314[7]:700.

Local and state municipalities have enacted legislation, adding e-cigarettes and other electronic nicotine delivery systems (ENDS) to existing tobacco regulations.

On May 5, 2016, a long-anticipated ruling from the FDA extended oversight to include all tobacco products, including e-cigarettes and hookahs, allowing the agency to address public health concerns, such as youth access.

However, a key provision of the new tobacco "deeming" rules was subsequently removed less than a month later – one that would have removed flavored e-cigarettes, cigars, hookahs, and other flavored tobacco products from the market in November pending review by the Food and Drug Administration (Boyles. MedPage Today. medpagetoday.com/pulmonology/smoking/58274).

ENDS as a smoking cessation tool, a "safer" alternative to combustible tobacco, is much debated (Green et al. *N Engl J Med*. 2016;374[14]:1301).

There is accumulating evidence of its in vivo and in vitro toxicity (Bhatnagar et al. *Circulation*. 2014;130[16]:1418; Gibbs et al. *Chest*. 2016;149[2]:552).

Studies have shown that the varied concentration and flavorings used are cytotoxic to human embryonic stem cells as well as mice neural stem cells (Bahl et al. *Reprod Toxicol*. 2012[4];34:529) and that exposure to propylene glycol and glycerin, main base ingredients in e-liquids, can result in eye and respiratory irritation (Grana et al. *Circulation*. 2014; 129[19]:1972).

Additionally, current evidence does not support e-cigarettes for smoking cessation (Grana et al. *Circulation*. 2014;129[19]:1972).

The accumulating evidence of adverse effects and the increased use in adolescents underscores the need for stricter regulations by the FDA in order to prevent renormalization of the smoking behavior and to protect public health. The rollout of the FDA's ruling will warrant ongoing evaluation.

Linda S. Efferen, MD, MBA
Consultant
Amanpreet Kaur, MD
Steering Committee Member

MOC 10-year assessment

The American Board of Internal Medicine (ABIM) has responded to physicians' and other stakeholders' input regarding the Maintenance of Certification (MOC) 10-year assessment and will begin offering an alternate option in January 2018.

The new option will include shorter assessments taken more frequently that will be able to be completed from a physician's office or home. These shorter assessments will identify knowledge gaps, so physicians can tailor their continuing education in order to stay current in knowledge and practice. Successful performance on the shorter assessments will allow physicians to opt out of the longer 10-year exam.

The program will be piloted for Internal Medicine and select subspecialties and, based on feedback, will be extended to additional subspecialties at a later date.

Physicians whose certifications expire prior to the new assessment option becoming available will need to pass the current exam in order to maintain certification but then will not need to take another assessment for 10 years.

ABIM's full announcement can be viewed at abim.org/news/abim-announces-plans-to-offer-physicians-moc-assessment-options-in-january-2018.aspx.

Any questions regarding this development should be directed to the ABIM by visiting www.abim.org/contact.

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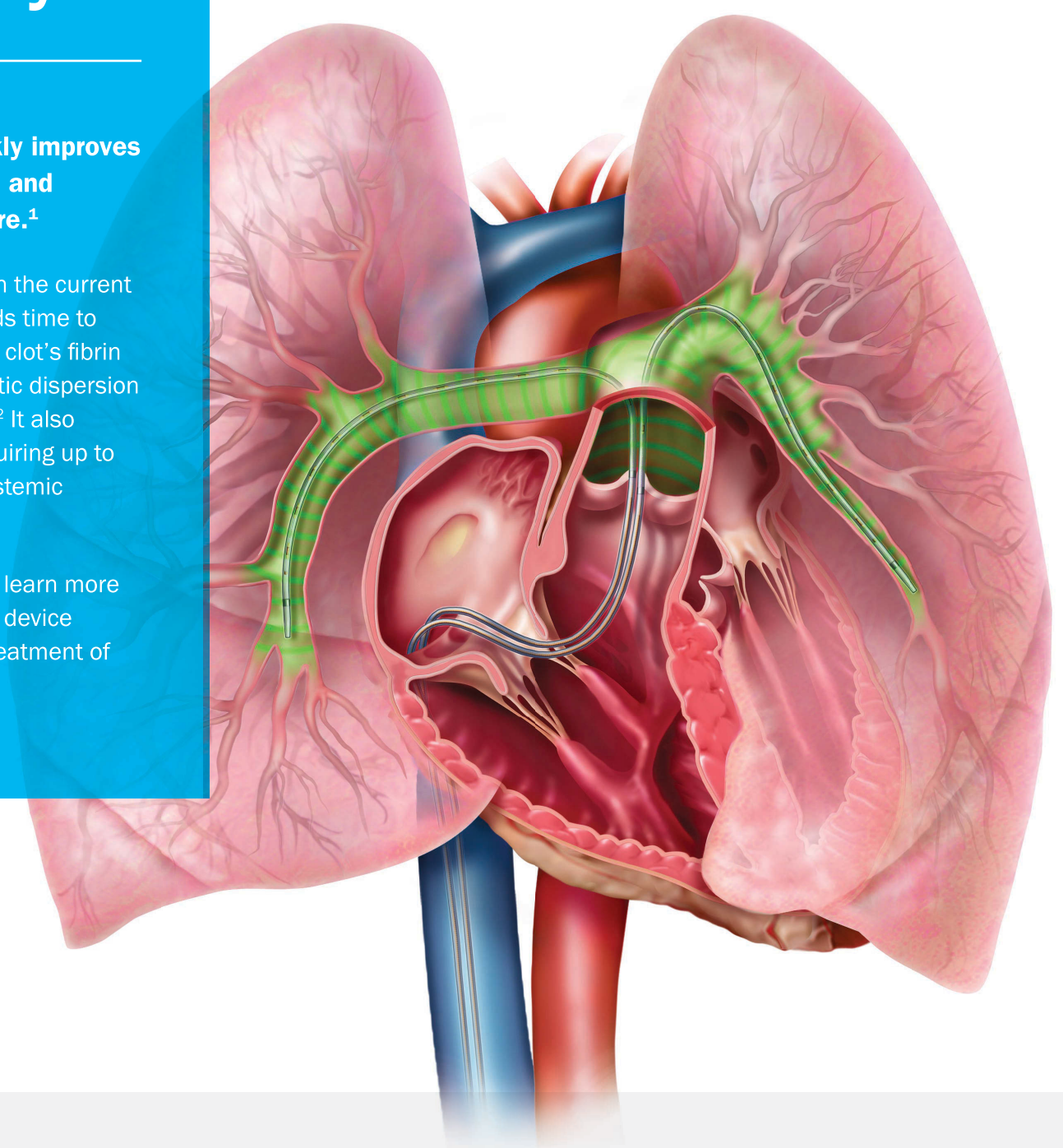

1 *In the Seattle II study of 150 patients with massive or submassive PE using an EKOS® and lytic combination, the mean RV/LV ratio decreased from 1.55 pre-procedure to 1.13 at 48 hours post-procedure (P<0.0001) while PA systolic pressure decreased from 51.4mmHg to 36.9mmHg (P<0.0001).*

2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

3 *Kucher, N., et al., Circulation, Vol. 129, No. 4, 2014, 479–486.*

4 *Piazza, G., et al., American College of Cardiology 63rd Annual Scientific Session, Wash D.C., March 30, 2014.*

FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. **THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS:** ***Peripheral Vasculature:*** The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. ***Pulmonary Embolism:*** The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25mmHg) or echocardiographic evaluation.

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