



COURTESY DR. NAIR

**Dr. Parameswaran Nair: "Long-term use of systemic corticosteroids can lead to potentially life-threatening complications."**

## Biologic cut steroid dose in severe asthma

BY ELI ZIMMERMAN  
Frontline Medical News

WASHINGTON – The biologic benralizumab cut glucocorticoid dosage by nearly 75% among patients with severe, uncontrolled asthma, compared with a 25% reduction in dosage among patients using a placebo, a study showed.

In this three-armed, double-blind study of 220 patients, those administered benralizumab every 4 and 8 weeks were 4.09 (95% confidence interval, 2.22-7.57) and 4.12 (95% CI, 2.22-7.57) times as likely to see a reduc-

tion in glucocorticoid dose, compared with those in the placebo group, the investigators reported (N Engl J Med. 2017 May 21. doi: 10.1056/NEJMoa1703501). The study was presented at an international conference of the American Thoracic Society and published simultaneously in the New England Journal of Medicine.

The results of this phase III trial could be significant for patients with severe asthma who must choose between passing on treatment and facing the potential risks associated with glucocorticoid use.

See **Biologic** • page 4

## Imatinib cuts mast cells, reduces airway response

*Studied in adults with severe asthma.*

BY MARY ANN MOON  
Frontline Medical News

Imatinib decreased airway mast-cell counts and airway hyperresponsiveness in adults with asthma, who were not responding well to maximal therapy, according to a report published online May 17 in the New England Journal of Medicine.

Imatinib is an inhibitor of the stem-cell factor receptor KIT, which is essential for mast-cell development and survival in bodily tissues. This study's findings suggest that KIT-dependent processes and mast cells contribute to the pathobiology of severe asthma.

"These data are not clinically directive, but they set the stage for follow-up studies targeting mast cells," said Katherine N. Cahill, MD, of Brigham and Women's Hospital and Harvard Medical School, both in Boston, and her associates.

The researchers undertook this study because imatinib is known to reduce bone-marrow mast cells and tryptase levels in chronic myeloid leukemia and to reduce serum tryptase in patients with pulmonary hypertension. Tryptase is a marker of mast-cell burden and activation when detected in extracellular fluids,

See **Imatinib** • page 7

## MK-7264 reduced chronic cough frequency in phase II study

BY MITCHEL L. ZOLER  
Frontline Medical News

WASHINGTON – A new oral drug that blocks a nerve ion channel was generally tolerable and effective at reducing chronic, refractory cough in a placebo-controlled,

dose-ranging, phase II study with 252 patients.

A 50-mg b.i.d dosage of MK-7264 cut cough frequency by at least 30% in 80% of patients, compared with 44% of patients on placebo, Jaclyn A. Smith, MD, said at an international conference of the Amer-

ican Thoracic Society.

At that dosage, 48% of patients reported some change in their taste sensations, an expected drug effect, with about 40% characterizing it as very bothersome or extremely bothersome. An additional 9% reported a

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## COMING SOON

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## Some ceased glucocorticoid use

**Biologic** *from page 1*

“Frequent or long-term use of systemic corticosteroids can lead to potentially life-threatening complications, including osteoporosis, diabetes, cardiovascular disease, and

adrenal suppression,” Parameswaran Nair, MD, PhD, professor of medicine at McMaster University, Hamilton, Ont., said in a press release. “We need new, safe therapies that would

replace the need for systemic corticosteroids for patients with severe asthma.”

To test benralizumab’s effectiveness, the investigators measured a baseline level of glucocorticoid dosage of 220 patients with severe, uncontrolled asthma. Patients were then given one of three treatment

options: one dose of benralizumab every 4 weeks, one dose of benralizumab every 8 weeks, or a placebo. All three treatments were decreased each time until minimal dosage was found while still maintaining asthma control.

The average age of patients was approximately 50 years; the majority of

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patients in both treatment groups and the placebo group were female.

The researchers also analyzed patients' accounts of any worsening asthma symptoms, which were recorded in an electronic asthma daily diary.

Along with the median 75% decrease in glucocorticoid dosage seen

in both groups of patients receiving benralizumab, 24 patients (33%) in the 4-week group and 27 patients (37%) in the 8-week group showed a 90% reduction from their baseline glucocorticoid dosage. In contrast, only nine patients (12%) in the placebo group experienced a 90% drop in glucocorticoid use.

The researchers also found benralizumab might be useful in a subgroup of patients with a baseline prednisone dose of less than 12.5 mg. These patients were more likely to stop taking their glucocorticoid dose if they were taking benralizumab instead of the placebo. Specifically, patients who took

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ELI ZIMMERMAN/FRONTLINE MEDICAL NEWS

**Dr. Parameswaran Nair speaks during a session at the ATS.**

benralizumab every 4 weeks were 5.23 times more likely, and those who took the biologic every 8 weeks were 4.19 times more likely, to cease using glucocorticoids.

Similar to the current biologics used to treat severe eosinophilic asthma, mepolizumab and reslizumab, benralizumab is a form of a monoclonal antibody. Instead of targeting interleukin-5, benralizumab works against a subunit of the interleukin-5 receptor. The investigators said this aspect of benralizumab may explain why it was successful in this study.

“Targeting of the alpha subunit of the interleukin-5 receptor with benralizumab has potential advantages over existing anti-interleukin-5 therapies,” Dr. Nair said. “By targeting the interleukin receptor rather than the cytokine, luminal depletion of eosinophils can occur, which may be related to greater clinical efficiency.”

The investigators noted that forced expiratory volume in 1 second levels seemed relatively unaffected by benralizumab.

This study was limited by the length of the trials, which lasted 28 weeks. Investigators also noted that 20% of the original patients were not used in the final population.

This study was sponsored by, and organized in partnership with, AstraZeneca. All of the investigators reported receiving personal fees, grants, or other support from AstraZeneca, or being under contract with the company. Most of the authors also reported relationships with other pharmaceutical companies.

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# Mepolizumab boosts remission in EGPA

*Eosinophilic granulomatosis with polyangiitis went into remission for 24 weeks in 28% of those treated.*

BY MARY ANN MOON  
Frontline Medical News

Adding mepolizumab to standard-of-care glucocorticoids with or without immunosuppressive agents can induce remission in many patients who have eosinophilic granulomatosis with polyangiitis (EGPA), according to a report published online May 18 in the New England Journal of Medicine.

EGPA, a rare disorder characterized by asthma, sinusitis, pulmonary infiltrates, neuropathy, and eosinophilic vasculitis in at least one end-organ, frequently relapses de-

spite glucocorticoid therapy or fails to respond adequately to the treatment. Patients have elevated levels of the cytokine interleukin-5, which regulates eosinophil maturation, differentiation, and proliferation. Neutralizing this cytokine is thought to be a potential therapeutic approach, said Michael E. Wechsler, MD, of National Jewish Health, Denver, and his associates.

Proof-of-concept studies have demonstrated the efficacy of subcutaneous mepolizumab, an anti-interleukin-5 monoclonal antibody, in EGPA, so Dr. Wechsler and his colleagues assessed the safety and

efficacy of a 1-year course of mepolizumab (300 mg) as add-on therapy in a double-blind, randomized, phase III trial, which involved 136 adults treated at 31 academic medical centers in nine countries. The study was

in remission for a full year (19% vs. 1%; OR, 19.65). The time to first relapse was significantly longer for mepolizumab, with only 56% of that group experiencing a relapse within 1 year, compared with 82% of the placebo group.

**Significantly more patients in the mepolizumab group (32%) than in the placebo group (3%) were in remission at both week 36 and week 48 (odds ratio, 16.74).**

sponsored by GlaxoSmithKline and the National Institute of Allergy and Infectious Diseases.

The first of two primary efficacy endpoints was the total accrued weeks of remission. A total of 28% of the mepolizumab group achieved remission for at least 24 weeks, compared with only 3% of the placebo group, for an odds ratio of 5.91.

The second primary efficacy endpoint was the proportion of patients in remission at both week 36 and week 48. Again, significantly more patients in the mepolizumab group (32%) than in the placebo group (3%) met this endpoint (OR, 16.74).

Mepolizumab also proved superior to placebo regarding numerous secondary endpoints, the investigators said (N Engl J Med. 2017 May 18. doi: 10.1056/NEJMoa1702079). More patients who received active treatment achieved remission within the first 6 months of treatment and remained

in remission for a full year (19% vs. 1%; OR, 19.65). The time to first relapse was significantly longer for mepolizumab, with only 56% of that group experiencing a relapse within 1 year, compared with 82% of the placebo group.

The annualized relapse rate was half as high with mepolizumab (1.14) as with placebo (2.27). In addition, patients in the mepolizumab group were more likely to reduce their doses of glucocorticoids (OR, 0.20) or discontinue the drugs altogether (18% vs. 3% taking placebo).

Mepolizumab was most effective among the 79 patients who had a high absolute eosinophil count (150 or more cells per cubic millimeter) at baseline. In this subgroup, 33% of patients taking mepolizumab achieved remission for 6 months or more, compared with none of the patients taking placebo (OR, 26.1).

Although the effectiveness of mepolizumab in this difficult-to-treat population was noteworthy, only about half of the patients given the active treatment achieved remission as defined by the study protocol. It is unclear why the drug was not effective in

*Continued on following page*

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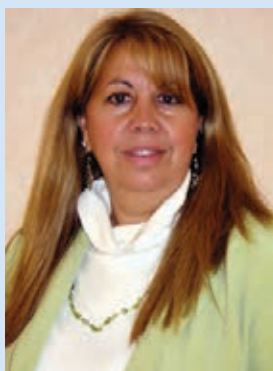
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Vera A. De Palo, MD, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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the other half of patients.

One possible reason is that some manifestations of the disorder are not driven by eosinophils. Another is that nonresponsive patients may have sustained longstanding, irreversible vasculitic damage that is no longer amenable to anti-interleukin-5 therapy.

Alternatively, it's possible that mepolizumab reduced eosinophils in the blood but not those in the body tissues of nonresponsive patients or that the patients who didn't respond well simply required a higher dose of the drug, Dr. Wechsler and his associates said.

The NIAID is now supporting a study of blood, urine, sputum, and tissue samples from some of these participants "to address questions related to disease risk and pathological features, as well as response to treatment," they added.

Many authors reported receiving payments from pharmaceutical companies, including several from GlaxoSmithKline. Four authors are employees of the company.

## VIEW ON THE NEWS

### Directions for future research

**T**he study by Michael E. Wechsler, MD, and his associates can be considered proof of concept. Now, researchers must turn to identifying biomarkers that predict the success or failure of mepolizumab in patients.

Researchers must also elucidate the fate of eosinophils in the tissues, especially in vasculitic lesions, after treatment with mepolizumab. And they should address possible synergistic activity when the drug is given together with immunosuppressants such as azathioprine and cyclophosphamide.

In addition, future studies should include patients who have organ-threatening or life-threatening eosinophilic granulomatosis with polyangiitis, who were excluded from

this trial but who are most in need of novel treatments.

*Ratko Djukanovic, MD, is with the University of Southampton (England) and the National Institute for Health Research Southampton Biomedical Research Centre. Paul M. O'Byrne, MD, is with the Firestone Institute for Respiratory Health within St. Joseph's Healthcare and McMaster University in Hamilton, Ont. Dr. Djukanovic and Dr. O'Byrne both reported financial relationships with pharmaceutical companies outside their editorial. They made these remarks in an editorial accompanying Dr. Wechsler and colleagues' report (N Engl J Med. 2017 May 18. doi: 10.1056/NEJMe1704402).*

## Serum tryptase down by 43%

Imatinib from page 1

and it is elevated in the bronchoalveolar lavage fluid from patients with uncontrolled asthma.

To examine whether imatinib would decrease mast-cell counts and activation in the airways of adults with severe, refractory asthma, the investigators performed the randomized double-blind proof-of-principle trial at seven academic centers across the United States over the course of 5 years.

A total of 62 patients were assigned to 24 weeks of either oral imatinib (32 participants) or a matching placebo (30 participants). Fifty patients, 24 in the imatinib group and 26 in the placebo group, completed the trial.

The primary outcome measure

was the change in airway hyperresponsiveness at 6 months, as measured by the increase in the concentration of methacholine that causes significant bronchoconstriction ( $PC_{20}$ ).

Imatinib decreased airway hyperresponsiveness to a greater degree than did placebo. Imatinib increased  $PC_{20}$  by a mean of 1.20 doubling doses at 3 months and by a mean of 1.73 doubling doses at 6 months, compared with 0.03 and 1.07, respectively, for placebo.

The small improvement in the placebo group is consistent with a phenomenon reported in other studies, in which patients show a delayed improvement in airway hyperresponsiveness for several months after they started inhaled glucocorticoids, Dr. Cahill and her associates noted (N Engl J Med. 2017 May 18. doi: 10.1056/NEJMoa1613125).

Imatinib also reduced mast-cell activity as measured by serum and airway levels of tryptase. Serum tryptase decreased by 43% in the imatinib group, compared with a 12% decline in the placebo group. And tryptase levels in bronchoalveolar lavage fluid tended to decrease in the imatinib group but to increase in the placebo group.

Imatinib also increased mean forced expiratory volume in 1 second ( $FEV_1$ ).

"Although the increase in  $FEV_1$  may not seem substantial, it suggests that mast-cell-dependent processes contribute to airway obstruction in these patients despite high-dose, anti-inflammatory gluco-

corticoid therapy. The near-50-mL difference in the change in baseline  $FEV_1$  between the imatinib and placebo groups is small, but it is likely to be important in light of the population we studied," Dr. Cahill and her associates wrote.

In addition, exploratory analyses showed that the reduction in airway

**The near-50-mL difference in the change in baseline  $FEV_1$  between the imatinib and placebo groups is small, but it is likely to be important in light of the population we studied, the authors wrote.**

hyperresponsiveness with imatinib "negatively correlated with baseline blood eosinophil counts, and baseline numbers of neutrophils in bronchoalveolar lavage fluid were strongly correlated with increases in  $FEV_1$ . Together, these findings support a role for mast cells in noneosinophilic asthma. Since almost half of the patients with severe asthma have neutrophilic airway inflammation, we speculate that KIT inhibition might represent an important approach to treatment for this group," they said.

This study was supported by the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, the Vinik family, and the Kaye family; Novartis provided imatinib free of charge.

The authors' financial disclosures are available at [www.nejm.org](http://www.nejm.org).

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## VIEW ON THE NEWS

**Vera A. De Palo, MD, MBA, FCCP, comments:** This study

presents important findings that continue to deepen our understanding of the key factors in the different phenotypes of asthma.

The authors point out that this sets the stage for further research in the exploration of targeted therapies that could help some of our sickest and most difficult-to-treat asthmatic patients.





# Invasive mediastinal staging for high-risk NSCLC

BY MARK S. LESNEY  
*Frontline Medical News*

**E**ndobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA) appears to be cost effective for use in non-small cell lung cancer (NSCLC) staging if the prevalence of mediastinal lymph node metastasis (MLNM) is greater than or equal to 2.5%, according to the results of single institution modeling study. In addition, the study found that confirmatory mediastinoscopy should be performed in high-risk patients in cases of negative EBUS-TBNA.

Katarzyna Czarnecka-Kujawa, MD, of the University of Toronto and Toronto General Hospital, and

her colleagues performed a decision analysis to compare health outcomes and costs of four mediastinal staging strategies. They assessed the following: no invasive staging, endobronchial ultrasound-guided

transbronchial need aspiration, mediastinoscopy, and EBUS-TBNA followed by mediastinoscopy if EBUS-TBNA results were negative. They determined incremental cost-effectiveness ratios (ICER) for

all strategies and performed comprehensive sensitivity analyses using a willingness to pay threshold of \$80,000 (Canadian)/quality-adjusted life-year (QALY).

They used data obtained for

## Flu shots may spark adverse events in NSCLC

BY NEIL OSTERWEIL  
*Frontline Medical News*

GENEVA – The influenza vaccine may interact with immune checkpoint inhibitors in patients with lung cancer, results of a small study suggest.

Among 23 patients with non-small cell lung cancer (NSCLC) treated with a drug targeted against programmed death-1 (PD-1), the seasonal flu vaccine appeared to produce good serologic protection against infection, but at the possible cost of an increase in the rate of immune-related adverse events (irAE), reported Sacha Rothschild, MD, PhD, of University Hospital Basel (Switzerland) at the European Lung Cancer Conference.

“Over 50% of patients overall had an immune-related adverse event, and that’s certainly higher than what we have seen in all the studies, and it’s also clearly higher than what we see in our daily clinical practice, especially with grade 3/4 toxicity,” he said in an interview at the meeting.

Among 23 patients with lung cancer treated with a PD-1 inhibitor, 12 (52.2%) had one or more irAEs. In contrast, the most frequent irAE in a key registration trial for nivolumab (Opdivo) was skin rash, which occurred in 9% of patients (N Engl J Med. 2015 Jul 9;373:1627-39).

“It’s a very small study, but it raises some concern that there might be an interaction between the vaccine and PD-1 blockade,” Dr. Rothschild said.

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staging, outcomes, and costs from the patients in the lung cancer program at the Toronto General Hospital from Jan. 1, 2005, to Dec. 31, 2014, as detailed in a report published in the June issue of the *Journal of Thoracic and Cardiovascular Surgery* (2017. doi: 10.1016/j.jtcvs.2016.12.048).

After exclusions, they utilized a final case count of 499 cases for developing their surgical and procedure cost analysis, and a total of 750 cases in their endoscopy database for endoscopy analysis. For the base-case analysis, they assumed a prevalence of mediastinal metastasis of 9%, and obtained the prevalence of a pathologic lymph nod-

al stage disease following EBUS-TBNA from their institutional data.

Their results showed that EBUS-TBNA followed by mediastinoscopy was the strategy that resulted in the highest QALYs, but that it had a prohibitive ICER of greater than \$1.4 million/QALY. Accordingly, it may not be justifiable to use medi-

astinoscopy after negative EBUS-TBNA in all patients, the researchers noted. However, the researchers' data suggest that invasive screening may be justified in a very-low-risk population (MLNM above 2.5%).

In addition, the researchers stated that "[the] benefit conveyed

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by detecting mediastinal metastatic disease becomes more apparent as the prevalence of MLNM increases, with confirmatory mediastinoscopy becoming cost effective in cases of negative EBUS-TBNA in patients with moderate to high probability of

MLNM" (greater than 57%).

Our model points out that there is a well-defined role for the use of different modalities, including mediastinoscopy. This stresses the need for ongoing focus on maintenance of competency and skill acquisition in mediastinoscopy and EBUS-TBNA by currently practicing and future

thoracic surgeons respectively," the researchers concluded.

Dr. Czarnecka-Kujawa disclosed that she is a research consultant with Olympus America. The study was funded in part by agencies of the Austrian government.

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## VIEW ON THE NEWS

### Endobronchial US appears to remain the method for all seasons

The authors make a compelling argument for invasive mediastinal staging in patients with clinical stage I non-small cell lung cancer and acknowledge that this conflicts with current guidelines, according to Biniam Kidane, MD, of the University of Manitoba, Winnipeg, in his invited comments on the study in the *Journal of Thoracic and Cardiovascular Surgery* (2017 Mar 10. doi: 10.1016/j.jtcvs.2017.02.051).



Their single-payer system is likely to have a different willingness-to-pay threshold, compared with those in other countries, especially the United States, where the EBUS-TBNA strategy without invasive staging is likely to remain the cost-effective choice.

Dr. Kidane applauded the authors on their methodologically rigorous analysis with robust sensitivity analyses to capture a wide range of mediastinal lymph node metastasis (MLNM) prevalence and EBUS-TBNA proficiencies and "provide a brilliant pictorial representation of their analyses that allows readers to identify the most cost-effective strategy by finding the intersection of their local MLNM prevalence and EBUS sensitivities.

"Cost-economic analyses such as these provide a window into the factors necessary to bridge guidelines from the realm of the abstract to the realm of local reality. When interpreting these findings, clinicians should consider: (1) What EBUS resources are available? (2) What is your local EBUS sensitivity? (3) What is the prevalence of MLNM?" Dr. Kidane concluded, with the caveat that such studies are not infallible and models are based on assumptions and must be treated with care.





*Dr. Kidane reported no disclosures with regard to commercial support.*



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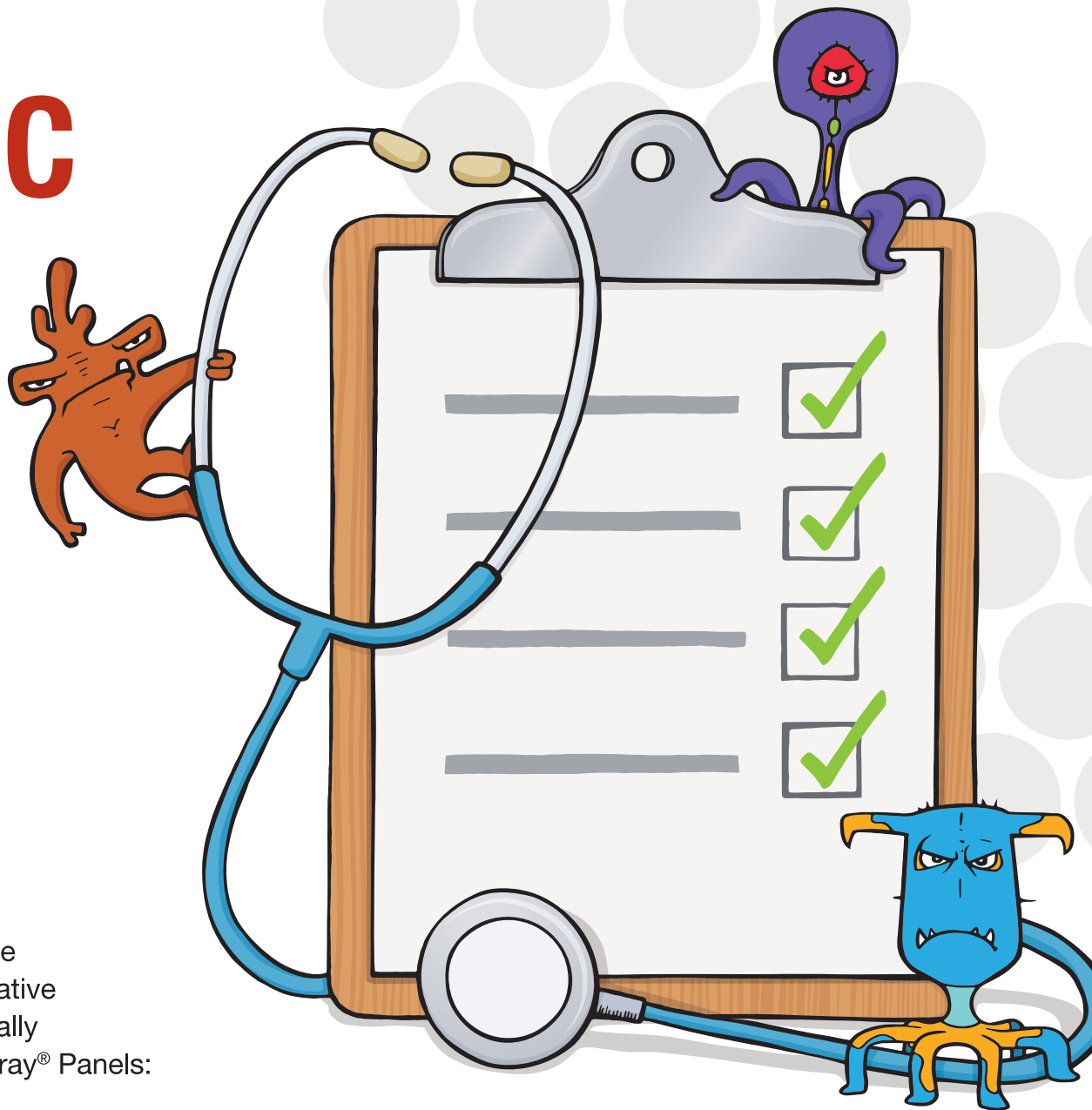
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# Sleep disorder diagnoses less common in women

BY ELI ZIMMERMAN  
Frontline Medical News

**W**omen are less likely to be diagnosed with and treated for sleep-disordered breathing, despite having symptoms similar to those of men, a Swedish study showed.

In a survey of 10,854 subjects, 14% of women reported being diagnosed with obstructive sleep apnea (OSA), compared with 25% of men ( $P$  less than .001), and 9% of women reported having any OSA treatment, compared with 16% of men (Sleep Med. 2017. doi: 10.1016/j.sleep.2017.02.032).

Underdiagnosis of sleep-disordered breathing (SDB) in women may have dire consequences, as symptoms, specifically snoring and excessive daytime sleepiness (EDS), correlate with increased risk for hypertension and diabetes, regardless of gender, according to Eva Lindberg, PhD, professor in the department of medical sciences, respiratory, allergy, and sleep research at Uppsala (Sweden) University, and her colleagues.

The mean age of the patients at baseline was 41 years. Mean body mass index was 25.4 kg/m<sup>2</sup> for men and 24 kg/m<sup>2</sup> for women.

On initial testing, approximately three times the percentage of men reported having issues with snoring and no EDS, compared with women (19% vs. 6% respectively), while more women reported the opposite, EDS but no snoring (19% vs. 11%). A slightly larger percentage of men reported having both symptoms (7.3% vs. 4.5%).

Investigators hypothesized the disparity be-

tween women and men reporting problems with snoring may be caused by gender expectations.

"It is more probable that SDB is still assumed to be a condition associated predominantly with men, and women feel ashamed of reporting these symptoms and seeking medical advice," said Dr. Lindberg and her coinvestigators. These gender expectations may "contribute to females being less inclined to seek medical advice due to SDB symptoms."

In a follow-up survey conducted 11 years after the initial one, doctors found 1,716 and 319 patients had received a new diagnosis for hypertension and diabetes, respectively.

While incidence was greater in men than in women for both (hypertension: 18.6% vs. 15.8% [ $P$  less than .001] and 3.6 vs. 2.4% [ $P$  less than .001], respectively), the investigators found "after adjusting for BMI and snoring at baseline, none of these gender differences remained significant."

Physicians' perception of SDB is partially responsible for the number of women who go undiagnosed, according to the researchers. Because SDB is considered to occur predominantly in males, doctors may overlook symptoms in female patients that would otherwise be a cause for further testing, they noted.

"[Even] among health professionals, SDB is still usually attributed to a male population, and female patients are therefore less frequently asked about the cardinal symptoms of snoring and sleepiness and do not therefore undergo sleep recordings. ... Also, among patients with obesity hypoventilation syndrome, females are

generally diagnosed when the disease is more advanced and significantly more frequently develop acute disease before achieving treatment," the investigators wrote.

Dr. Lindberg and her team suggested engaging female patients more frequently about SDB symptoms, as well as referring patients with positive symptoms to participate in a sleep study.

The current study was limited by the nature of the data, which were self-reported. Patients were not surveyed via the Epworth Sleepiness Scale.

The study was funded by grants from the Norwegian Research Council, the Icelandic Research Council, Aarhus University, the Swedish Heart-Lung Foundation, and the Estonian Science Foundation.

The investigators reported no relevant financial disclosures.

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## VIEW ON THE NEWS

**Krishna Sundar, MD, FCCP, comments:** The authors discuss the important topic of differing expression of OSA in male versus female subjects that may lead to under-recognition of sleep apnea in women.



# Oxygen desaturation index produces disparate data

BY ELI ZIMMERMAN  
Frontline Medical News

WASHINGTON – Oxygen desaturation index (ODI) scores showed significant variation across two software systems, a study showed.

The researchers assessed the ODI scores of 106 patients using the ResMed ApneaLink Plus system (AL) and the Compumedics Grael Profusion PSG3 system (Comp). "AL ODI values tended to be higher than Comp ODI values, but with significant variability," they said.

AL showed a bias of an additional 4.4 events per hour (95% limits of agreement, -5.8 to 14.6 events per

hour) for ODI scores at 4% desaturation and a bias of an additional 7.1 events per hour (95% limits of agreement, -6.4 to 20.6 events per hour) at 3% desaturation (J Clin Sleep Med. 2017;13[4]:599-605).

This may be problematic for physicians evaluating patients during sleep studies who rely on ODI scores at 3% and 4% desaturations to create accurate apnea severity assessments, the investigators said.

"[The] wide limits of agreement in our study highlight that clinicians cannot be confident that an ODI4% recorded in the AL is the same as that recorded in the Comp," wrote Yvonne Ng, MBBS, of the department of lung and sleep medicine at Monash Health, Victoria, Australia, and her colleagues. "The differences are large enough to significantly affect diagnostic thresholds for OSA [obstructive sleep apnea] and, in particular, moderate-severe OSA."

The researchers gathered data from patients undergoing sleep analysis at the Monash Medical Centre, who

were, on average, 47 years of age, had a body mass index score of 32 kg/m<sup>2</sup>, and had an apnea hypopnea index (AHI) of 23.2.

ODI3% scores analyzed through Comp diagnosed 66 patients with OSA (ODI3% greater than or equal to 5 events per hour), while desaturation events analyzed through the AL system diagnosed 90 patients, a 36% increase over Comp ( $P$  = .0002).

When researchers tested for moderate to severe OSA (ODI3% greater than or equal to 15 events per hour), 32 patients were diagnosed using the Comp system, compared with 59 patients using the AL system.

Disparities in these measurements create uncertainty among clinicians, who rely on ODI measurements for scores that are accurate and can be easily replicated using an algorithm, the researchers said.

"The current work demonstrates that significantly more patients would receive a diagnosis of OSA, or more particularly, moderate-severe OSA, with the AL ODI, compared to

the Comp ODI," Dr. Ng and her colleagues wrote.

When sensitivity scores for Comp and AL were compared, AL ODI3% scores were significantly more sensitive than Comp, with sensitivity scores of 96% vs. 58%.

Using different fingers for measuring desaturation during the test or differences in algorithms used to assess ODI scores were possible sources of the disparities, the researchers noted. Differences in internal processing between the two systems were the most likely causes of the discrepancies between the data collected using each system, they added.

Because there is no universal standard for ODI measurements, the researchers were unable to determine which system was more accurate.

Several of the researchers reported receiving financial support, research equipment, or consultancy fees from various entities.

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## VIEW ON THE NEWS

**Krishna Sundar, MD, FCCP, comments:** This article raises significant concerns about the role of different oximeters in contributing to the variation in hypopnea scoring.

# Patients accepted side effects

**Chronic cough** *from page 1*

complete loss of taste.

However, only 6 patients out of 63 who were randomized to this dosage stopped taking their medication.

The finding suggests that the drug was tolerable for most of the patients.

The results also suggested that lower dosages with less potent adverse effects on taste produced significant cough reductions in some patients.

“Patients with chronic, refractory cough are often “willing to accept some taste change to reduce their cough count.



**Dr. Jaclyn A. Smith**

“Patients are willing to put up with the taste side effects,” Dr. Smith said in a video interview.

The study enrolled patients with chronic, refractory cough at U.S. and U.K. centers and randomized 63 to each of three active treatment arms receiving 7.5 mg, 20 mg, or 50 mg b.i.d. of MK-7264 or to placebo for 12 weeks.

The patients averaged 60 years of age and about three-quarters were women.

On average, they had their cough for more than 10 years, and these patients coughed roughly 30 times an hour when awake.

The study’s primary endpoint was reduction in awake cough frequency, and, after 12 weeks on treatment with 50 mg b.i.d., this had fallen an average of 37%, compared with placebo, said Dr. Smith, who is a professor of respiratory medicine at the University of Manchester (England).

The 7.5-mg and 20-mg b.i.d. dosages each led to cough frequency reductions of about 22% over placebo

that were not statistically significant. This was likely a result of the unexpectedly strong placebo effect in the study, Dr. Smith said.

Most of the cough effect was

evident after the first 4 weeks on treatment.

Dr. Smith noted that she and her associates “most definitely” plan to progress to a phase III trial. “We really lack effective treatments for cough,” she said.

The study was sponsored by Merck, the company that is

developing MK-7264.

Dr. Smith is a consultant with Merck and has a licensing agreement with Vitalograph. A video interview with her on this topic is available at [mdedge.com/chestphysician](http://mdedge.com/chestphysician).

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# Stage IV sarcoidosis differs in blacks and whites

BY MITCHEL L. ZOLER  
*Frontline Medical News*

WASHINGTON – Black patients with advanced-stage sarcoidosis generally have a pattern of fibrotic scar

in their lungs that is different from that of whites, a finding with potentially important implications for prognosis and management.

Systematic assessment of 349 American patients diagnosed with

sarcoidosis – 264 whites and 85 blacks – showed that black patients had nearly double the prevalence of advanced, end-stage, Scadding stage IV fibrosis in their lungs, with a 19% rate among whites and a 34% rate

among blacks, confirming that blacks generally have worse sarcoidosis, Andy Levy, MD, said at an international conference of the American Thoracic Society.

All these sarcoidosis patients par-

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**This research confirmed that black patients generally have worse sarcoidosis than white patients.**

DR. LEVY

ticipated in the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study, and underwent CT scanning as part of the study's protocol. The scans showed that 16 of the 29 black patients with stage IV disease (19% of the total group of 85) had a "honeycomb" structure to their fibrotic scar, com-

pared with 10 of the 50 white patients (4% of the total group of 264).

Honeycomb scar is associated with more restrictive disease, characterized by reduced total lung capacity and reduced diffusing capacity of the lungs for carbon monoxide, features seen in these black stage IV patients, said Dr. Levy, a pulmonologist at

National Jewish Health in Denver. Bronchovascular distortion, the more common scar pattern seen in the white patients, results in more obstructive symptoms, such as a reduced ratio of forced expiratory volume in 1 second to forced vital capacity, which Dr. Levy reported as

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a characteristic of the white GRADS patients.

Even though the pulmonary fibrosis was end stage in all the black and white stage IV patients examined, “where the scar occurs may depend on genetics or environment, and may

affect how the disease manifests. We don’t fully know what it means yet,” Dr. Levy said in an interview. “There is this difference in the sarcoidosis of some black patients compared with white patients that needs further investigation to figure out why the scar is different.”

The different distribution of

**Even though the pulmonary fibrosis was end stage in all the black and white stage IV patients examined, “where the scar occurs may depend on genetics or environment, and may affect how the disease manifests,” Dr. Levy noted.**

lung fibrosis in blacks and whites “could have huge implications for prognosis and management,” said

Laura Koth, MD, a pulmonologist and professor at the University of California, San Francisco, and lead

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investigator for the study reported by Dr. Levy.

The GRADS data collection also showed that a significantly higher percentage of black patients had most recently received prednisone treatment for their sarcoidosis, 45% compared with 29% in whites, Dr. Levy reported. Ideally most

sarcoidosis patients would be on a steroid-sparing regimen, such as methotrexate. The excess prednisone treatment the black patients received confirmed prior reports of treatment disparities by race among American sarcoidosis patients, he said.

GRADS includes patients enrolled at seven U.S. research centers. The

study's primary goal is to try to identify "genomic signatures" that link with the clinical phenotypes identified through spirometry, bronchoscopy, CT scans, and physical examinations, Dr. Koth explained. The investigators plan to enroll more patients into the program to validate the findings, she said. "This is an

early stage, but we have seen some signals we want to follow-up."

GRADS is funded by the National Heart, Lung, and Blood Institute. Dr. Levy and Dr. Koth had no relevant financial disclosures.

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# CRT-D helpful in mild HF with high ejection fraction

BY BRUCE JANCIN  
*Frontline Medical News*

WASHINGTON – Patients with mild heart failure symptoms, left bundle branch block, and a left ven-

tricular ejection fraction of 31%-44% who received cardiac resynchronization therapy with a built-in defibrillator experienced a significant reduction in all-cause mortality, compared with those randomized to an

implantable cardioverter-defibrillator alone during 7 years of follow-up.

These results from a new MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

long-term follow-up substudy “suggest that patients with a relatively preserved ejection fraction greater than 30% benefit from a CRT-D [cardiac resynchronization therapy defibrillator] and could potentially be considered for this therapy,” said Katherine Vermilye, MD, at the annual meeting of the American College of Cardiology.

This represents a broadening beyond the conclusions earlier reached in the landmark MADIT-CRT. In the primary report, MADIT-CRT investigators concluded that CRT-D significantly reduced the risk of heart failure events, compared with an implantable cardioverter defibrillator (ICD) alone during an average follow-up of 2.4 years in patients with mild symptoms of either ischemic or nonischemic cardiomyopathy, a wide QRS duration, an left ventricular ejection fraction (LVEF) of 30% or less, and left bundle branch block, but not in those who didn’t have left bundle branch block (N Engl J Med. 2009 Oct 1;361[14]:1329-38).

In a subsequent publication, the MADIT-CRT investigators reported that, with extension of follow-up to 7 years, CRT-D also provided a significant benefit in terms of all-cause mortality in addition to the reduced rate of heart failure events (N Engl J Med. 2014 May 1;370[18]:1694-701).

However, even though an LVEF of 30% or less was a requirement for participation in MADIT-CRT, it turned out that, when the initial screening echocardiograms were eventually analyzed in a central core laboratory, one-third of study participants actually had a baseline LVEF of 31% to 44%, with the majority of excessive values being in the 31%-35% range.

Dr. Vermilye, of the University of Rochester in New York, presented a post hoc analysis of long-term outcomes in the subgroup having a baseline LVEF greater than 30%. They totaled 450 of 1,224 MADIT-CRT participants with left bundle branch block. They were significantly older

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## VIEW ON THE NEWS

**Frank Podbielski, MD, FCCP, comments:** The authors demonstrate the benefit of cardiac resynchronization therapy in patients with a defibrillator. The reduction in mortality at 5 years was greater in high responders to CRT-D, although overall mortality was significantly reduced in all comers.

# A transdermal mitral valve replacement pipe dream

BY BRUCE JANCIN  
Frontline Medical News

SNOWMASS, COLO. – Percutaneous mitral valve replacement is unlikely to ever catch on in any way remotely approaching that of transcatheter aortic valve replacement for the treatment of aortic stenosis, Blase A. Carabello, MD, predicted at the Annual Cardiovascular Conference at Snowmass.

“We’ve spent \$2 billion looking for methods of percutaneous mitral valve replacement, and yet, I have to wonder if that makes any sense,” said Dr. Carabello, professor of medicine and chief of cardiology at East Carolina University in Greenville, N.C.

“If repair is superior to replacement in primary MR [mitral regurgitation], which I think we all agree is true, and you don’t need to get rid of every last molecule of blood going backward across the mitral valve when you’ve got a good left ventricle, then a percutaneous replacement in primary MR would have only the niche of patients who are inoperable and whose leaflets can’t be grabbed by the MitraClip or some new percutaneous device down the road. And, in secondary MR, it doesn’t seem to matter whether you replace or repair the valve, so why not just repair it with a clip?” he argued.

Numerous nonrandomized studies have invariably demonstrated superior survival for surgical repair versus replacement in patients with primary MR.

## VIEW ON THE NEWS

### Francis J. Podbielski, MD, FCCP, comments:

The author provides valuable insight into how the definition of “success” of a procedure can change depending on the approach to the problem. While the gold standard of open mitral valve repair is 1+ regurgitation or less, those promoting percutaneous valve replacement are willing to accept long term 1+ to 2+ regurgitation. New technology and innovation is critical in medicine, provided the results are at least equivalent or superior to the standard techniques.

“There’s never going to be a randomized controlled trial of repair versus replacement; there’s no equipoise there. We all believe that, in primary MR, repair is superior to replacement. There are no data anywhere to suggest the opposite. It’s essentially sacrosanct,” according to the cardiologist.

In contrast, a major randomized trial of surgical repair versus replacement has been conducted in patients with severe secondary MR. This National Institutes of Health–funded study conducted by the Cardiothoracic Surgical Trials Network found no difference in survival between the two groups (N Engl J Med. 2016 Jan 28; 374[4]:344-53). That’s not a surprising result, Dr. Carabello said, since the underlying cause of this type of valve disease is a sick left ventricle. But, since surgical repair entails less morbidity than replacement – and a percutaneous repair with a leaflet-grasping device such as the MitraClip is simpler and safer than a surgical repair – it seems likely that the future treatment for secondary MR will be a percutaneous device, he said.

That future could depend upon the results of the ongoing COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy), in which the MitraClip is being studied as an alternative to surgical repair for significant secondary MR. The MitraClip, which doesn’t entail a concomitant annuloplasty, is currently approved by the Food and Drug Administration only for patients with primary, degenerative mitral regurgitation not amenable to surgical repair. But, if COAPT yields positive results, the role of the MitraClip will greatly expand.

An intriguing and poorly understood difference exists in the significance of residual mitral regurgitation following surgical repair as opposed to percutaneous MitraClip repair, Dr. Carabello observed.

“I go to the OR a lot, and I know of no surgeon [who] will leave 2+ MR behind. Most surgeons won’t leave 1+ MR behind. They’ll put the patient back on the pump to repair even mild residual MR, accepting only trace MR or zero before they leave the OR because they know that the best predictor

of a failed mitral repair is the presence of residual MR in the OR,” he said.

In contrast, following successful deployment of the MitraClip most patients are left with 1-2+ MR. Yet, as was demonstrated in the 5-year results of the randomized EVEREST II trial (Endovascular Valve Edge-to-Edge Repair Study), this residual MR wasn’t a harbinger of poor outcomes long-term (J Am Coll Cardiol. 2015 Dec 29;66[25]:2844-54).

“You would have expected, with that much residual MR, there would be a perpetually increasing failure rate over time, but that didn’t happen. In Everest II, there was an early failure rate for percutaneous repair, where the MitraClip didn’t work and those patients required surgical mitral valve repair. But, after the first 6 months, the failure rate for the clip was exactly the same as the surgical failure rate, even though, with the clip, you start with more MR to begin with,” the cardiologist noted.

The MitraClip procedure is modeled after the surgical Alfieri double-orifice end-to-end stitch technique, which has been shown to have durable results when performed in conjunction with an annuloplasty ring for primary MR.

“The MitraClip essentially joins the valve in the middle the way the Alfieri stitch does, but it doesn’t appear to behave the same way. Why is that? Maybe the clip does something different than the Alfieri stitch on which it was modeled. Maybe that bar in the middle of the mitral valve does something in terms of scarring or stabilization that we don’t know about yet,” he speculated.

As for the prospects for percutaneous mitral valve replacement, Dr. Carabello said that this type of procedure “is a very difficult thing to do, and so far, has been met with a fair amount of failure. It’ll be very interesting to see what percentage of market share it gets 10 years down the road. My prediction is that, for mitral regurgitation, repair is always going to be it.”

Dr. Carabello reported serving on a data safety monitoring board for Edwards Lifesciences.

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and more likely to be female than the 824 subjects with an LVEF of 30% or less. They also had a shorter QRS duration – an average of 160 ms, versus 165 ms in patients with an LVEF of 30% or lower – and a smaller baseline left ventricular end systolic volume of 151 mL, compared with 196 mL in patients with a lower LVEF.

In a multivariate Cox regression analysis adjusted for potential confounders, CRT-D in patients with a baseline LVEF greater than 30% was associated with a 54% reduction in the risk of all-cause mortality at 7 years of follow-up, compared with receipt of an ICD-only device and with a smaller yet significant 31% reduction in risk in those with an LVEF of 30% or less. Worsening heart fail-

ure events were reduced by 64% in patients with a baseline LVEF greater than 30% who received CRT-D, compared with ICD-only, and by 54% in those with a lower baseline LVEF.

The reduction in all-cause mortality seen with CRT-D was confined to patients who were high responders to CRT as defined echocardiographically by at least a 35% change in left ventricular end systolic volume 1 year post implantation. They had an 85% reduction in the risk of death during 7 years of follow-up with CRT-D if their baseline LVEF was greater than 30% and a 58% relative risk reduction if their LVEF was 30% or less.

In contrast, CRT-D brought a significantly reduced risk of heart failure events regardless of whether a patient was a low or high responder, although the magnitude of benefit was greater

in the high responders. Among patients with a baseline LVEF greater than 30%, CRT-D low responders had a 52% reduction in risk of heart failure events, compared with ICD recipients, while CRT-D high responders had an 81% relative risk reduction. Similarly, in patients with a baseline LVEF of 30% or less, CRT-D low responders had a 48% reduction in heart failure events and high responders had a 79% risk reduction, compared with the ICD-only group.

Because this is a post hoc analysis, these new MADIT-CRT findings require validation in future studies, Dr. Vermilye observed.

MADIT-CRT was supported by Boston Scientific. Dr. Vermilye reported having no financial conflicts.

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Dr. Katherine Vermilye



## FROM THE EVP/ CEO

BY STEPHEN J. WELCH

It is an incredible honor to be recently confirmed as the EVP/CEO for the CHEST organization. As a 23-year veteran of CHEST, I have had the privilege of working with and for many of our leaders, volunteers, and members. Being only the fifth person to lead the organization in an executive leadership role is both humbling and invigorating. CHEST is a dynamic and innovative organization, with a mission to “champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.” That mission resonates deeply with me on a personal level, because my mother had COPD. Toward the end of her life, I saw firsthand how it impacted her quality of life and her ability to be a mother and grandmother, and I also saw the important role her pulmonologist and respiratory health-care providers played in managing her disease. Working for CHEST reminds me every day of the importance of what we do as an organization in order to support what



MR. WELCH

you do as a physician or advanced practice provider.

I am both fortunate and grateful to have such a phenomenal professional staff to work with here at CHEST and to have the outstanding leadership of our Presidents, Past Presidents, Boards, Committees, and NetWorks – all of which have been tremendously supportive during the past 9 months as I filled the Interim EVP role. I am also deeply grateful to those of you who choose to be members and Fellows of CHEST and

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to be engaged as volunteer leadership, faculty, content experts, authors, and more. It is your time, energy, involvement, and vision that make this organization what it is. The fact that you choose to give some of your valuable time toward helping CHEST achieve its mission and vision is so greatly appreciated by all of us in this organization. Thank you for all that you do for CHEST.

In recent years, the College has continued to realize the following significant achievements:

1. Growth of our educational programs in simulation, skills training, and procedures;
2. The building and of our new global HQ and Innovation, Simulation, and Training Center;
3. An increasingly global footprint as we deliver education to our physician and advance practice provider members and nonmembers in the US and around the world;
4. Increasing development of digital publications and essential content, such as our journal; CHEST®, CHEST-SEEK™ products, e-learning modules, evidence-based guidelines, and more that can be served up to anyone on any device;
5. Growth and maturation of our CHEST Foundation and its research and service awards;
6. Expansion of patient education initiatives and materials;
7. Development of a data warehouse that will allow us to serve our members and partners more effectively; and
8. Far too many more achievements to list here.

Since taking on the EVP/CEO role, I've been asked what do I consider my primary responsibilities to be. I think this is best summed up by Rick Moyers, in The Nonprofit Chief Executive's Ten Basic Responsibilities (BoardSource, 2006). In it, he outlines the executive's responsibilities as follows:

1. Commit to the mission.
2. Lead the staff and manage the organization.

3. Exercise responsible financial stewardship.
4. Lead and manage fundraising.
5. Follow the highest ethical standards, ensure accountability, and comply with the law.
6. Engage the board in planning and lead the implementation.
7. Develop future leadership.
8. Build external relationships and serve as an advocate.
9. Ensure the quality and effectiveness of programs.
10. Support the board.

These 10 basic responsibilities provide the framework and foundation for how I plan to serve as EVP/CEO of CHEST. In many cases, I've been doing much of this as a senior executive at CHEST for the past 23 years, and I look forward to continuing to build on that foundation.

I am also often asked what my vision for the organization is, as its new EVP/CEO. And my answer is simple: to ensure that the American College of Chest Physicians stays relevant in this environment of change and disruption, that it continues to fulfill its mission, and that members, leadership, volunteers, and staff work together, make a positive impact on patient care, and, ultimately, have fun doing the good work of CHEST. This organization has an outstanding reputation, legacy, and brand. I will do everything I can to maintain and improve upon those key attributes.

It is my ultimate responsibility to ensure that we operationalize the educational programs and activities that align with the strategic plan and achieve the organizational goals of CHEST, which have been set by your Boards and Committees. I look forward to proudly and humbly serving as the CHEST evangelist and advocate to our members, patients, partners, and sister societies. I look forward to hearing from you, our members, about how CHEST is doing, and how we can continue to meet – and exceed – your educational and professional needs.

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# Building bridges: CHEST Foundation collaborations

Partnering with like-minded advocates and organizations strengthens our collective voice to improve patient outcomes. We choose to partner with others who share our values in creating sustainable, long-lasting change by engaging clinicians, patients, caregivers, and the public on the importance of understanding lung health.

**Pulmonary Fibrosis Foundation**

We recently collaborated with the Pulmonary Fibrosis Founda-

tion (PFF) and the Feldman Family to host the *4th Annual Irv Feldman Texas Hold'em and Casino Night* in Deerfield, Illinois. The Irv Feldman Texas



Hold'em and Casino Night was founded by the Feldman Family in 2013 in memory of their father who had succumbed to idiopathic pulmonary

fibrosis (IPF). For the last 4 years, Laury, Mara, and Mitch Feldman have hosted poker and casino nights to raise money to help end pulmonary fibrosis, and this year's event

*Continued on following page*

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

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

**GIANTS IN CHEST MEDICINE**

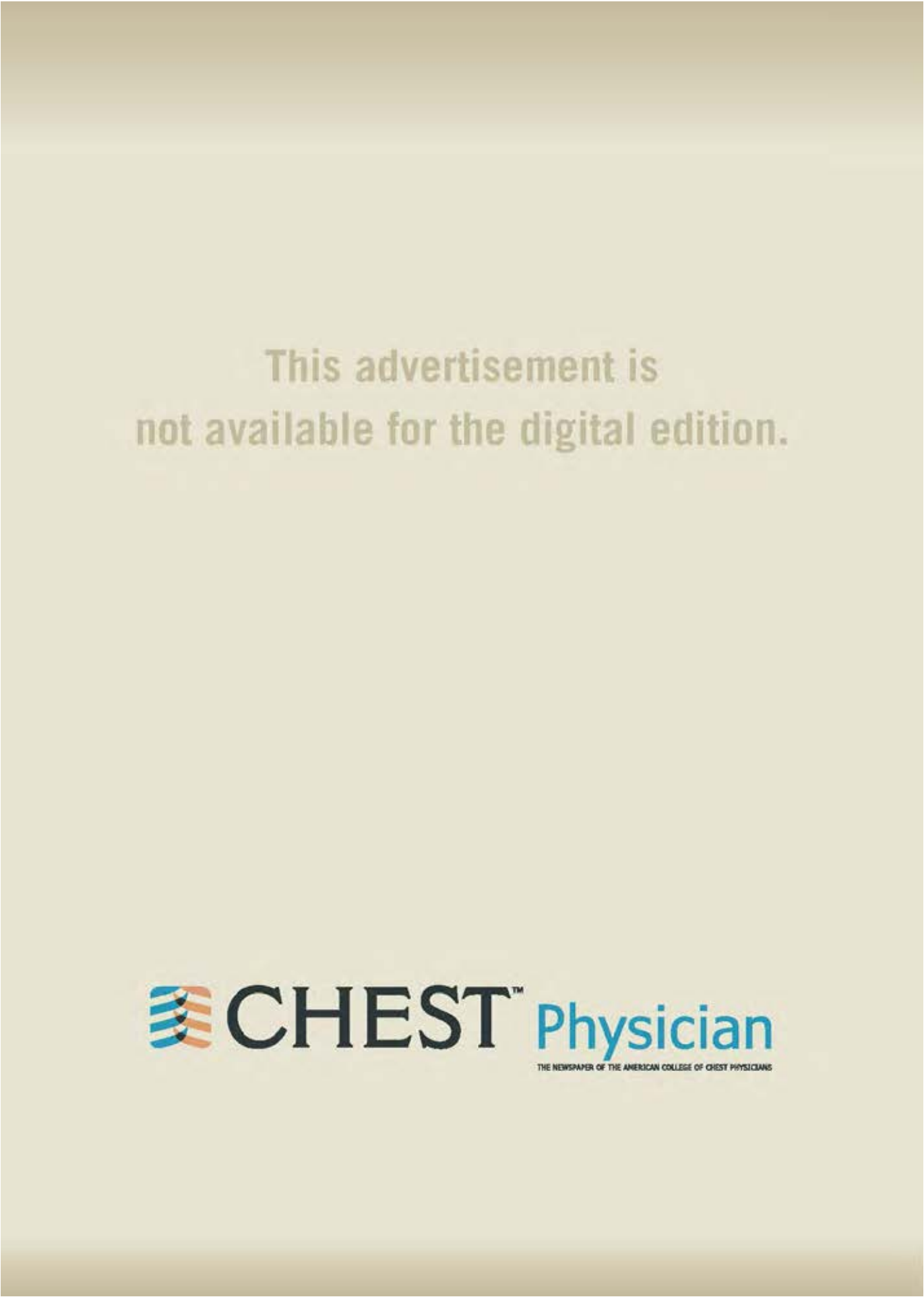
Karlman Wasserman, MD, PhD, FCCP. By Dr. T. Kisaka, et al.

**ORIGINAL RESEARCH**

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. By Dr. P. Marik, et al.

A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia: IASIS Trial. By Dr. M. H. Kollef, et al.

Quantitative CT Measures of Bronchiectasis in Smokers. By Dr. A. A. Diaz, et al.



*Continued from previous page*

featured a poker tournament, silent auction, dinner buffet, and live entertainment. This local community-based support resulted in almost \$200,000 raised at the poker night to fight against pulmonary fibrosis. In collaboration with the Pulmonary Fibrosis Foundation,

these proceeds will support pulmonary fibrosis patient education, disease awareness, and clinical research. We thank the Feldman Family and the Pulmonary Fibrosis Foundation for making this successful event possible.

#### **Allergy & Asthma Network**

Over the past 2 years, our relationship

with the Allergy & Asthma Network (AAN) has grown to include collaborative disease awareness campaigns, co-branded and co-created patient education materials in asthma and COPD, and an exciting expansion of the platforms we utilize to reach patients. Partnering with the AAN has allowed us to reach new audiences and bring asthma

and COPD education to local communities with opportunities, including:

- A Lifetime television segment on Access Health that focuses on asthma education;
- Co-hosted asthma Twitter chats reaching thousands of clinicians and patients; and
- “The Air We Breathe,” an Atlantic

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Live Summit in Chicago which focused on the relationship between air quality and respiratory health.

#### **COPD Foundation**

The COPD Foundation, along with Allergy & Asthma Network, have partnered with us to support our Lung Health Experience, a lung

health expo touring Oklahoma City, Nashville, Chicago, and Toronto in 2017. The Lung Health Experience focuses on bringing lung health experts to the public in a comfortable, relaxed, and fun setting. The COPD Foundation and AAN have attended these events to provide the public with educational materials on lung

diseases, which support the spirometry screenings performed by local respiratory therapists. We thank the Allergy & Asthma Network and the COPD Foundation for their outstanding support.

It is with these and many other partnerships that the CHEST Foundation is able to elevate its mission to

champion lung health and provide local communities with an opportunity to interact with clinicians and physicians outside of a hospital setting. These experiences and collaborations are the key to strengthening the patient and clinician conversation and bridging the gap to improve patient care and outcomes.

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# Low payment for pulmonary rehab explained

BY PHIL PORTE  
*Executive Director, NAMDR*

**A** new review of 2015 Medicare data clearly points fingers at hospitals for the historically low

payment rates for pulmonary rehabilitation.

To fully understand these data, everyone involved in the delivery of pulmonary rehabilitation services needs to know some of the specifics regarding

Medicare's rate setting process for hospital outpatient services. Those services are paid on the basis of a prospective payment methodology, similar to the DRG system for inpatient services. Under the outpatient system, APCs (am-

bulatory payment classifications) are computed with two key data sources, both provided by hospitals.

First, every claim submitted to Medicare for an outpatient service must include the hospital's "charge"

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for the service. (IMPORTANT NOTE: It is very easy to use the terms cost, charge, payment, and reimbursement interchangeably, but when discussing this issue, it is critically important to make key distinctions). This “charge” is not what the hospital expects to get paid – it is information from the hospital’s

**Knowing some of the specifics regarding Medicare’s rate setting process for hospital outpatient services is necessary in order to fully understand these data.**

“chargemaster” that identifies what, in theory, a self-pay patient might pay for a certain service. Therefore, every claim submitted to CMS for payment

of code **G0424** (pulmonary rehabilitation services) must include this “charge” data.

The second key component used

by CMS for rate setting is the hospital cost report, submitted annually to CMS tied to the individual hospital’s fiscal year. This flow of data to CMS is ongoing because of differing fiscal years and is somewhat attributable to changes in Medicare proposed rates for the following year, published in

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July, compared with final rates, published in early November.

The other key historical fact that needs emphasis is what happened in 2010 when CMS began reimbursing for pulmonary rehab under new HCPCS code **G0424**. Clearly, there were no

charge data to examine, so the Agency had to do a bit of guesswork, estimating what would be a reasonable payment. CMS turned to payment information tied to codes **G0237** and **G0238**, codes that had been used by many institutions for the previous decade for billing pulmonary rehab. But one critical difference existed. The

new code, **G0424**, was a 1-hour code, while **G0237-38** were 15-minute codes. Over the next 2 years, even CMS cited the failure of hospitals to adjust their charges to reflect all the component services included in this new, bundled 1-hour code, compared with the unbundled 15-minute code.

The new review of CMS data

bears out this problem. With approximately 1,350 institutions billing for hospital outpatient pulmonary rehab via code **G0424**, there is incredibly wide variance in charge data. The range is from a high of \$1,981 to a low of \$44, with 1,350 institutions in-between. The average charge was \$247, but the difference between the lowest charge and the highest charge is approximately 44-fold.

For cost report data, the spread is from \$1,265 to \$4 (yes, \$4, based on data provided to CMS). Approximately 750 hospitals, more than half, submit data to CMS reflecting costs associated with the delivery of pulmonary rehab, per hour, at \$50 or less.



MR. PORTE

There are probably several reasons why hospitals behave this way. First, there is the historical phenomenon cited by CMS that it often takes years for hospitals to adjust charges appropriately when any new HCPCS code is adopted by CMS. And, in fact, CMS cited pulmonary rehab as a glaring example of that failure by hospitals. Second, there is the cost report data, and we believe it, too, falls victim to hospital neglect. We can understand that a service such as pulmonary rehab falls so far below the radar by chargemasters, hospital administrators and others associated with information submitted to CMS that little attention is paid to accuracy of charges or administrative costs culled from the hospital cost report. And then, there is the matter of community relations. The hospitals at the very high end of the spectrum in terms of charges (\$1,100 and up) are unlikely to build good community relations if they let people know of those charges. Ironically, it is fair to presume that hospitals do pay very close attention to their charges and cost report data for very high-end hospital outpatient services, micro-examining that information to ensure desirable payment rates.

So, the critical challenge to the pulmonary community is to focus on those two very specific bits of data submitted by hospitals to CMS: what a hospital identifies as the “charge” for code **G0424** and is then entered on every claim submitted to **G0424**; and second, information correlated to the administrative aspects of pulmonary rehab that hospitals submit to CMS annually in their cost report to CMS. Until those adjustments are made, pulmonary rehab will live with unacceptable payment rates.

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## SPECIAL REPORT RELEASED BY FIRS

## The Global Impact of Respiratory Disease – Second Edition

**T**he Global Impact of Respiratory Disease – Second Edition was released by the Forum of International Respiratory Societies (FIRS) at the World Health Assembly May 25, 2017, in Geneva, Switzerland, calling attention to the global burden of lung disease and the benefits of prevention and clean air.

We often take our breathing and our respiratory health for granted, but respiratory diseases are a leading cause of death and disability in the world. Sixty-five million people suffer from COPD, and 3 million die of it each year, now making it the third leading cause of death worldwide.<sup>1,2</sup> Asthma affects 334 million people in the world and is the most common chronic disease of childhood.<sup>3</sup> Pneumonia kills millions of people annually and is a leading cause of death among children under 5 years old.<sup>4</sup> Over 10 million people develop TB, and 1.4 million die of it each year, making it the most common deadly infectious disease.<sup>5</sup> Lung cancer kills 1.6 million people each year and is the most deadly cancer.<sup>6</sup> Globally, at

least 2 billion people are exposed to indoor toxic smoke, 1 billion inhale outdoor pollutant air, and 1 billion are exposed to tobacco smoke. Many

**We often take our breathing and our respiratory health for granted, but respiratory diseases are a leading cause of death and disability in the world.**

of us, and the world, are naïve to these staggering realities.

The American College of Chest Physicians® (CHEST), together with FIRS, is working hard to change these realities. CHEST, and our more than 19,000 members around the world, want a better future, one that has less suffering. We want a future that enables and allows everyone to breathe freely.

The 2017 Global Impact of Respiratory Disease report objectively speaks to these issues and outlines an

eight-step action plan to impact these serious concerns. It highlights the importance of prevention, control, and cure of these diseases and announces that promotion of respiratory health must be a top priority for health-care systems and decision-makers. In emphasizing that these goals are achievable, it also highlights the reality that the prevention and cure of respiratory diseases are among the most cost-effective health interventions available – a “best-buy” in the view of the World Health Organization (WHO). In addition to reducing so much suffering, investment in respiratory health will pay manifold dividends in longevity, healthy living days, and national economies.

Darcy Marciniuk, MD, FCCP, FRCPC, and Co-Chair of the Report notes, “The Global Impact of Respiratory Disease” report calls attention to the importance of respiratory health in the world. The report and these efforts are required to ensure respiratory health becomes a top priority in global decision-making.”

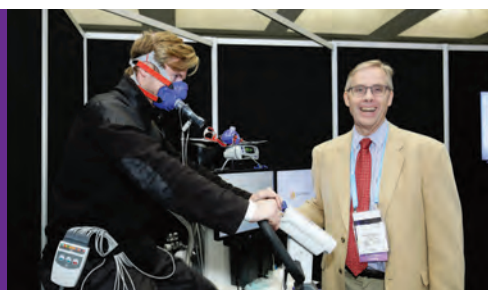
In addition to focusing attention to

the importance of respiratory health in the world and ensuring it becomes a global priority, the 2017 Global Impact of Respiratory Disease report also includes practical information for our members. The report summarizes the current state of our understanding with the “Big 5”: COPD, asthma, pneumonia, lung cancer, and TB, as well as with the environment and clean air, sleep-disordered breathing, pulmonary hypertension, and pulmonary embolism. It highlights key controllable factors, such as a reduction in tobacco smoking and improvement in air quality, which includes reduction in second-hand tobacco smoke, smoke from indoor fire, and unhealthy public and workplace air. The report underlines the value of trained health-care professionals and the need for health-care systems and policies to support those trained professionals. Finally, it emphasizes the reality that investment in respiratory research is more than the hope for today – it is the promise and a genuine commitment for tomorrow.

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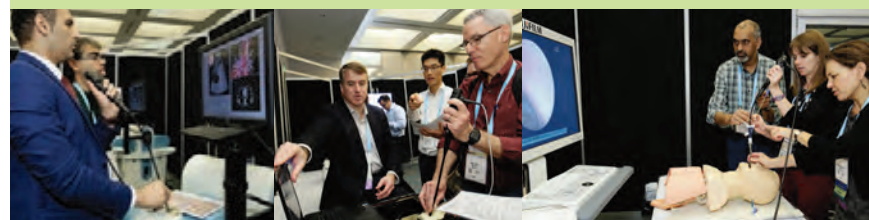
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# ABIM Internal Medicine Summit

BY HEATHER DETHLOFF, MA  
CHEST Education and Accreditation Manager

**O**n April 7, four members of CHEST staff and leadership, along with staff and leadership from other medical specialty societies, participated in the Internal Medicine Summit, hosted by the American Board of Internal Medicine, in Philadelphia. The meeting covered an array of topics related to

certification and maintenance of certification (MOC), including the alternative assessment model announced in December 2016, quality improvement (QI) as part of MOC, and practicing medicine in an ever-changing

political landscape.

The meeting began with Dr. Richard Baron, President and CEO of the ABIM, explaining how the notion of certification has changed over the years. According to Dr. Baron, the

concept of lifetime certification no longer makes sense in the rapidly changing field of medicine. As part of the evolution of certification, the ABIM has moved away from “rules to follow” toward something, co-created

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CHEST’s involvement in this important project is only one component of our global engagement and impact. We support and help to educate lung specialists and health-care teams, no matter where they live and work. Our journal *CHEST*®, and other education offerings, are used every day and in every part of the world. The American College of Chest Physicians® focuses on the prevention, diagnosis, and treatment of chest diseases by providing innovative education and advancing best patient outcomes around the globe.

*About the Forum of International Respiratory Societies (FIRS) Formed in 2001, the Forum of International Respiratory Societies (FIRS) is composed of the leading international respiratory societies, with more than 70,000 members who devote their working lives to respiratory health and disease. The goal of FIRS is to speak with one voice in promoting respiratory health worldwide and to call for action to reduce, prevent, cure, and control the terrible burden of respiratory disease.*

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with societies, that is more relevant and less burdensome. This shift includes aligning certification and MOC requirements with things physicians are already required to do by their states and institutions. Dr. Baron also stressed that in today's cultural and political landscape, along with the prevalence of "fake news," the

need for trust in the doctor-patient relationship is increasing; trust is no longer a "given." Therefore, in an age when credentials can be purchased online, there's an increasing need for an external certification to build trust and boost credibility.

Dr. Marianne Green, member of the ABIM Board of Directors and the

ABIM Council, gave an update on the recertification assessment options. While currently, only an every 2-year assessment option will be offered as an alternative to a 10-year higher stakes exam, the ABIM is looking to partner with societies to deliver education, based on the needs identified via the assessment. Furthermore, in

addition to partnering with societies to address the identified knowledge gaps, the ABIM plans to collaborate with societies in future alternatives to both the 2-year and 10-year assessments, with the shared goal of "maintenance and support of a community of life-long learners who hold

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ourselves accountable to peer-defined standards.” Initially, the 2-year lower stakes assessment will cover the breadth of the knowledge in the specialty/subspecialty, but the ABIM is committed to taking a more modular approach in the future. When asked

about the fee structure for the new assessment options, Dr. Green communicated that details regarding fees would be announced in fall 2017.

While the first part of the meeting focused on MOC Part 2, the conversation turned toward quality improvement, or QI, later part of the meeting. The practice improvement,

or MOC Part 4, requirement is on hold through the end of 2018. Both the ABIM and represented societies value the importance of quality measures. Dr. Graham McMahon, president and CEO of Accreditation Council for Continuing Medical Education (ACCME), laid the framework for QI as being “activities that address

a quality or safety gap with interventions intended to result in improvement and with specific, measurable goals. QI activities are learner-driven, as learner engagement is a key target of ACCME’s standard. Representatives from the Heart Rhythm Society, the Society of Hospital Medicine, the Arthritis Foundation, and the American

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College of Rheumatology shared their organization's initiatives related to QI.

Apart from the focus on certification and MOC, the meeting also focused on the needs arising from a changing political world, including what is at stake with the repeal of the Affordable Care Act (ACA) and the challenges arising with the wide

dissemination of questionable news and the general disregard of science. Stephen Welch, CHEST EVP/CEO, participated in a panel entitled "Practicing Medicine in a Fact-Free World." He, along with other media professionals, discussed the challenges that physicians, patients, and physician educators encounter in a

time when false facts are published as truth and information is sensationalized to attract more attention.

Since the meeting, CHEST leadership sent a letter to the ABIM leadership noting a desire to be one of the societies with whom the ABIM collaborates for both alternative assessment methods and the open-book resourc-

es selected. Additionally, CHEST expressed interest in receiving the data that are culled from the assessments, an interest aligned with CHEST's current data analytics initiatives. CHEST will continue to collaborate with the ABIM to ensure CHEST members' needs are represented and prioritized in future discussions.

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## PULMONARY PERSPECTIVES® China's Pulmonary Crisis

BY FRASER MACKAY, MD; AND  
ERIC FLENAUGH, MD, FCCP

**O**ver the past 2 years, we had the opportunity to participate in an annual cross-cultur-

al exchange that has broadened our horizons. Xi'an, the ancient capital of China and home of the Terracotta warriors, is a sprawling megapolis similar to Los Angeles. In the southern suburb of Huxian,

US trained pulmonary, neurosurgical, and critical care physicians from Cooper University Hospital and Morehouse School of Medicine partnered with physicians of Ji-Ren Teaching Hospital to deliver a Chi-

nese Medical Association accredited continuing medical education conference. The conference agenda included a variety of pulmonary and critical care topics highlighting sepsis, neurovascular disease, and lung

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cancer screening and diagnosis. We also provided a hands-on workshop for point of care ultrasound, and, in return, received education about Chinese medicine.

We found our hosts appreciative and hospitable, and they treated us with the highest level of respect (the cornerstone of Chinese culture).

The audience was receptive and very interested in learning. However, while we were impressed with their rapid growth and interest in incorporating western medicine into their daily practice, it was impossible to overlook the major pulmonary health-care concerns threatening their communities. Tobacco use was

omnipresent, and the haze of air pollution made the sky a constant shade of grey. In both public and private spaces, powerful echoes of a once familiar America resonated, and they served to underscore the obstacles the Chinese medical community now faces in caring for their country's pulmonary health.



DR. MACKAY



DR. FLENAUGH

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### An Old, Familiar Foe

The China National Tobacco Corporation (CNTC) is the largest tobacco company in the world, as well as China's most profitable state-owned enterprise (Pratt, A, et al. WHO Report. 2017. ISBN 9789290617907 [[http://www.wpro.who.int/china/publications/2017\\_china\\_tobacco\\_control\\_report\\_en\\_web\\_final.pdf?ua=1](http://www.wpro.who.int/china/publications/2017_china_tobacco_control_report_en_web_final.pdf?ua=1)]). As such, the CNTC controls every aspect of its production and supply chain with the force of the federal government and also exerts heavy influence over regulatory policy. It controls about 98% of domestic crop production and manages to price cigarettes just short of one American dollar per pack, yet contributes about \$170 billion annually to the government (Rich, et al. *Nicotine Tob Res.* 2012;14[3]:258). This accounted for nearly 7% of total governmental revenue in 2015 (Pratt, 2017).

To date, nearly 44% of the world's cigarettes are manufactured and consumed in China (Pratt 2017, Rich 2012). In 2015, more than 315 million Chinese adults were daily smokers, or about 28% of the adult population and nearly half of all men (Pratt, 2017). This is about double the proportion of US smokers (about 15.1%) and more than eight times the 36.5 million daily smokers in the United States (CDC Online Tobacco Use Report, 2016 [[https://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/adult\\_data/cig\\_smoking/](https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/)]). However, to visit China is not only to know a love for tobacco, but also an overwhelming guest and gift culture. Gift giving and hospitality is central to the Chinese identity, from business meetings to afternoon tea. Given their economy and such rich supply, people gift cigarettes to one another at all times for nearly any occasion. Unfortunately, tobacco smoke in China is as inescapable as its health consequences.

The direct effects of smoking on China's pulmonary health have been catastrophic. Cancers of the lung and bronchus constitute their most common malignancy across both sexes, accounting for the

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majority of the annual 4.3 million new cancer diagnoses (Chen et al. *CA Cancer J Clin*. 2016;66[2]:115). In Chinese men, lung cancer is the second most common cancer before the age of 60, and over the age of 75, it is the most common malignancy and also accounts for the majority of that group's cancer mortality. Women fare only slightly better, with breast cancer being their most common malignancy, but with lung cancer remaining the most pervasive across all age groups, and, by far, the most deadly (Chen, 2016). All told, of the projected 2.8 million cancer deaths occurring in 2015 in China, 21% were directly a result of lung cancer.

Likewise, COPD also threatens China. The Global Burden of Disease study conducted in 2004 demonstrated that nearly 3 million people die of COPD each year. Chinese adults over the age of 40 had an overall prevalence of COPD of 9% for the last decade, though this may be higher given the high rate of underdiagnosis in rural China (Fang X, et al. *Chest*. 2011;139[4]:920). After 2004, the Chinese Ministry of Health affirmed that COPD was the fourth leading cause of mortality in urban areas, but third in rural ones (Fang, 2011). When investigators analyzed deaths secondary to cor pulmonale coexisting with COPD, they found COPD-related mortality increased to 179.9 for men and 141.3 for women per 100,000 persons, which is about double the COPD mortality for other countries in the Asian-Pacific region (Reilly K, et al.

*Am J Epidemiol*. 2008;167[8]:998).

Both cancer and COPD in China disproportionately affect those in rural areas and with lower socioeconomic status, with smoking being the most potent causative exposure. On average, the annual direct and indirect per-patient cost of treating COPD amounted to about \$2,000, comprising about 40% of a family's total annual income (Fang, 2011). The cost of treating malignancy is even more expensive, but the higher likelihood of death results in an additional 10% to 20% reduction of family income when a working family member dies (Pratt, 2016). Taken together, and especially since rural Chinese citizens spend close to 20% of their income on tobacco products, the pulmonary health consequences of smoking are a significant driver of both health and economic inequality.

### The Air We Breathe

Air pollution comprises a second pulmonary insult to China's health. The International Agency for Research on Cancer designated particulate matter (PM) as a class I carcinogen (Kurt O, et al. *Curr Opin Pulm Med*. 2016;22[2]:138). PM forms from combustion of bio-mass fuel, as well as from dust storms or construction. Once particulates are smaller than 2.5 microns (PM2.5), they cause substantial harm to the pulmonary microenvironment. Guo and colleagues demonstrated markedly increased lung cancer risks associated with spatial mapping of ozone and PM2.5 concentrations (Guo Y, et al. *Environ Res*. 2016;144:60). PM2.5 also doubles the odds of contracting COPD in non-

smoking adults, conferring as much as a three-fold risk of contracting the disease in nonsmoking women (Fang, 2011).

Apart from causing pulmonary disease, studies also implicate air pollution as frequently causing exacerbations of existing disease. One study found an incremental increase in ED visits for respiratory illnesses for every 10 µg/m<sup>3</sup> above the median PM2.5 level (Xu, et al. *PLoS One*. 2016;11(4): e0153099). In 2013, 83% of Chinese lived in places where PM2.5 levels exceeded China's own ambient air standard. In this cohort, elevated PM2.5 levels contributed directly to 300,000 premature deaths from lung cancer and COPD, with PM2.5 causing 1.2 million premature deaths overall (Liu J, et al. *Sci Total Environ*. 2016;568:1253).

### Moving Forward

The Chinese have few illusions about these pulmonary concerns, and they are making progress. The government recently introduced stricter smoking controls in Beijing and Shanghai and continues to explore ways to decrease emissions. President Xi has put forward strong initiatives to improve the health of the Chinese. However, the nation is trying to balance its national priorities in the context of a fluid, and, at times, perilous geopolitical climate. In some ways, their position is not too dissimilar from the US geopolitical and health-care situation of the 1970s. While challenging, the issue of Chinese health care should not overshadow the remarkable resources or the truly remarkable culture of their people. Friendship, cooperation, the

reduction of suffering; these are ideals where all clinicians find common ground, regardless of nationality.

*Dr. Mackay is Chief Fellow of Critical Care Medicine, Cooper University Hospital, Cooper Medical School of Rowan University, Camden, New Jersey; Dr. Flanagan is Associate Professor of Medicine, Division Chief of Pulmonary and Critical Care Medicine, Director of Advance Diagnostic and Interventional Pulmonary, Morehouse School of Medicine, Atlanta, Georgia.*

### Editor's Note

This excellent, up-close Pulmonary Perspective details observations of Drs. Mackay and Flanagan as they have participated in cross-cultural exchanges in China with realization of the many obstacles to good pulmonary health for the Chinese population, obstacles including tobacco use, COPD, and air pollution. We appreciate their bringing these observations to the forefront.

The American College of Chest Physicians, likewise concerned about pulmonary health in China, has approached the problem on a different front, working closely with partners, such as the Chinese Thoracic Society, the Chinese Association of Chest Physicians, and the Chinese Medical Doctor Association, to implement China's first ever fellowship program offering standardized training in PCCM for Chinese physicians. Read more at <http://www.mdedge.com/chestphysician/article/131179/society-news/pccm-endorsed-pilot-subspecialty-chinese-national-health>.

*Nitin Puri, MD, FCCP, is the section editor of Pulmonary Perspectives.*

## CHEST NetWORKS

# Submassive PE, antibiotic resistance, advanced practice providers

## Cardiovascular Medicine and Surgery

### Catch 22 of Submassive Pulmonary Emboli

Venous thromboembolism (including deep vein thrombosis [DVT] and pulmonary embolism [PE]) occurs in approximately 1 per 1,000 patients (Piran S, Schulman S. *Thromb J*. 2016;14[S1]:23) and can be fatal. Pulmonary embolus severity is classified as low risk, intermediate-risk/submassive PE, and massive PE. There is significant controversy about the management of submassive PE, which is defined as PE with right-sided heart strain (elevated



DR. NAGEL

troponin or B-type natriuretic peptide, right-axis deviation on ECG, or evidence of RV dysfunction on CT or echocardiogram), and the absence of hypoten-

sion (systolic blood pressure > 90 mm Hg). In addition to the acute manifestations of VTE, there are potential long-term complications, including postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. Several trials

have examined the utility of systemic thrombolysis in submassive PE (MAPET-3 [Konstantinides, et al. *N Engl J Med*. 2002;347:1143], PEITHO (Meyer, et al. *N Engl J Med*. 2014;370:1402; Konstantinides, et al. *JACC*. 2017;69[12]:1536); MO-PETT (Sharifi, et al. *Am J Cardiol*. 2013;111:273); and TOPCOAT (Kline, et al. *J Thromb Haemost*. 2014;12:459), but all have failed to establish a mortality benefit. However, thrombolytics demonstrated decreased clinical deterioration and may mitigate the development of postthrombotic syndrome. Yet thrombolysis has been associated with increased bleeding (PEITHO:

11.5% vs 2.4% had major bleeding, and 2% vs 0.2% experienced hemorrhagic stroke). Current CHEST guidelines (Kearon, et al. *Chest*. 2016;149[2]:3150) recommend against the use of thrombolytics in submassive PE without hypotension. Treatment of intermediate-risk PE remains an enigma for physicians, but it is hoped that with further investigation, optimal management will be elucidated.

David J. Nagel, MD  
Steering Committee Member  
Olivier Axler, MD, FCCP  
Vice-Chair

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## Chest Infections

### Antibiotic Resistance

One-hundred years ago, infectious diseases caused 5 of the 10 most common causes of deaths in the United States. In 2016, only one infection remained on this list (influenza/pneumonia) (*MMWR Morb Mortal Wkly Rep.* 2017;66:413).

How medicine has improved with antibiotics. An unfortunate and unintended consequence of widespread antibiotic use has been the progressive resistance to these drugs. It is estimated that, if current trends continue, 10 million



DR. FEINSTEIN

lives a year will be at risk from resistant organisms by 2050 (O'Neill, J. (2016). [https://amr-review.org/sites/default/files/160518\\_Final%20paper\\_with%20cover.pdf](https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf)).

Pathogens acquire antibiotic resistance by passing genetic material to one another through plasmids, bacteriophages, or naked DNA. Once acquired, resistance manifests via a number of mechanisms under the stress imposed by antibiotics (Levy SB, et al. *Nat Med.* 2004;10:S122).

Among the best studied is enzymatic degradation of the antibiotic. This occurs when beta-lactamases degrade penicillin. A second mechanism alters cell transport, thereby blocking cell entry or actively ejecting the antibiotic from the cell. Finally, overexpression or alteration of the antibiotic target may render a drug ineffective at inhibiting any vital cell function.

At the pace with which resistance now develops, the medical community faces a crisis, whereby infections caused by evolving superbugs are no longer effectively controlled by the available menu of antimicrobial agents.

This challenge must be met collectively by the more prudent prescribing of antibiotics, potentially with the help of rapid diagnostics; isolation of patients potentially infected with resistant organisms; and a focus on developing newer drugs that defy known resistant mechanisms.

Marc Feinstein, MD, FCCP  
Steering Committee Member

## Clinical Pulmonary Medicine

### COPD and sleep-disordered breathing; A missing comorbid condition

Subjective, as well as objective, sleep complaints are common in patients with COPD (Krachman S, et al. *Proc Am Thorac Soc.* 2008;5[4]:536),

and sleeping difficulties are ranked the third most frequent complaint (behind dyspnea and fatigue) in patients with COPD (Kinsman RA, et al. *Chest.* 1983;83[5]:755). Also, sleep quality is poor, and patients with moderate to severe COPD may have higher-than-expected incidence of OSA (Soler X, et al. *Ann Am Thorac*

*Soc.* 2015;12[8]:1219).

Unfortunately, sleep is usually not assessed during a COPD evaluation. Up to 27% of patients with COPD without hypoxia during wakefulness can experience important desaturation during sleep, so called nocturnal oxygen desaturation (NOD) (Fletcher

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EC, et al. *Chest*. 1987;92[4]:604), that may lead to pulmonary hypertension (Chaouat A, et al. *Am J Respir Crit Care Med*. 1995;151[1]:82). Little is known about the pathophysiologic and clinical consequences of having concomitant COPD and OSA, but recent studies have demonstrated that patients with both disorders have a high risk of hospitalizations (30-day readmission rate



DR. SOLER

for rehospitalization ranges from 20% to 39%), and death from acute exacerbations if OSA remains untreated (Marin JM, et al. *Am J Respir Crit Care Med*. 2010;182[3]:325; Machado MC, et al. *Eur Respir J*. 2010;35[1]:132). Another study has found that in patients with OSA, the presence of COPD increases the risk of death seven-fold (Lavie P, et al. *J Sleep Res*. 2007;16[1]:128).

Although identification and effective treatment of COPD comorbidities are becoming the cornerstone of COPD management, sleep-disordered breathing has not been identified in current

guidelines yet as a true potential contributor in poor outcomes despite emergent clinical evidence. Multidisciplinary programs, such as pulmonary rehabilitation, that improve dyspnea, exercise capacity, and quality of life may also positively impact sleep (Soler X, et al. *COPD*. 2013;10[2]:156). Because of the background of the staff involved, the comprehensive approach to patient assessment, and access to number of COPD subjects, pulmonary rehabilitation may be an optimal opportunity to assess sleep and identify an important comorbid condition often overlooked in patients with more advanced COPD.

Xavier Soler, MD, PhD  
Steering Committee Member

## Interprofessional Team

### Finding Home

Outside our internal medicine curriculum, there is no formal pulmonary training or post-masters fellowship in pulmonary medicine for Advanced Practice Providers (APPs). Because of this, APPs are left to their own devices to fill educational gaps. To perform at the level expected by the physicians I work for, journal reviews and memorizing guidelines were not going to be enough. Since there is no formal pulmonary APP society, there were no peers to reach out to either.



DR. YOUNG

day with my nametag turned around worried I'd be found out as a non-physician attendee who snuck in. And then the unthinkable happened, I ran into another unicorn—another APP seeking the same information, only her nametag was turned the right way. The

Off to conferences I went.

At first, I found CHEST daunting. After all, it's run by the American College of Chest "Physicians," not Nurse Practitioners. I spent most of the first

best advice she gave was to attend the Interprofessional NetWork meeting. This was ground zero of the conference as far as I was concerned. There I found myself surrounded by RTs, RNs, NPs, PAs, and yes, even physicians.

Over the years, as I've gotten further involved with CHEST NetWorks, I have found from top to bottom CHEST striving to incorporate APPs and advance our education. From including us in the FCCP program, reducing conference pricing for APPs, and focusing this year's conference theme around being team focused, CHEST is creating a home for APPs.

Corinne Preston Young, FNP, FCCP  
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# Learn What's New at CHEST Annual Meeting 2017

**W**e've listened and considered all of your feedback to enhance your experience at CHEST 2017, Oct 28-Nov 1, Toronto, Canada. This year, we have changed the format of our postgraduate courses, updated our interdisciplinary sessions, and added new ways to register. Take a look at what's new.

## Postgraduate courses

New this year at CHEST 2017 is the option to attend a half-day or full-day course for a more flexible experience. There are nine, half-day sessions that include lunch, and the afternoon sessions allow people to fly in that morning to

avoid an extra hotel night and missing work.

## Interdisciplinary sessions

Bring your entire care team to attend programs that will address clinical issues across disciplines. Each role and perspective will be represented through session speakers, so your group can collectively experience practical, relevant updates. Sessions will combine lecture-based, case-based, and hands-on learning opportunities. Here are updated sessions:

*These sessions are free but require a ticket.*

**Monday, October 30**

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**Tuesday, October 31**

- Challenges in ICU Management

**Wednesday, November 1**

- Enhancing Quality of Pulmonary Rehabilitation Programs and Integrated COPD Disease Management

## Don't forget to register for CHEST 2017!

You can now register as a group! Ten or more health-care professionals from your team can register as a group for discounted tuition rates. Group registration is open through October 22 and will not be offered on-site. Learn more about CHEST 2017 updates and how to register at [chestmeeting.chestnet.org](http://chestmeeting.chestnet.org).



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2017

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**FRONTLINE**  
MEDICAL COMMUNICATIONS



# It's been a good year for heart failure research ...

BY BRUCE JANCIN  
Frontline Medical News

WASHINGTON – It's been a "relatively positive" year for heart failure research and advances in patient care, said Christopher M. O'Connor, MD, and president-elect of the Heart Failure Society of America, at the annual meeting of the American College of Cardiology.

## The good news

• **Empagliflozin (Jardiance) earns FDA approval for reduction in risk of cardiovascular death in type 2 diabetes patients.** "This is one of the most amazing stories in heart failure," said Dr. O'Connor, who is also professor of medicine at Duke University in Durham, N.C.

The pivotal EMPA-REG OUT-COME study showed a highly significant 35% reduction in the secondary endpoint of risk of hospitalization for heart failure, as well the decrease in cardiovascular mortality which was the primary endpoint and proved persuasive to the FDA (N Engl J Med. 2015 Nov 26;373[22]:2117-28).

"It was a remarkable development. Because of this trial, there are now a number of ongoing phase III clinical trials looking at this class of drugs in heart failure patients with and without diabetes, which makes this a very important research movement. We are now looking deeper at phenotypes and trying to get more specific with these drug therapies," he said.

• **A new and improved LVAD is developed.** This fully magnetically levitated centrifugal-flow pump type of left ventricular assist device for advanced heart failure showed superior event-free survival, compared with a commercially available axial continuous-flow pump LVAD in the randomized MOMENTUM-3 trial (N Engl J Med. 2017 Feb 2;376[5]:440-50).

The novel pump was designed to overcome a significant problem with axial continuous-flow LVADs: a proclivity for pump thrombosis. The magnetically levitated centrifugal-flow pump proved a smashing success in this regard, with zero cases of pump thrombosis occurring during the 6-month study.

"This may be the first time in the history of heart failure research that the engineers have beaten the biologists in important clinical outcomes," the cardiologist quipped.

• **Omecamtiv mecarbil successfully addresses impaired contractility in heart failure with reduced ejection fraction (HFrEF).** This drug, a selective cardiac myosin activator, resulted



Dr. Christopher M. O'Connor

in increased duration of systole and improved stroke volume accompanied by reductions in heart rate, left ventricular end-diastolic and -systolic dimensions, and NT-proBNP in the 87-site, 13-country, phase II COSMIC-HF study (Lancet. 2016 Dec 10;388[10062]:2895-903).

"This is probably the most novel new drug mechanism out there in clinical trials," said Dr. O'Connor, who is also CEO and executive director of the Inova Heart and Vascular Institute in Falls Church, Va.

On the basis of the highly encouraging results for the surrogate endpoints assessed in COSMIC-HF, a large phase III clinical trial known as GALACTIC is underway.

• **Palliative care gets a welcome boost.** Dr. O'Connor was a coinvestigator in PAL-HF, a single-center study presented at the 2016 annual meeting of the Heart Failure Society of America.

"This is a very important trial of palliative care in advanced heart failure. We probably don't have as much evidence in this space as we should," he observed. "This was a multidisciplinary intervention in which we gave the patients a medical tool kit to alleviate pain, dyspnea, and discomfort. The tool kit included benzodiazepines, sleep medications, sublingual nitroglycerin, and morphinelike products."

The primary outcome was change in two validated heart failure quality of life measures. Both instruments documented significant improvement compared with usual care.

"There was no decrease in mortality, which wasn't a goal in this advanced heart failure population, and no reduction in heart failure hospitalizations, but there were significant reductions in depression and anxiety," Dr. O'Connor said.

• **Vericiguat is under study.** This oral soluble cyclic guanylate cyclase stimulator missed its primary endpoint in the phase II dose-escalation SOCRATES-REDUCED trial in patients with HFrEF (JAMA. 2015 Dec

1;314[21]:2251-62), but showed an impressive improvement in quality of life. It is now the subject of the ongoing, randomized, phase III VICTORIA trial involving a planned 4,000 patients with HFrEF with the composite primary endpoint of cardiovascular death or heart failure hospitalization.

The phase II SOCRATES-PRESERVED trial also missed its primary endpoint but showed a clinically meaningful improvement in quality of life in patients with heart failure with preserved ejection fraction (HFpEF) (Eur Heart J. 2017 Mar 22. doi: 10.1093/eurheartj/ehw593). Discussions are ongoing as to whether the next step should be a confirmatory phase II study or a move straight to phase III.

## The bad news

• **NSAIDs linked to increased risk of heart failure.** European investigators analyzed five population-based databases totaling more than 8.3 million individuals and determined that current use of any of more than two dozen NSAIDs was associated with significantly increased risk of hospital admission for heart failure. The risk appeared to be dose dependent and varied between individual agents, ranging from a 16% increased risk with naproxen to an 83% increase with ketorolac (Toradol) (BMJ. 2016 Sep 28. doi: 10.1136/bmj.4857).

• **Therapeutic natriuretic peptides hit bottom.** The negative results for the investigational agent ularitide in patients with acute decompensated heart failure in the large phase III TRUE-AHF trial presented at the 2016 meeting of the American Heart Association, following upon an earlier negative study of the related drug nesiritide (Natrekor) in more than 7,100 acute heart failure patients (N Engl J Med. 2011 Jul 7; 365:32-43), probably spells the end of the line for this strategy of boosting outcomes in acute heart failure, according to Dr. O'Connor.

Moreover, Novartis has announced that the phase III RELAX-AHF-2 trial of serelaxin in 6,600 patients with acute heart failure failed to meet its primary endpoints of reduced cardiovascular deaths or reduced worsening of heart failure. The trial will be formally presented later this year.

"Ularitide seemed to show an early improvement in heart failure events that was not sustained in-hospital, and there was absolutely no difference in mortality. The drug probably acts like a pharmacologic tourniquet, in my view. So I think this field of therapeutic natriuretic peptides is probably closed," he said.

• **ICDs don't reduce mortality in patients with nonischemic heart failure.** This was the conclusion reached in the DANISH trial, in which more than 1,100 patients with symptomatic systolic heart failure were randomized to an ICD or usual care (N Engl J Med. 2016 Sep 29;375[13]:1221-30).

"This study really shook up the field, raising the question, 'Are we using defibrillators too frequently in this population?' It has stimulated a lot of discussion, including within the guidelines committee," Dr. O'Connor noted.

• **Tolvaptan nixed for acute decompensated heart failure.** The TACTICS-HF trial studied the use of tolvaptan (Samsca), an oral vasopressin-2 receptor antagonist, to reduce dyspnea in patients hospitalized with acute decompensated heart failure. Dr. O'Connor was a coinvestigator in the study, which showed that tolvaptan was no better than placebo at 8 and 24 hours (J Am Coll Cardiol. 2017 Mar 21;69[11]:1399-406).

"For now, the routine use of vasopressin antagonists in acute heart failure is not to be encouraged, although there may still be subsets where it's worth trying – certainly in severe hyponatremia," the cardiologist said.

• **GUIDE-IT gets lost.** This was a roughly 1,000-patient randomized trial of a treatment strategy aimed at improving clinical outcomes by aggressively titrating evidence-based heart failure therapies in order to suppress natriuretic peptide biomarkers. GUIDE-IT was stopped early by the data safety monitoring board for a lack of discernible difference in outcomes, compared with usual care.

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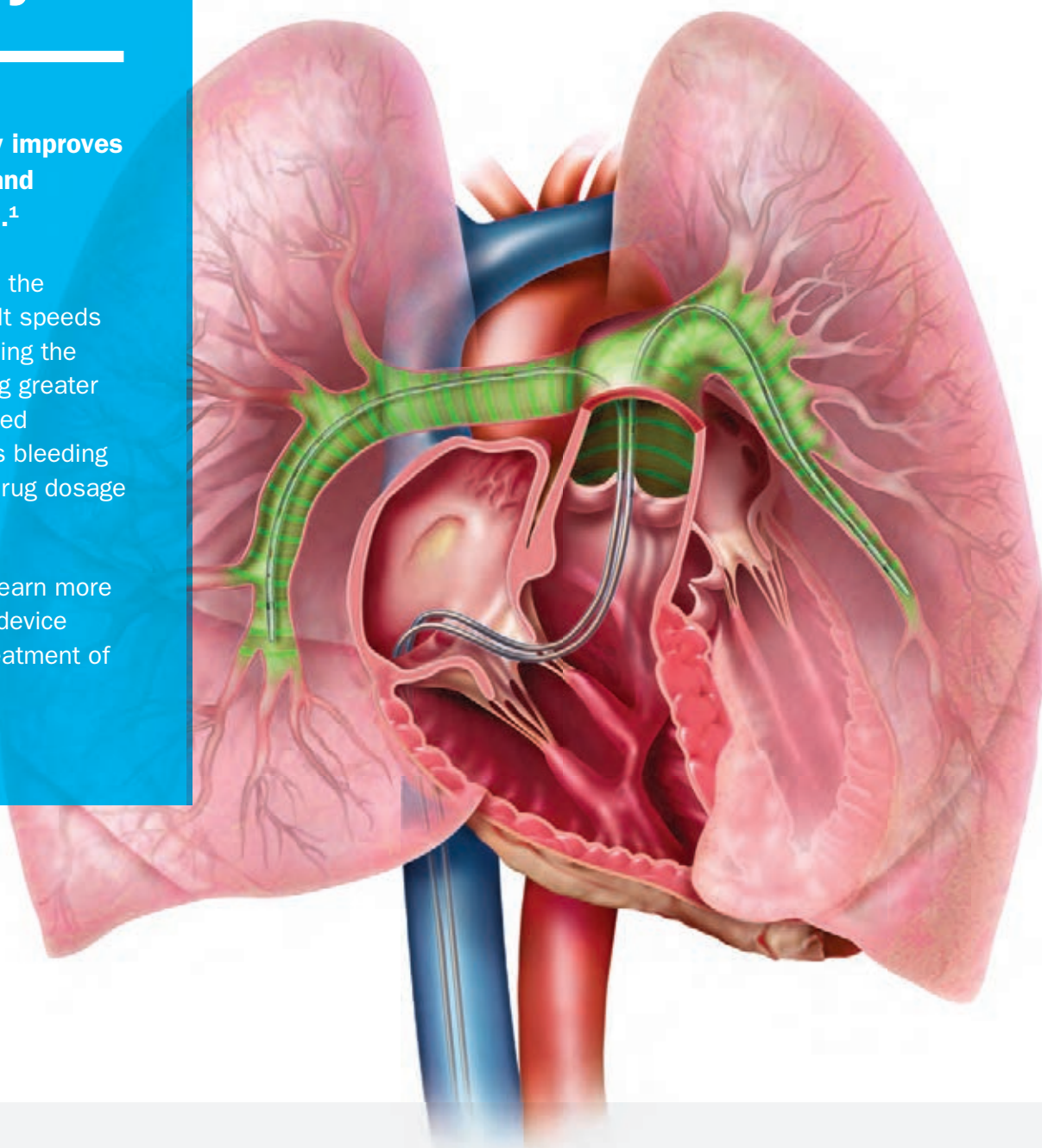
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<sup>2</sup> Braaten, J et al., *Thromb Haemost* 1997;78:1063-8; Francis, C et al. *Ultrasound in Medicine and Biology* 1995; 21(3):419-424; Soltani, A et al., *Physics in Medicine and Biology* 2008; 53:6837-6847

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

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

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