correctly with a spacer. Additionally, 23 of 27 (85%) children aged 4 to 5 years were able to use the device correctly without a spacer, but only 12 of 30 (40%) children aged 3 to 4 could use the Respimat® Soft Mist™ correctly without a spacer.

When paired with the spacer, all children in the 3 to 4 year and 4 to 5-year age groups could use the inhaler properly. Rates of correct usage decreased without parental assistance.

"The majority of subjects aged 4 to 5 can handle the Respimat® Soft Mist™ inhaler without a spacer but with considerable variability in technique," Dr. Kamin concluded. "Thus, to ensure standardized dosing, children below 5 years of age are recommended to use the Respimat® Soft Mist™ inhaler with a spacer."

In general, patient and parental satisfaction with the Respimat® Soft Mist™ inhaler was high, with or without the spacer. Satisfaction rates for reliability, instructions, ease of use, and overall ability to use the inhaler were 90% or higher, declining to 75% when children were handling the device alone. The Respimat® Soft Mist™ inhaler plus spacer had satisfaction rates that ranged from 83% to 97% for all components of use.

## Comparing Combination Therapies for COPD Maintenance

Combination therapy with tiotropium and salmeterol led to greater improvement in lung function parameters in patients with chronic obstructive pulmonary disease (COPD) than did the combination of fluticasone and salmeterol, reported Helgo Magnussen, MD, PhD, Hospital Grosshansdorf, Grosshansdorf, Germany.

Thoracic gas volume (TGV) improved significantly after 8 weeks of therapy with tiotropium+salmeterol ($p<0.05$), and exercise endurance time (EET) also improved.

The findings come from a randomized, crossover clinical trial to provide information about the relative effects of different combination maintenance therapies for COPD. Current clinical guidelines recommend combination therapy when response to single-agent therapy is suboptimal.

The study involved 309 patients whose mean age was 61 years and who had a mean baseline postbronchodilator forced expiratory volume at one second ($FEV_1$) of 1.36 L (47% of predicted), TGV of 5.42 L (165% of predicted), and EET of 458 seconds. The trial lasted 16 weeks, during which time patients were randomized to 8 weeks of therapy with tiotropium+salmeterol or fluticasone+salmeterol and then crossed over to the opposite therapy for an additional 8 weeks of treatment.

The co-primary endpoints were TGV and EET at 8 weeks. The tiotropium+salmeterol combination led to significantly greater improvement in TGV compared with fluticasone+salmeterol, averaging 87 mL after 8 weeks ($p=0.0482$). The difference between groups emerged early and averaged 182 mL after 4 weeks ($p<0.0001$).

Improvement in EET did not differ significantly between groups, averaging 15 seconds more with tiotropium+salmeterol after 8 weeks. The difference averaged 26 seconds for patients who reported dyspnea and 12.5 seconds for patients who reported dyspnea and leg discomfort.

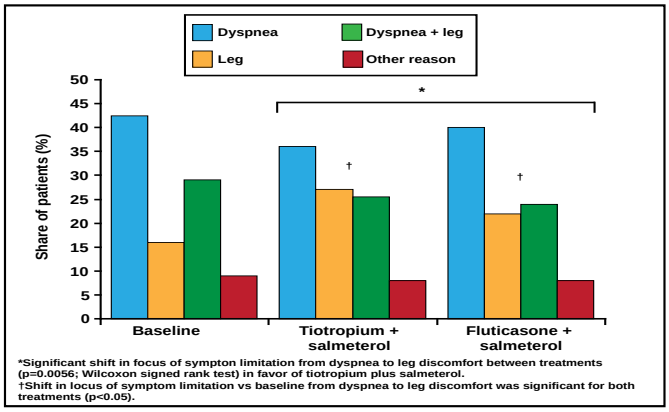
Several other parameters of lung function improved significantly during treatment with tiotropium+salmeterol. Postbronchodilator differences at 8 weeks were:

- $FEV_1$, 71 mL; $p<0.0001$
- Forced vital capacity, 154 mL; $p<0.0001$
- Inspiratory capacity, 115 mL; $p=0.0005$
- Residual volume, -154 mL; $p=0.0011$

The change from baseline in the Borg dyspnea score at exercise isotime favored tiotropium+salmeterol (-0.21; $p=0.07$) and was significantly greater after 4 weeks (-0.23; $p<0.05$).

The results demonstrated a significant shift in the locus of exercise-limiting symptoms from breathing discomfort (-20 patients) to leg discomfort (+35 patients) after treatment with tiotropium+salmeterol compared with fluticasone+salmeterol (-1, +19 patients; $p=0.0056$ between groups; Figure 1).

**Figure 1. Exercise-Limiting Symptoms.**

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"This observation indicates that a ceiling effect on exercise duration may occur on leg deconditioning that can impact the potential improvements observed through improved lung mechanics," Dr. Magnussen noted.

## Comorbidity Burden in Clinical Trials Versus Clinical Practice

Epidemiological studies have documented a high prevalence of comorbid conditions among patients who have chronic obstructive pulmonary disease (COPD), including hypertension, ischemic heart disease, hypercholesterolemia, diabetes, and anxiety and depression (Barr RG et al. *Am J Med* 2009; Carrasco-Garrido P et al. *BMC Pulm Med* 2009; Finkelstein J et al. *Int J COPD* 2009). The epidemiological data underscore the need to know whether clinical trial results have come from studies that adequately represent the comorbidities of COPD patients.

To examine comorbidities in clinical trials of tiotropium, Marc Miravitlles, MD, Ciber de Enfermedades Respiratorias, Barcelona, Spain, and colleagues analyzed data from 26 placebo-controlled clinical trials that were at least 4 weeks in duration. Baseline evaluation included documentation of patients' concomitant diseases and relevant medical history of the previous 5 years.

The analysis comprised 17,014 patients with COPD whose mean age was 64.6 years. The data showed that 76% of the patients were men, 84.4% was Caucasian, and baseline mean forced expiratory volume in one second ($FEV_1$) was 41% of predicted.

Information on baseline comorbid conditions was available for 15,375 patients. Overall, 90.4% of the patients had concomitant diseases at baseline.

The most frequently cited categories of comorbid conditions were vascular disorders (44.0%), musculoskeletal and connective tissue disorders (35.2%), gastrointestinal disorders (32.6%), metabolism and nutrition disorders (28.8%), dyslipidemia (16.7%), diabetes (9.8%), and anxiety or depression (13.7%).

Because COPD and cardiovascular conditions frequently occur together, the investigators analyzed the data for specific references to individual disorders within the broader category of cardiovascular disease. They found that 38.7% of patients had hypertension, 15.6% had conditions that were suggestive of ischemic heart disease, and 16.7% had hypercholesterolemia or hyperlipidemia.

With the exception of lipid and cholesterol abnormalities, the comorbidities of patients in the tiotropium clinical trials had prevalences that were similar to those of previous epidemiological studies, investigators concluded. Epidemiological data have generally shown higher rates of hypercholesterolemia or hyperlipidemia among patients with COPD.

## Effects of COPD Therapies on Lung Function Parameters

A year of treatment with tiotropium significantly improved blood gas parameters in hypoxemic patients with severe chronic obstructive pulmonary disease (COPD), as compared with inhaled corticosteroids plus a long-acting beta-agonist (LABA), reported Maria-Christina L. Machado, MD, Federal University, Sao Paulo, Brazil.

Partial arterial oxygen pressure ($PaO_2$) increased significantly ($p<0.001$) from baseline and partial carbon dioxide pressure ($PaCO_2$) decreased significantly ($p<0.01$) during treatment with tiotropium versus the standard therapy. Additionally, forced expiratory volume in one second ($FEV_1$) increased significantly ($p<0.001$) with the bronchodilator compared with inhaled steroids plus LABA.

"These results confirm that tiotropium usage has a significant impact on lung function variables, including arterial blood gas levels in hypoxemic stable outpatients with COPD under long-term oxygen therapy," said Dr. Machado.

Despite the proven benefits of tiotropium on lung function in COPD patients, the agent's impact on spirometric and arterial blood gas parameters remained uncertain in hypoxemic and severe COPD, according to Dr. Machado. In an effort to resolve the uncertainty, she and her colleagues evaluated outcomes in 67 consecutive patients with severe COPD and a requirement for long-term oxygen therapy. Each patient successively completed 12 months of treatment with each of two therapies: Treatment 1: inhaled steroids plus LABA; Treatment 2: inhaled corticosteroids + LABA and tiotropium. The primary objective was to compare the relative effects of the two therapeutic strategies on three parameters of lung function: $PaO_2$, $PaCO_2$, and $FEV_1$.

Analysis of baseline characteristics showed that the patients had a mean $PaO_2$ of 49.9 mm Hg, mean $PaCO_2$ of 47.9 mm Hg, and mean $FEV_1$ of 34% of predicted. After 12 months of treatment with inhaled corticosteroids and