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# COPD 2016: Some Answers, More Questions

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Chronic obstructive pulmonary disease (COPD) affects close to 400 million people[1] and is the third leading cause of death worldwide.[2] Despite its substantial prevalence and mortality, much has yet to be learned about how to optimize management. Several important studies published in 2016 provide interesting perspectives on many controversial areas of COPD care, including screening, diagnosis and treatment that have immediate implications for clinical practice.

Given the significant burden of disease and cost associated with COPD, early diagnosis is an appealing strategy for the implementation of disease-modifying interventions. In its 2016 update, the US Preventive Services Task Force (USPSTF) maintained its 2008 recommendation against screening for COPD in asymptomatic adults, citing a lack of net benefit in this patient population.[3] While this recommendation is based on the best available evidence, it is worth noting the key word “asymptomatic”. Hence the recommendation should not be interpreted as precluding thorough evaluation of those at increased risk for COPD who are not truly asymptomatic due to self-restriction of activity to minimize symptoms. The best approach for such COPD case-finding strategies needs to be further investigated.

Currently, a diagnosis of COPD is made based on a post-bronchodilator forced expiratory volume in 1 second ($FEV_1$) to forced vital capacity (FVC) ratio of less than 0.70 on spirometry.[4] However, many smokers without airflow obstruction ($FEV_1/FVC > 0.70$) still experience dyspnea, cough, sputum production and wheezing similar to those with airflow obstruction. Woodruff and colleagues showed that among current or former smokers with preserved pulmonary function, those who were symptomatic, as defined by a COPD Assessment Test (CAT) score ≥ 10, had a higher rate of respiratory exacerbations, a shorter 6-minute walk distance and greater airway wall thickening on chest CT compared to those who were asymptomatic.[5] It remains uncertain, however, whether these patients represent a transitional pre-COPD phase or a separate clinical entity. Moreover, many of the individuals studied were already being treated with bronchodilators, underscoring the need to establish a therapeutic evidence basis for this patient population.

While COPD exacerbations significantly contribute to the morbidity and mortality of the disease, the relationship between exacerbations and lung function decline has until now been informed by relatively small studies. In a longitudinal analysis of 2,000 subjects followed for

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5 years, Dransfield and coworkers showed that respiratory exacerbations are associated with an accelerated decline of lung function that was most pronounced in those with mild disease.[6] This association was not observed in current or former smokers without airflow obstruction. Whether reduction in exacerbation frequency through early aggressive therapy results in less rapid lung function decline is unknown.

Although there are a growing number of LABA-LAMA (long-acting beta-agonist – long-acting muscarinic antagonist) combination inhalers on the market, their effectiveness in the prevention of COPD exacerbations relative to ICS-LABA (inhaled corticosteroid – long-acting beta-agonist) combination therapy has been unclear. In the FLAME trial, a LABA-LAMA (indacaterol-glycopyrronium) decreased the annual rate of COPD exacerbations when compared to an ICS-LABA (fluticasone proprionate-salmeterol) in patients with a history of at least one exacerbation in the prior year.[7] The rate of exacerbations remained lower in the indacaterol-glycopyrronium group regardless of the baseline blood eosinophil count. SUMMIT, a double-blind randomized clinical trial, demonstrated that fluticasone furoate-vilanterol did not affect all-cause mortality or cardiovascular events in patients with moderate COPD and high cardiovascular risk when compared to placebo.[8] The combination, however, did appear to reduce the rate of $FEV_1$ decline and COPD exacerbations in pre-specified secondary analyses. These studies can be interpreted as evidence to support the efficacy and safety of these inhaler combinations, but important questions remain. Perhaps the most important is how best to identify individuals at increased exacerbation risk who would experience greater net benefit from ICS-LABA than LABA-LAMA. The role of blood eosinophil count and other phenotypic characteristics in guiding that selection is still uncertain.

Finally, data from the Salford Lung Study, a “real world” clinical trial, were also released this year.[9] This randomized study compared once-daily fluticasone furoate-vilanterol to usual care in unrestricted COPD patients recruited from clinics in Salford and South Manchester, England. The trial was designed to simulate an everyday clinical practice environment where the general practitioners served as the main investigators. Those assigned to fluticasone furoate-vilanterol experienced 8.4% lower rates of moderate or severe COPD exacerbations over a one-year period. As a significant proportion of patients in the usual care arm were also on ICS-LABA inhalers, the reduction in exacerbation frequency seen in the treatment arm may be due to the once-daily frequency of the medication which may have improved adherence. However, it is also possible that outcomes were influenced by bias introduced by the unblinded nature of the trial.

In summary, these studies offer important insights into the significance of symptoms in smokers without airflow obstruction, the impact of exacerbations on lung function decline, and the efficacy of combination therapy on reducing exacerbations both in clinical trial and “real world” settings. However, data is sorely to develop personalized management algorithms that will maximize treatment benefit with respect to symptoms, exacerbation reduction and lung function decline while minimizing potential harms in individual patients.

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