Patients with symptomatic chronic obstructive pulmonary disease (COPD) are commonly treated with inhaled medications that fall into three classes: beta-agonists, muscarinic antagonists, and glucocorticoids. Most patients with moderate-to-severe COPD are receiving one or more inhaled agents; inhaled glucocorticoids and inhaled long-acting beta-agonists (LABAs) are more commonly used than are long-acting muscarinic antagonists (LAMAs). However, the track record for inhaled medications in COPD is mixed. All three classes of drugs produce modest improvements in airflow obstruction, provide symptomatic benefit, and reduce the rate of COPD exacerbations. But they do not appear to alter the rate of the progressive decline in the forced expiratory volume in 1 second (FEV₁) that is the hallmark of the disease, nor do they affect mortality. Therefore, their therapeutic role is to improve symptoms and prevent exacerbations. Current guidelines provide recommendations concerning stepwise intensification of therapy but do not address “stepping down” therapy in COPD. In the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial, now reported in the Journal, Magnussen and colleagues address methods for a step-down process in patients with moderate-to-severe COPD. In this study, investigators sought to answer the question of whether the tapered withdrawal of glucocorticoids from a maximal inhaled regimen including two classes of long-acting bronchodilators would result in an increase in the rate of exacerbations. The trial design incorporated two key elements: it was a noninferiority trial, with prespecified statistical criteria for evaluating the effect of glucocorticoid withdrawal on the primary outcome, and it recruited a population of patients at increased risk for exacerbation. The latter made it feasible to undertake a trial with sufficient statistical power to test the primary hypothesis. “Feasible” does not mean easy or inexpensive: investigators at 200 study centers in 23 countries participated in the enrollment of 3426 patients over a period of 40 months; 2488 of these patients underwent randomization into the two study groups. All patients received 6 weeks of maximal inhaled therapy with tiotropium, salmeterol, and fluticasone and then were randomly assigned either to continue to receive the triple therapy or to undergo a three-step reduction in the glucocorticoid dose during a 12-week period.

There was a strong rationale for this study. In patients with COPD, exacerbations are an independent determinant of health-related quality of life and are associated with an accelerated rate of decline in lung function. They are also associated with increased mortality and health care expenditures. Understandably, there is much interest in reducing the occurrence of these events. Glucocorticoids are commonly prescribed in COPD, as evidenced by the fact that approximately 70% of the study patients were receiving glucocorticoids at the time of enrollment. Among patients with a history of exacerbations and moderate-to-severe COPD, the downsides of continuing to use glucocorticoids are both side effects and economic costs. Although patients in this study did not have an increased risk of pneumonia, this risk has been associated with long-term glucocorticoid use in other studies. Less severe but more common side effects of long-term use are thrush, dysphonia, bruising, and modest effects on bone density. The costs of glucocorticoids are not trivial: in the United States, the average annual cost per patient for inhaled glucocorticoids is approximately $1500.