TO THE EDITOR: The article on the Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial (ClinicalTrials.gov number, NCT00563381) by Vogelmeier et al. (March 24 issue) provides valuable information on choosing between inhaled therapies to prevent exacerbations in moderate-to-very-severe chronic obstructive pulmonary disease (COPD). However, the high prevalence of smoking among subjects in the trial (48% of the subjects were current smokers) highlights the continued importance of smoking cessation. Stopping smoking with pharmacotherapy is the only treatment, other than long-term oxygen therapy, proved to reduce mortality in COPD, and it has also been shown to be a treatment with a much higher value than inhaled therapy, when outcome is considered relative to cost. It is remarkable, given the high continuing smoking prevalence among patients with COPD exemplified by this study, that the effect of smoking-cessation interventions on morbidity still awaits a trial. The study that is needed is an evaluation of smoking-cessation interventions involving effective outcome measures of morbidity as in the POET-COPD trial. Meanwhile, one of the outcome measures we, as clinicians, should be judged on is the reduction of the prevalence of smoking among our patients with COPD. Louise Restrick, M.D. National Health Service (NHS) London Respiratory Team London, United Kingdom louise.restrick@whittington.nhs.uk Myra Stern, M.D. Whittington Health London, United Kingdom Noel Baxter, M.D. NHS London Respiratory Team London, United Kingdom No potential conflict of interest relevant to this letter was reported.


TO THE EDITOR: Vogelmeier et al. conclude that tiotropium is more effective than a β2-agonist (salmeterol) in preventing exacerbations of COPD. In the trial, the use of concomitant medica-
tions is a serious methodologic issue that limits the interpretation of the results. During the run-in period, anticholinergic drugs and long-acting β₂-agonists, but not short-acting β₂-agonists, were discontinued. Fifty-two percent of the patients in the tiotropium group and 53% of the patients in the salmeterol group were also receiving a short-acting β₂-agonist. Thus, the comparison seems unfair, since half the tiotropium group received two bronchodilators with two different mechanisms of action, but all the patients in the salmeterol group received only one class of bronchodilators. Did the superiority of tiotropium remain in the subgroup of patients who did not use short-acting β₂-agonists?

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No potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: I do not think that the study comparing salmeterol with tiotropium treatment of COPD will result in much change in clinical practice, since the greatest effect was seen in patients with severe disease. In daily practice, such patients would most likely be receiving triple therapy of tiotropium, inhaled glucocorticoids, and long-acting β₂-agonists, rendering the question of which bronchodilator is better to secondary importance. The pertinent question would be which long-acting bronchodilator a patient should receive first; this could have been answered by limiting recruitment to patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I and II disease only.

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No potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: There has been a concern that inhaled anticholinergic drugs might increase the risk of cardiovascular adverse events. As in the Understanding Potential Long-Term Impacts on Function with Tiotropium trial (NCT00144339), the study by Vogelmeier et al. excluded high-risk patients with cardiac disease. The exclusion of patients with cardiac disease may have favored tiotropium. Caution should be advised in patients at high risk for cardiovascular complications given the paucity of data regarding such patients.

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No potential conflict of interest relevant to this letter was reported.


THE AUTHORS REPLY: We agree with Restrick et al. that evaluating the clinical efficacy of smoking cessation with the use of solid patient-relevant outcomes, such as exacerbations, could complement the already existing body of evidence in support of such an intervention.

In response to Lloret-Linares and Bergmann: in our trial, any previous use of an anticholinergic drug or a β₂-agonist had to be discontinued at randomization, and all patients were offered albuterol as rescue medication only. We are not aware of any published data suggesting that the efficacy of a long-acting bronchodilator to prevent exacerbations may be affected by the addition of a short-acting bronchodilator agent given on an as-needed basis. International COPD guidelines do not provide guidance on the choice of rescue medication. Albuterol has been the standard rescue medication in almost all COPD trials, irrespective of the mechanism of action of the regular long-acting bronchodilator under investigation.

Regarding the comment by Schembri: the majority of patients included in our study had moderate (stage II) or severe (stage III) COPD according to the GOLD classification. Patients in each of these subgroups benefited similarly from tiotropium treatment (hazard ratios, 0.88 and 0.86, respectively, in favor of tiotropium vs. salmeterol).
Given the high proportion of patients with moderate COPD (49%) for whom therapy with inhaled glucocorticoids is not recommended, we believe that the question of which long-acting bronchodilator one should use first has been adequately addressed.

We agree with Oba that, for patients with COPD who have high-risk cardiac conditions, there is incomplete clinical evidence regarding the comparative benefit–risk ratio of individual treatment options. However, it is unclear which of the study drugs may have been favored by excluding such patients, who are typically also excluded from other COPD trials, irrespective of the therapeutic intervention investigated. In addition, some of the exclusion criteria regarding concomitant cardiovascular diseases were required for consistency with approved warnings and precautions associated with the use of a long-acting β₂-agonist, salmeterol. It should also be noted that 26% of the patients in our study had stable concomitant cardiac disease (e.g., angina pectoris, previous myocardial infarction, cardiac failure, or hypertensive heart disease) at baseline (Section 11 in the Supplementary Appendix, available with the full text of our article at NEJM.org). Patients with COPD who have characteristic cardiac coexisting conditions are therefore represented in the study population. Nevertheless, including high-risk patients with cardiac disease remains a challenging issue for COPD trials.

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Since publication of their article, the authors report no further potential conflict of interest.

5. Prescribing information: Serevent Diskus. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020692s032lbl.pdf)

Prenatal versus Postnatal Repair of Myelomeningocele

TO THE EDITOR: In the report on the results of the Management of Myelomeningocele Study (MOMS) (March 17 issue), a randomized trial comparing the efficacy of prenatal repair of myelomeningocele with that of postnatal repair, Adzick et al. state that prenatal closure reduced the need for ventriculoperitoneal shunting and improved gait function postnatally. However, lower urinary tract function was not addressed.

We cared for 5 children who participated in MOMS but who received postnatal care at Children’s Hospital Boston because of its proximity to their domiciles. They ranged in age from 1.5 to 36 months; all showed complete external urethral sphincter denervation on needle electromyography and detrusor overactivity on urodynamic studies. This denervation causes intractable wetting that will require surgery when the patients are older. These findings were compared with those in 88 children of similar age in whom the neurologic level of the myelomeningocele was similar and whose defect was closed postnatally at Children’s Hospital Boston. We found significantly less denervation of the external urethral sphincter and near-normal detrusor activity in the children who underwent postnatal surgery as compared with those who received prenatal surgery.

Given our experience, we are concerned that any enthusiastic adoption of prenatal closure that MOMS may generate will not be advantageous in the long term because of the urologic problems that may ensue. We believe that further study of the effects of prenatal repair on the urologic and other organ systems should be conducted in children who participated in MOMS before this approach to myelomeningocele repair is wholeheartedly endorsed.