

## CORRESPONDENCE



## Prevention of Death in COPD

**TO THE EDITOR:** Calverley et al. do not sufficiently emphasize some aspects of their study on the use of salmeterol and fluticasone in patients with chronic obstructive pulmonary disease (COPD) (Feb. 22 issue).<sup>1</sup> Their study, called the Towards a Revolution in COPD Health (TORCH) trial, showed that treatment with fluticasone alone actually increased mortality at the end of 3 years, although the increase was not significant. This finding contrasts markedly with retrospective analyses and meta-analyses showing a substantial reduction in mortality from all causes by about 25% associated with the drug.<sup>2,3</sup> This discrepancy between the results of a well-conducted, randomized, controlled trial and historical analyses highlights how misleading the latter may be. The net effect of therapy with inhaled corticosteroids for patients who have COPD may be detrimental in view of the increased episodes of pneumonia associated with such agents.<sup>1,4</sup> Another important result of the TORCH study was the failure of inhaled corticosteroids, even when combined with salmeterol, to reduce the annual decline in lung function. The lack of effect of inhaled corticosteroids on mortality and disease progression may reflect resistance to the antiinflammatory effects of corticosteroids in COPD.<sup>5</sup>

Peter J. Barnes, D.M., D.Sc.

National Heart and Lung Institute  
London SW3 6LY, United Kingdom  
p.j.barnes@imperial.ac.uk

Dr. Barnes reports being a member of advisory boards at and receiving research funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Pfizer. No other potential conflict of interest relevant to this letter was reported.

1. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-89.

2. Sin DD, Wu L, Anderson JA, et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 2005;60:992-7.

3. Macie C, Wooldrage K, Manfreda J, Anthonisen NR. Inhaled corticosteroids and mortality in COPD. *Chest* 2006;130:640-6.

4. Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:144-9.

5. Barnes PJ. Reduced histone deacetylase in COPD: clinical implications. *Chest* 2006;129:151-5.

**TO THE EDITOR:** The TORCH trial is described as a parallel-group study primarily comparing the combination of salmeterol and fluticasone with placebo but also comparing the combination with each component alone. The same data can be analyzed according to a factorial design<sup>1</sup> to estimate the main effect of each drug with adjustment for the other (Table 1).

The factorial analysis indicates that the effect of the combination therapy on mortality was entirely due to salmeterol, and this effect (a reduction in mortality of 19%) was highly significant ( $P=0.004$ ) on the basis of data from 3054 patients who received the drug and 3058 who did not. By contrast, the fluticasone component had no effect on mortality among 3067 patients who received the drug and 3045 who did not. The re-

## THIS WEEK'S LETTERS

2211 Prevention of Death in COPD

2214 Posaconazole Prophylaxis in Hematologic Cancer

2218 Treatment of Symptomatic Uterine Fibroids

2219 New Treatments for Diabetes

2223 Monoclonal Gammopathy of Undetermined Significance

2224 Pulmonary-Valve Endocarditis

**Table 1. Analysis of Main Effects of Treatment with Salmeterol and Fluticasone on Mortality.**

Factor	Placebo (A)	Salmeterol (B)	Fluticasone (C)	Salmeterol plus Fluticasone (D)	Main Effect*			
					Salmeterol Received		Fluticasone Received	
					yes (B+D)	no (A+C)	yes (C+D)	no (A+B)
No. of subjects	1524	1521	1534	1533	3054	3058	3067	3045
No. of deaths	231	205	246	193	398	477	439	436
Probability of death at 3 yr (%)	15.2	13.5	16.0	12.6	13.0	15.6	14.3	14.3
Hazard ratio (95% confidence interval)					0.81(0.70–0.94)		1.00 (0.87–1.15)	
Chi-square					8.20		0.00	
P value					0.004		0.99	

\* Data for each treatment were adjusted for the other treatment.

sults of the factorial analysis support the conclusions of the editorial by Rabe<sup>2</sup> accompanying the TORCH report.

Considering that the combination of salmeterol and fluticasone is superior to either drug alone in reducing exacerbations of COPD and improving health status and lung function, the reduction of mortality associated with salmeterol alone should be balanced against the more favorable pattern of symptomatic effects of the combination of the two drugs, with allowances made for the increased frequency of pneumonia.

Carlo La Vecchia, M.D.

Istituto di Ricerche Farmacologiche Mario Negri  
20157 Milan, Italy  
lavecchia@marionegri.it

Leonardo M. Fabbri, M.D.

University of Modena e Reggio Emilia  
41100 Modena, Italy

Dr. La Vecchia has been asked by GlaxoSmithKline to review and comment on the TORCH study, and financial aspects are under discussion. Dr. Fabbri reports receiving consulting and lecture fees from Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck, Novartis, Roche, and Pfizer and grant support from Altana Pharma, AstraZeneca, Boehringer Ingelheim, Menarini, Miat, Schering–Plough, Chiesi Farmaceutici, GlaxoSmithKline, Merck, UCB, and Pfizer. No other potential conflict of interest relevant to this letter was reported.

1. Peto R. Clinical trial methodology. *Biomedicine* 1978;28 Spec No.:24-36.
2. Rabe KF. Treating COPD — the TORCH trial, P values, and the dodo. *N Engl J Med* 2007;356:851-4.

**TO THE EDITOR:** The TORCH study investigators report that inhaled fluticasone at high doses may reduce exacerbation rates in COPD but that the drug may cause more harm than good overall.

The finding that pneumonia occurred more frequently in the two groups receiving fluticasone (in an average of 19% of the patients) than in the placebo group or the salmeterol-only group (in an average of 13%) is worrisome. The number needed to harm is 17 ( $P < 0.001$ ). This could be explained by immunosuppression due to systemic activity.

How do Calverley et al. explain how they derived the numbers needed to treat? They state that “the number needed to treat to prevent an exacerbation in 1 year was 4, and the number needed to treat to prevent a hospitalization was 32.” This statement relates to placebo as compared with combination therapy. This finding is not immediately apparent from the data provided. For example, the number needed to treat for exacerbations seems counterintuitive, given a reduction in the annual rate of exacerbation from 1.13 to 0.85, an absolute difference of 0.28. Likewise, the annual hospitalization rate was reduced from 0.19 to 0.16, a difference of 0.03.

Martin Duerden, M.B., B.S., M.R.C.G.

Meddygfa Gyffin, Conwy  
North Wales LL32 8LT, United Kingdom

**TO THE EDITOR:** By assigning a group of symptomatic patients with COPD to a placebo group without the use of long-acting bronchodilators, Calverley et al. violated paragraph 29 of the Declaration of Helsinki, which states that “the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and thera-

peutic methods.” These patients had some degree of airway reversibility. Comparing the post-bronchodilator response with the percent of the predicted value for forced expiratory volume in 1 second (FEV<sub>1</sub>) rather than with the prebronchodilator FEV<sub>1</sub> minimized the amount of reversibility. It is no wonder that so many symptomatic patients dropped out of the placebo group.

Yizhak Kupfer, M.D.

Sidney Tessler, M.D.

Maimonides Medical Center  
Brooklyn, NY 11219  
stessler@maimonidesmed.org

**TO THE EDITOR:** In the editorial accompanying the report on the TORCH study, Rabe refers to a 25% prevalence of venous thromboembolism in patients hospitalized with a severe exacerbation of COPD, citing a study by Tillie-Leblond et al.<sup>1</sup> An instinctive response of defensive medical practice may now be to order a computed tomographic scan with a pulmonary-embolism protocol for every patient with a severe COPD exacerbation on the assumption that a 25% return must be cost-effective.

Tillie-Leblond et al. actually report that “25% of COPD patients with severe unexplained breathlessness have been shown to have pulmonary embolism.” The subjects were selected because of “the absence of a lower respiratory tract infection” — in other words, an exacerbation of COPD “of unknown origin.” Experience tells us that the prevalence of venous thromboembolism with exacerbations of COPD is low — only 3.3% in a recent study of 123 consecutive patients.<sup>2</sup> The discussion in that report echoes that of Robin and McCauley,<sup>3</sup> who bemoaned the ingrained belief that a low partial pressure of arterial oxygen is of positive predictive value for the diagnosis of venous thromboembolism.

Niall Keaney, M.B., Ph.D.

Sunderland Royal Hospital  
Sunderland SR4 7TP, United Kingdom  
niall.keaney@chs.northy.nhs.uk

1. Tillie-Leblond I, Marquette C-H, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006;144:390-6.

2. Rutschmann OT, Cornuz J, Poletti P-A, et al. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax* 2007;62:121-5.

3. Robin ED, McCauley RF. The diagnosis of pulmonary embolism: when will we ever learn? *Chest* 1995;107:3-4.

**THE AUTHORS REPLY:** Barnes is concerned that inhaled corticosteroids increase mortality in COPD. Although in our study, numerically more patients died in the group that received fluticasone alone than in the placebo group (hazard ratio, 1.06), the difference was not significant ( $P=0.53$ ). Space limitations precluded a discussion of differences between our data and those from database analyses, but we agree that a large, randomized, controlled trial such as ours provides a more robust test of the effect of inhaled corticosteroids on survival than do such analyses. The rate of decline in lung function cannot be inferred from the spirometric data in our study.

La Vecchia and Fabbri have undertaken an interesting post hoc analysis suggesting that the salmeterol component has a substantial effect on mortality. Factorial analysis assumes that each treatment has the same additive effect in the absence and presence of the other treatment. This was not the case for the TORCH trial. Our data show the clear clinical superiority of combination treatment with salmeterol and fluticasone, including fewer exacerbations and better health status.

Kupfer and Tessler suggest that our study was unethical. During the trial design, there was concern about the safety and efficacy of the component treatments, questions that our data have resolved. Patients in the placebo group received regular short-acting bronchodilators, but our results show that this treatment will not be an appropriate standard of care in the future. The degree of bronchodilator reversibility in our patients was similar to that in other large COPD trials, which failed to show any relationship between clinical outcomes and reversibility.<sup>1-3</sup>

Duerden suggests that treatment with inhaled corticosteroids may do more harm than good. More patients with pneumonia were reported in groups that received inhaled corticosteroids, although there was no disproportionate mortality from pneumonia among patients receiving inhaled corticosteroid monotherapy, nor did the overall rate of hospitalization for COPD differ from that in the placebo group. We agree that more data are needed to better understand this finding. Large data sets will be needed, since pneumonia was relatively infrequent, as compared with other serious outcomes (about 1000 cases of pneumonia in 780 patients vs. 13,000 exacerbations of COPD in 4000 patients). We calculated

the number needed to treat as the number of patients required to prevent one exacerbation, according to published methods.<sup>4</sup> This number is not the same as the number needed to treat to prevent one patient from having an exacerbation, a number more appropriate for a binary event such as mortality. Although attractive in clinical practice, the number needed to treat should be viewed with caution, since it depends on the background event rate in the population under study.

Peter Calverley, M.D.

University Hospital Aintree  
Liverpool L9 7AL, United Kingdom  
pmacal@liverpool.ac.uk

Julie Anderson, M.A.

GlaxoSmithKline  
Greenford UB6 0HE, United Kingdom

Bartolome Celli, M.D.

Caritas St. Elizabeth's Medical Center  
Boston, MA 02135-2997

1. Calverley PMA, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 2003;58:659-64.
2. Calverley PMA, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449-56. [Erratum, *Lancet* 2003;361:1660.]
3. Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. *Chest* 2003;123:1441-9.
4. Halpin DMG. Evaluating the effectiveness of combination therapy to prevent COPD exacerbations: the value of NNT analysis. *Int J Clin Pract* 2005;59:1187-94.

## Posaconazole Prophylaxis in Hematologic Cancer

**TO THE EDITOR:** Ullmann et al. and Cornely et al. (Jan. 25 issue)<sup>1,2</sup> report on posaconazole prophylaxis in patients with hematologic cancers. Ullmann et al. found that posaconazole was superior to fluconazole for protection against invasive aspergillosis, and Cornely et al. found that posaconazole was superior to fluconazole and also to itraconazole in preventing fungal infections. After the widespread use of fluconazole and voriconazole as prophylaxis<sup>3</sup> and antifungal treatment, an increase in the risk of infections with resistant fungi was observed.<sup>4,5</sup> Selection pressure due to continuous exposure to azoles appears to play a crucial role in the emergence of resistance to these drugs. Prophylactic use of such a highly active and broad-spectrum antifungal agent as posaconazole, even in high-risk patients, could favor the emergence and amplification of resistant strains. In addition, such use might be associated with a risk of cross-resistance with other azoles, reducing their efficacy in the treatment of life-threatening fungal infections.

Stefan Weiler, M.D.

Romuald Bellmann, M.D.

Innsbruck Medical School  
A-6020 Innsbruck, Austria  
romuald.bellmann@i-med.ac.at

Dr. Weiler reports receiving salary support from Pfizer and Torrex-Chiesi. No other potential conflict of interest relevant to this letter was reported.

1. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007;356:335-47.
2. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007;356:348-59.
3. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992;326:845-51.
4. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med* 1991;325:1274-7.
5. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med* 2004;350:950-2.

**TO THE EDITOR:** Aspergillosis and infection with not-uncommon opportunistic fungi were the most frequent breakthrough infections in the studies of posaconazole prophylaxis reported by Ullmann et al. and Cornely et al. One point mutation in aspergillus cytochrome P-450 (CYP) demethylase could result in posaconazole resistance.<sup>1</sup> It is unclear whether the cases of aspergillosis occurred because aspergillus isolates developed resistance or tolerance to posaconazole or because some patients with mucositis, poor oral intake, or both had suboptimal posaconazole levels. Since another triazole, voriconazole, has emerged as the preferred treatment for aspergillosis,<sup>2</sup> it will be important to determine whether preexposure of