

Data in the Current Controlled Trials register (ISRCTN) refer to inclusion only and do not specify plans for monitoring and evaluation. Unfortunately, there were no data available from Portugal that would have justified the inclusion of those findings.

Fritz H. Schröder, M.D.
Monique Roobol, Ph.D.

Erasmus Medical Center
3000 CA Rotterdam, the Netherlands
secr.schroder@erasmusmc.nl

Sue Moss, Ph.D.
Institute of Cancer Research
Sutton SM25NG, United Kingdom
for the ERSPC Investigators

1. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;95:868-78.
2. Bill-Axelsson A, Holmberg L, Filén F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian Prostate Cancer Group-4 randomized trial. *J Natl Cancer Inst* 2008;100:1144-54.
3. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002;360:103-6.
4. Platz EA, Leitzmann MF, Visvanathan K, et al. Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst* 2006;98:1819-25.

Esomeprazole for Asthma

TO THE EDITOR: In their article on the use of esomeprazole in patients with poorly controlled asthma (April 9 issue),¹ Mastronarde et al. conclude that treatment with proton-pump inhibitors does not improve asthma control in such patients. They also state that despite a high prevalence of asymptomatic gastroesophageal reflux in these patients, the condition is not a likely cause of poorly controlled asthma. In clinical practice, esophageal reflux is usually confirmed by ambulatory pH monitoring with the use of an instrument that assesses reflux episodes in patients with acid reflux but not in those with nonacid reflux.^{2,3} In addition, acid-reflux events that are identified by pH monitoring probably represent a subgroup of reflux events, and pH monitoring during treatment has been considered to be a low-yield measurement.⁴ The data reported by Mastronarde et al. show only that acid reflux is not a likely cause of poorly controlled asthma. In the subgroup analyses, no significant interaction was found between gastroesophageal reflux and factors that are known to be associated with risk, including body-mass index, older age, sex, and former smoking status.⁵ Thus, other possibilities should be explored to explain the high prevalence of asymptomatic gastroesophageal reflux in these patients.

Ching-Sheng Hsu, M.D.
Buddhist Tzu Chi General Hospital
Taipei 231, Taiwan

Jia-Horng Kao, M.D., Ph.D.
National Taiwan University Hospital
Taipei 100, Taiwan
kaojh@ntu.edu.tw

1. The American Lung Association Asthma Clinical Research Centers. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med* 2009;360:1487-99.
2. Canning BJ, Mazzone SB. Reflex mechanisms in gastroesophageal reflux disease and asthma. *Am J Med* 2003;115:Suppl 3A:45S-48S.
3. Kahrilas PJ, Sifrim D. High-resolution manometry and impedance-pH/manometry: valuable tools in clinical and investigational esophagology. *Gastroenterology* 2008;135:756-69.
4. Poelmans J, Tack J. Extraesophageal manifestations of gastroesophageal reflux. *Gut* 2005;54:1492-9.
5. Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut* 2007;56:756-62.

TO THE EDITOR: Mastronarde et al. conclude that asymptomatic gastroesophageal reflux may not be a frequent cause of poor asthma control. We disagree, because although the use of proton-pump inhibitors diminishes the acidity of the refluxate, it does not reduce either the number or proximal extent of reflux events.¹ Microaspiration and esophageal reflexes may still contribute to airway inflammation in patients with asthma who are receiving a high-dose proton-pump inhibitor. Only trials that include a study group undergoing effective reflux control could possibly support the conclusion cited above. As the authors point out, asymptomatic reflux may be responsible for adverse health effects that are unrelated to asthma. Endoscopy with bi-

opsy specimens obtained from the squamocolumnar junction or segments of columnar-lined esophagus would be a more useful approach than pH monitoring for identifying asymptomatic patients who require treatment for gastroesophageal reflux disease (GERD) or surveillance.²

Johannes Lenglinger, M.D.

Martin Riegler, M.D.

Medical University Vienna

1090 Vienna, Austria

johannes.lenglinger@meduniwien.ac.at

1. Hemmink GJ, Bredenoord AJ, Weusten BL, Monkelbaan JF, Timmer R, Smout AJ. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? *Am J Gastroenterol* 2008;103:2446-53.
2. Lenglinger J, Eisler M, Wrba F, et al. Update: histopathology-based definition of gastroesophageal reflux disease and Barrett's esophagus. *Eur Surg* 2006;40:165-75.

TO THE EDITOR: Mastrorarde et al. report that esomeprazole had no benefit in patients with poorly controlled asthma and asymptomatic gastroesophageal reflux. An alternative explanation for the lack of efficacy is related to bacterial overgrowth in the stomach, promoted by acid suppression. A gastric pH of more than 4 favors the growth of predominantly gram-negative bacteria in the stomach.^{1,2} Although proton-pump inhibitors reduce both the volume and acidity of gastric contents, they do not prevent pulmonary microaspiration. In large population studies, the use of acid-suppressing drugs has been associated with the development of community-acquired pneumonia.^{3,4} We suggest that recurrent microaspiration of bacteria-enriched gastric contents might not have been sufficient to overwhelm pulmonary defense mechanisms but might have sustained lung inflammation in the group of patients with poorly controlled asthma evaluated by Mastrorarde et al.

Matt P. Wise, D.Phil.

Anton G. Saayman, M.B., Ch.B.

Paul J. Frost, M.B., Ch.B.

University Hospital of Wales

Cardiff CF14 4XW, United Kingdom

mattwise@doctors.org.uk

1. Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut* 1996;39:54-9.
2. Wang K, Lin HJ, Tseng GY, et al. The effect of H2-receptor

antagonist and proton pump inhibitor on microbial proliferation in the stomach. *Hepatogastroenterology* 2004;51:1540-3.

3. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955-60.
4. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med* 2007;167:950-5.

THE AUTHOR REPLIES: Both Hsu and Kao and Lenglinger and Riegler make the valid point that therapy with proton-pump inhibitors is effective only in reducing acid-reflux events. We agree that our study has not ruled out the possibility that nonacid reflux may contribute to asthma events. However, we know of no evidence that nonacid reflux can cause reflex bronchoconstriction in the same way as acid instillation into the esophagus or airways.

We do not address the question of whether body-mass index, age, smoking status, and sex differed in patients with reflux and in those without reflux. We report only that there was no difference in treatment effect in these subgroups. We speculate that the high prevalence of reflux in patients with asthma is a consequence of the underlying disordered lung mechanics, since a similarly high prevalence of acid reflux is also found among patients with cystic fibrosis, those with chronic obstructive pulmonary disease, and those with interstitial fibrosis.¹⁻³

Both the question of whether it is appropriate to screen asymptomatic patients who are at risk for GERD with endoscopy and biopsy and the question of whether asymptomatic patients with Barrett's esophagus should be treated with proton-pump inhibitors, as implied by Lenglinger and Riegler, are beyond the scope of our work and have been addressed by statements from other expert groups.^{4,5}

Wise and colleagues present the interesting hypothesis that bacterial colonization of the gastric contents and microaspiration in patients who are receiving proton-pump inhibitors might lead to worsening asthma. We did not find any convincing evidence that the use of proton-pump inhibitors leads to an increase in the rate of pneumonia or worsening of asthma. However, it is possible that there was a balanced trade-off be-

tween beneficial effects and harmful effects of acid suppression.

Robert A. Wise, M.D.

Johns Hopkins University School of Medicine
Baltimore, MD 21224
rwise@jhmi.edu

for the Writing Committee of the American Lung Association Asthma Clinical Research Centers

Since publication of this article, Dr. Wise reports receiving consulting fees from Genentech. No further potential conflict of interest relevant to this letter was reported.

1. Button BM, Roberts S, Kotsimbos TC, et al. Gastroesopha-

geal reflux (symptomatic and silent): a potentially significant problem in patients with cystic fibrosis before and after lung transplantation. *J Heart Lung Transplant* 2005;24:1522-9.

2. Kempainen RR, Savik K, Whelan TP, Dunitz JM, Herrington CS, Billings JL. High prevalence of proximal and distal gastroesophageal reflux disease in advanced COPD. *Chest* 2007;131:1666-71.

3. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J* 2006;27:136-42.

4. Wang KK, Sampliner RE Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008;103:788-97.

5. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008;135(4):1383-91, 1391.e1-1391.e5.

Long-Acting Beta-Agonists in Asthma

TO THE EDITOR: In her Perspective article, Kramer (April 16 issue)¹ succinctly summarizes the decisions of the Food and Drug Administration (FDA) regarding the continued availability of single-agent long-acting beta-agonist (LABA) inhalers for use in patients with asthma. She further clarifies that these drugs would remain on the market for patients with chronic obstructive pulmonary disease (COPD), even if the asthma indication were removed.

As a practicing pulmonary physician, I have a different perspective to offer for debate. A not insignificant number of patients that my colleagues and I see do not correctly differentiate between asthma and COPD, and therefore, it is quite possible that single-agent LABAs would end up being used in patients with asthma. Also, separate single-agent LABAs and corticosteroid prescriptions can often be used separately in real life, either because of a misunderstanding or because the inhaled corticosteroid runs out before the inhaled single-agent LABA does. Given the ready availability of two combined LABA-corticosteroid agents, the absence of evidence that single-agent LABAs are superior to single-agent corticosteroid inhalers in patients with asthma, and the well-defined risk of death from single-agent LABAs among patients with asthma, I submit that single-agent LABAs should be removed from the market as a public safety measure.

Arun Agarwal, M.D.

Putnam Hospital Center
Carmel, NY 10512
arun.agarwal.md@gmail.com

Dr. Agarwal reports receiving lecture fees from GlaxoSmithKline and Boehringer Ingelheim. No other potential conflict of interest relevant to this letter was reported.

1. Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists — the influence of values. *N Engl J Med* 2009;360:1592-5.

TO THE EDITOR: We respectfully disagree with the implication in the editorial by Drazen and O'Byrne¹ on the risks of LABAs in achieving asthma control that a large study on the safety of LABAs has not been performed because of financial considerations. GlaxoSmithKline has rigorously explored the conduct of a study of mortality associated with LABAs in patients with asthma. However, such a study is not feasible. Because of the low rate of asthma-related deaths, a study designed to rule out a 20% increase in mortality (relative risk, 1.2) would require approximately 700,000 subjects per group. If an appropriately powered mortality study had been feasible, we would have done it.

Recognizing that limitation, since the Salmeterol Multicenter Asthma Research Trial (SMART)² was completed, GlaxoSmithKline has sponsored important research on LABA safety, including a year-long study of asthma exacerbations in blacks,³ the largest prospective study to date examining asthma genotype and response to salmeterol,⁴ and epidemiologic studies of more than 80,000 patients receiving salmeterol. None of these varied approaches showed an increased risk of asthma-related death.⁵ At GlaxoSmithKline, patient safety is our highest priority. We continue to conduct