

previous myocardial infarction, bypass grafting, and other factors.

As suggested by Kiat, we are performing post hoc analyses to better delineate a high-risk subgroup on the basis of the ischemic burden as assessed on MPI at baseline and during a follow-up period of 6 to 14 months.

Nagajothi et al. acknowledge that our intention-to-treat analysis was appropriate but encourage further analysis according to actual treatment received. A detailed analysis of the “crossover” population is under way.

Finally, Mak emphasizes the incremental benefit of the use of dual antiplatelet therapy on the composite end point of death, myocardial infarction, or stroke at 1 year in the CREDO trial.<sup>2</sup> Enrollment in our trial antedated these results. However, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial,<sup>3</sup> involving patients with stable coronary artery disease, did not show a compelling benefit of combined treatment with aspirin and clopidogrel in reduc-

ing death, myocardial infarction, or stroke in long-term follow-up.

William E. Boden, M.D.

University at Buffalo School of Medicine  
and Biomedical Sciences  
Buffalo, NY 14214

Koon K. Teo, M.B., B.Ch., Ph.D.

McMaster University Medical Center  
Hamilton, ON L8N 3Z5, Canada

William S. Weintraub, M.D.

Christiana Care Health System  
Newark, DE 19718

for the COURAGE Trial Investigators

1. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina — summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 2003;41:159-68.
2. Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20. [Erratum, *JAMA* 2003;289:987.]
3. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.

## Diabetic Gastroparesis

**TO THE EDITOR:** In his review of diabetic gastroparesis, Camilleri (Feb. 22 issue)<sup>1</sup> states that in our clinical trial of exenatide,<sup>2</sup> nausea and vomiting led to the “cessation of treatment in about one third of patients.” This information is incorrect. Of 282 patients randomly assigned to receive exenatide, 54 withdrew from the study (27 withdrew because of an adverse event, 10 because of protocol violations, 7 because of the patient’s decision, 4 because of loss of glucose control, and 1 because of the physician’s decision, and 5 were lost to follow-up). As stated in our article, 18 of these patients withdrew from the study because of nausea or other gastrointestinal symptoms. This rate is in line with the dropout rates in other recent clinical trials, which range from 1.8 to 5.1%.<sup>3-5</sup> Mild-to-moderate nausea is the most common adverse event in patients receiving exenatide. However, the development of tolerance to these adverse gastrointestinal effects of exenatide has been suggested in our trial as well as in other long-term phase 3 trials of the drug that have been reported.<sup>3-5</sup>

Robert J. Heine, M.D., Ph.D.

VU University Medical Center  
1007 MB Amsterdam, the Netherlands

Robert Brodows, M.D.

Lilly Research Laboratories  
Indianapolis, IN 46285

1. Camilleri M. Diabetic gastroparesis. *N Engl J Med* 2007;356:820-9.
2. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 2005;143:559-69.
3. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005;28:1092-100.
4. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005;28:1083-91.
5. Nauck MA, Duran S, Kim D, et al. A comparison of twice daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 2007;50:259-67.

**TO THE EDITOR:** In Table 2 of his article, Camilleri lists the motilin-receptor agonists erythromycin,

clarithromycin, and azithromycin as recommended agents for the treatment of diabetic gastroparesis. I agree with the recommendation regarding erythromycin. However, clarithromycin, azithromycin, and other more acid-stable macrolides and azalides are likely to be poor alternatives. Erythromycin A in an acidic medium such as gastric juice is degraded into its anhydrous hemiketal and spiroketal forms.<sup>1</sup> Both forms are inactive microbiologically, but they have motilin-like activity that is several times greater than that of erythromycin A.<sup>1,2</sup> It is mostly because of this characteristic that erythromycin has a low oral bioavailability of the microbiologically active drug and considerable gastrointestinal adverse effects. Clarithromycin and azithromycin have modified chemical structures that are more acid-stable and do not form the highly active motilin mimics<sup>2,3</sup>; consequently, neither drug is likely to be as useful as erythromycin for the treatment of motilin-responsive disorders. Both clarithromycin and azithromycin are also more expensive than erythromycin.

Eufonio G. Maderazo, M.D.

William W. Backus Hospital  
Norwich, CT 06360

1. Weymouth-Wilson AC. The role of carbohydrates in biologically active natural products. *Nat Prod Rep* 1997;14:99-110.
2. Tsuzuki K, Sunazuka T, Marui S, et al. Motilides, macrolides with gastrointestinal motor stimulating activity. I. O-substituted and tertiary N-substituted derivatives of 8,9-anhydroerythromycin A 6,9-hemiacetal. *Chem Pharm Bull (Tokyo)* 1989;37:2687-700.
3. Gill CJ, Abruzzo GK, Flattery AM, et al. In vivo evaluation of three acid-stable azalide compounds, L-701,677, L-708,299 and L-708,365 compared to erythromycin, azithromycin and clarithromycin. *J Antibiot (Tokyo)* 1995;48:1141-7.

**TO THE EDITOR:** Camilleri compares gastrointestinal prokinetic agents with regard to their efficacy and side effects. For metoclopramide, neurologic side effects are reported from one 4-week trial. Tardive dyskinesia and other extrapyramidal effects are not mentioned in the text and are cited only briefly in Table 2 of the article. Since clinical trials of metoclopramide have been short-term trials, this review understates the risk of tardive dyskinesia among patients treated with metoclopramide on a long-term basis.

Metoclopramide is a dopamine-receptor antagonist that causes parkinsonism, acute dystonia, akathisia, and tardive dyskinesia. The risk of tardive dyskinesia after long-term treatment with antipsychotic drugs that are dopamine-receptor antagonists is 5% per year of drug exposure.<sup>1</sup> Although prospective data for metoclopramide are unavailable, the prevalence and severity of tardive

dyskinesia are increased after long-term treatment.<sup>2,3</sup> Diabetes is associated with an increased frequency and severity of tardive dyskinesia.<sup>2,4</sup> The risk of tardive dyskinesia is underrecognized by physicians who use metoclopramide for long-term treatment<sup>3</sup>; this is especially important in view of the increased use of metoclopramide since the withdrawal of cisapride in 2000.<sup>5</sup>

Daniel Tarsy, M.D.

Beth Israel Deaconess Medical Center  
Boston, MA 02215  
dtarsy@bidmc.harvard.edu

1. Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? *Mov Disord* 2006;21:589-98.
2. Ganzini L, Heintz RT, Hoffman WF, Casey DE. The prevalence of tardive dyskinesia in neuroleptic-treated diabetics: a controlled study. *Arch Gen Psychiatry* 1991;48:259-63.
3. Pasricha PJ, Pehlivanov N, Sugumar A, Jankovic J. Drug insight: from disturbed motility to disordered movement — a review of the clinical benefits and medicolegal risks of metoclopramide. *Nat Clin Pract Gastroenterol Hepatol* 2006;3:138-48.
4. Woerner MG, Saltz BL, Kane JM, Lieberman JA, Alvir JM. Diabetes and development of tardive dyskinesia. *Am J Psychiatry* 1993;150:966-8.
5. Shaffer D, Butterfield M, Pamer C, Mackey AC. Tardive dyskinesia risks and metoclopramide use before and after U.S. market withdrawal of cisapride. *J Am Pharm Assoc (2003)* 2004;44:661-5.

**THE AUTHOR REPLIES:** Heine and Brodows correctly point out that the withdrawal rate attributed to nausea in their clinical trial was overstated in my article. However, in trials involving longer-term treatment that may better reflect clinical experience,<sup>1-4</sup> as well as in the study by Nauck et al. cited by Heine and Brodows, there is a high prevalence of nausea (average prevalence, approximately 33%). The all-cause withdrawal rate in these randomized, controlled, or open-label treatment trials involving exenatide ranged from 21 to 45%. Approximately 4% of these withdrawals were attributed to a loss of glucose control and 7% were attributed to adverse events. It is unclear whether the withdrawal of consent by approximately 11% of patients and withdrawals because of protocol violations by approximately 10% of patients were due to nausea, which was by far the most frequent adverse event (57% in the article by Heine et al. cited by Heine and Brodows). Nausea and vomiting in patients with diabetes may be wrongly attributed to gastroparesis rather than to iatrogenic disease, which may be reversible.

I agree with Maderazo's statement regarding the different potencies of macrolides in the stimulation of gastric emptying. I included clarithromycin and azithromycin in Table 2 because this

table reflects national society guidelines, as noted in one of the table footnotes.

The potential for tardive dyskinesia during treatment with metoclopramide is important. However, as indicated in the article by Shaffer et al. (to which Tarsy refers in his letter), well-described risk factors are common in reports of metoclopramide-associated tardive dyskinesia. Moreover, Ganzini et al.<sup>5</sup> calculated that the relative risk of tardive dyskinesia was not significantly elevated with use of metoclopramide (relative risk, 1.67; 95% confidence interval, 0.93 to 2.97), although the risk appeared to be higher among patients with diabetes.

Michael Camilleri, M.D.

Mayo Clinic College of Medicine  
Rochester, MN 55905  
camilleri.michael@mayo.edu

Since publication of his article, Dr. Camilleri reports having received research support from Novartis.

1. Riddle MC, Henry RR, Poon TH, et al. Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes Metab Res Rev* 2006;22:483-91.
2. Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab* 2006;8:436-47.
3. Ratner RE, Maggs D, Nielsen LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2006;8:419-28.
4. Buse JB, Klonoff DC, Nielsen LL, et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clin Ther* 2007;29:139-53.
5. Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. *Arch Intern Med* 1993;153:1469-75.

## Case 15-2007: A Woman with Asthma and Cardiorespiratory Arrest

**TO THE EDITOR:** In the Case Record presented by Wechsler et al. (May 17 issue),<sup>1</sup> many possible causes of death in a patient with asthma are considered. However, the discussants do not sufficiently emphasize that lung mechanics and hemodynamic effects associated with airflow obstruction are the most important physiological disturbances in patients with severe acute asthma. Hemodynamic collapse related to dynamic hyperinflation is a common cause of obstructive shock, pulseless electric activity, and cardiac arrest in intubated patients with asthma.

Thiago Lisboa, M.D.

University Rovira Virgili  
43007 Tarragona, Spain

Diego de Mendoza, M.D.

Centro de Investigación Biomédica en Red (CIBER)  
43007 Tarragona, Spain

Jordi Rello, M.D., Ph.D.

Joan XXIII Hospital  
43007 Tarragona, Spain  
jrlo.hj23.ics@gencat.net

1. Case Records of the Massachusetts General Hospital (Case 15-2007). *N Engl J Med* 2007;356:2083-91.

**TO THE EDITOR:** Dr. Shepard is quoted as saying, "The pneumothorax results from the Macklin effect." I suspect that what she really said was, "The pneumomediastinum results from the Macklin effect."

Wallace T. Miller, M.D.

Hospital of the University of Pennsylvania  
Philadelphia, PA 19104

**THE DISCUSSANTS REPLY:** There are many causes of death in young patients with asthma. In addition to hypoxemia from prolonged bronchospasm, we agree with Lisboa et al. that a progressive increase in intrathoracic pressure associated with dynamic hyperinflation can lead to both diminished venous return and mechanical compression of the heart and associated vasculature, with resultant hemodynamic collapse. It is important to recognize these potential causes of complications in patients with asthma who have respiratory failure, since several ventilatory strategies (including the use of low tidal volumes and low respiratory rates) may minimize these risks.