TO THE EDITOR: In their letter to the editor, Braunstein and Polis (1) address the omission of important cardiovascular safety results from a 2003 report on the ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness) trial (2). The 2003 article, authored by Lisse and colleagues (including Polis), reported no statistically significant differences for any cardiovascular end points in comparisons of Vioxx (rofecoxib, Merck & Co., Inc., Whitehouse Station, New Jersey) and naproxen in a 12-week clinical trial. In fact, almost 3 years earlier, Merck gave the U.S. Food and Drug Administration (FDA) a data table that showed a statistically significant relative risk of 7.0 for cardiac events among patients receiving Vioxx compared with those receiving naproxen in the ADVANTAGE trial. The Merck data table is included in a 3-page letter (3) that was written in 2001 in response to the FDA’s request for additional information regarding the ADVANTAGE trial; it shows 7 serious adverse cardiac events in patients receiving Vioxx (6 events adjudicated as myocardial infarction and 1 event adjudicated as a “sudden/unknown” death) and 1 adjudicated myocardial infarction in a patient receiving naproxen. In addition, another event that was “reported as hypertensive heart disease and death by Merck” was reclassified by the FDA in November 2001 as a “sudden/unknown” death, pushing the cardiac event rate for Vioxx to 8 (4).

Merck’s letter and the FDA’s reclassification are emphatic evidence of Merck’s knowledge that the ADVANTAGE trial showed that Vioxx use caused an important and statistically significant excess risk for cardiac events, namely myocardial infarction and “sudden/unknown” death. Merck’s omission of this important risk information from its 2003 article in *Annals* presents a serious public health hazard because it misled the medical community. Braunstein and Polis said that Merck’s predefined procedures kept hypertensive heart disease and death from being externally adjudicated, which would explain their exclusion from the Antiplatelet Trialists’ Collaboration “cardiac event” group. Because Merck defined a list of external adjudication events that excluded such relevant events as hypertensive heart disease, it was fortunate that the FDA adjudicated the case. Merck still omitted this information when they published the trial.

Underlying this already egregious omission of safety data is more deeply disturbing evidence of medicine that has run amok. Internal Merck documents reveal that the ADVANTAGE trial did not have a medical purpose. Instead, it was a “seeding trial,” meant to seed the medical community with Merck’s new drug before it was approved for the market. Thus, the deaths of trial patients receiving Vioxx were deaths in an unnecessary trial. The real participants in the trial were the physician “investigators” (nonparticipants served as controls) who were chosen to participate by Merck sales representatives (5). Merck intended to promote the drug to influential doctors and their patients and then analyze the prescribing information of these physician-investigators for marketing purposes. A Merck public relations supervisor instructed employees to avoid revealing the true purpose of the trial: “I eliminated the reference to seeding. It may be a seeding study, but let’s not call it that in our internal documents” (6).

Merck’s conduct in designing, conducting, analyzing, and publishing the ADVANTAGE trial is disturbing at best. The ethical ramifications of drug-related deaths in a “seeding trial” deserve a more thorough examination than is possible here. The practice of selectively reporting drug safety data is evidence for the need for complete and public disclosure—perhaps on the Internet—of clinical trial data for new drugs. If anything, ADVANTAGE teaches us that we cannot rely on drug companies to honestly report all of the important data.

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Potential Financial Conflicts of Interest: Expert testimony: Dr. Egilman has served as an expert witness in Vioxx litigation. Mr. Presler is employed by Dr. Egilman.

References


Socioeconomic Status and Mortality

TO THE EDITOR: Alter and colleagues (1) address an important question regarding mediating factors that potentially account for the contribution of socioeconomic status to health care disparities. However, because of the potential social and political implications of these results, careful consideration should be given to several key issues that limit the authors’ interpretations. First, it has been previously suggested that socioeconomic status is a multidimensional construct. Although operational definitions are numerous, most incorporate aspects of educational attainment, occupation, and social class. Use of self-reported income as a single measure to represent this construct therefore has the potential to markedly reduce strength of the intended “signal” and underestimate its association with the outcome of interest (2). Second, the authors applied exclusion criteria that potentially attenuate an association between socioeconomic status and mortality and may introduce bias. The authors observe, for example, that patients with lower income had a significantly higher prevalence of cardiac risk factors and were less likely to receive specialty care. By eliminating from analysis those patients who died...
within 24 hours of admission or those with “very severe illness,” the authors have essentially removed the patients with the greatest “exposure” to the potential health effects of socioeconomic status. We find the work by Alter and colleagues potentially informative, but their failure to attend to the multidimensional nature of socioeconomic status leads us to conclude that they may have underrepresented the importance of this construct’s effects on health.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We appreciate the comments of Drs. Shishehbor and Litaker. We agree that socioeconomic status is a multidimensional construct of which income serves as only 1 of many social measures. Although such limitations were acknowledged in our paper, our study did adjust for individual education, employment status, ethnicity, and social support. Adjustment for such variables partially accounted for some of the heterogeneous features of socioeconomic status. Furthermore, the inclusion of more elaborate social measures, although intriguing, would not have mitigated the importance of exploring the causal pathway factors that mediate income–mortality associations—associations that have been consistently observed in the literature and require explanation (1).

We acknowledge that the exclusion of very high-risk patients (that is, those receiving mechanical ventilation or those who died before enrollment) may have introduced bias and attenuated the association between socioeconomic status and mortality. Unfortunately, the exclusion was unavoidable because income was ascertained by using self-administered surveys. Enrollment into the SESAMI (Socio-Economic and Acute Myocardial Infarction) study required patient consent, which also probably contributed to selection bias (2). Consequently, the magnitude of association between income and mortality after acute myocardial infarction might have been less than otherwise expected had we been able to examine a more representative “real-world” population.

Nonetheless, the extent to which such limitations altered our results remains speculative. For example, available evidence suggests that wealth-health gradients are more likely to narrow, not widen, among elderly patients than among younger subgroups—subgroups that disproportionately make up higher-risk “real-world” populations (1, 3). Of importance, the objective of our study was not to measure the true magnitude of association between income and mortality after acute myocardial infarction but to quantify the extent to which income–mortality associations were explained by traditional atherogenic or vascular factors, noncardiac comorbid conditions, and health service use. On the basis of our results and those of others (4), there is no reason to believe that age and cardiovascular risk factors would not have exerted similar explanatory effects on income–mortality associations if higher-risk populations had been examined.

To what extent, if any, can disparities between socioeconomic status and mortality rates be modified through intensive secondary prevention strategies? Are socially disadvantaged patients predestined to die after acute myocardial infarction (regardless of intensive secondary prevention initiatives) because of their baseline cardiovascular risk profiles at the time of presentation? These remain the pertinent questions for future study. Social–epidemiologic and health service research must now explore the impact of secondary preventive interventions to determine whether outcomes can be improved effectively and efficiently among high-risk populations in the real world.

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Potential Financial Conflicts of Interest: None disclosed.

References

CLINICAL OBSERVATIONS

Acute Myocardial Infarction Associated with the Serotonin Syndrome

Background: The serotonin syndrome is an adverse drug reaction manifesting as mental status changes, autonomic hyperactivity, and neuromuscular abnormalities caused by excess stimulation of central nervous system and peripheral serotonin receptors. Diagnosis of the syndrome is based on characteristic clinical findings and history of exposure to serotonergic agents (1). Although peripheral serotonin activity is important for maintaining vascular tone, cardiac ischemia is not a typical complication of the serotonin syndrome or of selective serotonin reuptake inhibitor therapy. On the contrary, use of these agents has been postulated to decrease the risk for acute myocardial infarction (MI), possibly by inhibiting platelet activation (2).

Objective: To describe a case of the serotonin syndrome causing an acute MI.

Case Report: A 31-year-old woman presented to the emergency department because of a change in mental status. She had a history of depression and bipolar disorder and had changed therapy from quetiapine to duloxetine 3 weeks before presentation. Her other medications were paroxetine, bupropion, and clonazepam. During the week before hospitalization, her mother described the patient as...
“twitchy.” On the day of admission, the patient had vomited and was then found somnolent and confused. She had no history of intentional overdose, and no empty pill bottles were found at the scene. Findings on physical examination were consistent with the serotonin syndrome (1). Her vital signs were significant for a heart rate of 120 beats/min and blood pressure of 160/104 mm Hg. She was awake and confused with intermittent lucidity; she did not follow commands. She had nystagmus, a fine tremor, lower-extremity hyperreflexia, and inducible ankle clonus. Initial electrocardiographic findings were unremarkable. Results of laboratory studies were significant for a serum creatine kinase level of 1638 U/L with normal fractionation and a serum troponin I level of 3.83 μg/L.

The patient was treated with aspirin, carvedilol, and lisinopril for cardiomyopathy. Over the next 3 days, her serum troponin I level decreased, and repeated electrocardiography showed inverted T waves in leads I, aVL, II, aVF, and V3 to V6. She had septal, anterior, and lateral hypokinesis; ejection fraction was 0.30 on echocardiography. Her mental status gradually improved. She was discharged home after 4 days but returned 1 week later with pericarditis-like chest pain. During this second admission, a cardiac catheterization showed patent coronary arteries and an ejection fraction of 0.74.

Discussion: Our patient had a cardiac biomarker leak with focal wall motion abnormalities that resolved after 1 week, consistent with myocardial stunning after acute MI. To our knowledge, the only case report of an acute MI associated with selective serotonin reuptake inhibitor therapy was a 69-year-old patient with diabetes and coronary artery disease who experienced an acute MI 5 days after starting venlafaxine therapy. This patient did not have clinical findings of the serotonin syndrome and, unlike our patient, had evidence of coronary atherosclerosis on cardiac catheterization (3).

Excess serotonergic activity may be associated with ischemia, as evidenced by multiple reports of sumatriptan-induced acute MI (4). The serotonin syndrome may result in ischemia through constriction of coronary arteries because serotonin constricts most vascular beds. Paradoxically, serotonin dilates normal coronary arteries while constriction of diseased ones (5). Endothelial 5-HT1 receptors release vasodilatory endothelium-derived relaxing factor; consequently, vessels with atherosclerosis may not have this protective effect, which would result in unopposed 5-HT2 receptor–mediated vasoconstriction (5). However, our patient must have had ischemia caused by vasospasm in the presence of normal coronary vasculature.

Conclusion: As the number of approved serotonergic agents increases and as more patients are given combination serotonergic therapy, the incidence of the serotonin syndrome will probably increase. Treatment is generally supportive; benzodiazepines (and possibly cyproheptadine) can be used to ameliorate serotonergic end-organ effects. Also, a conscious effort must be made not to prescribe new serotonergic agents for these patients because they may cause symptoms to worsen. Clinicians should consider the presence of myocardial ischemia in patients with serotonergic findings, particularly those known to have coronary artery disease or its risk factors.

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Potential Financial Conflicts of Interest: None disclosed.

References

Corrections

Correction: Nutrition and Blood Pressure: Is Protein One Link? Toward a Strategy of Hypertension Prevention
A recent editorial regarding nutrition for prevention of hypertension (1) contained an incorrect reference citation. The authors cited a study by Elliott and colleagues (2) that was still in press but has since been published by a different journal.

References

Correction: Efficacy and Safety of Inhaled Insulin Therapy
In a recent letter regarding efficacy and safety of inhaled insulin therapy (1), Dr. Zinman’s institutional affiliation should have read as follows: Mount Sinai Hospital and University of Toronto; Toronto, Ontario, Canada.

Reference