Correspondence

Pure Red-Cell Aplasia and Recombinant Erythropoietin

To the Editor: Casadevall et al. (Feb. 14 issue)[1] reported 13 cases of pure red-cell aplasia and antierythropoietin antibodies in European patients who received recombinant erythropoietin (epoetin). Data submitted to the Food and Drug Administration suggest important differences among brands of epoetin with regard to recent increases in reports of pure red-cell aplasia.

Epogen, Procrit, and Eprex are brands of epoetin licensed in the United States. Epogen and Procrit are identical formulations of the same active ingredient (epoetin) distributed only in the United States. Eprex is a different product, which is distributed only outside the United States. For all biologic agents licensed in the United States, postlicensure surveillance is conducted through the MedWatch system of the Food and Drug Administration,[2] which collects reports of adverse events among persons within and outside the United States.

For the period from July 1997 through December 2001, 82 cases of pure red-cell aplasia after the administration of

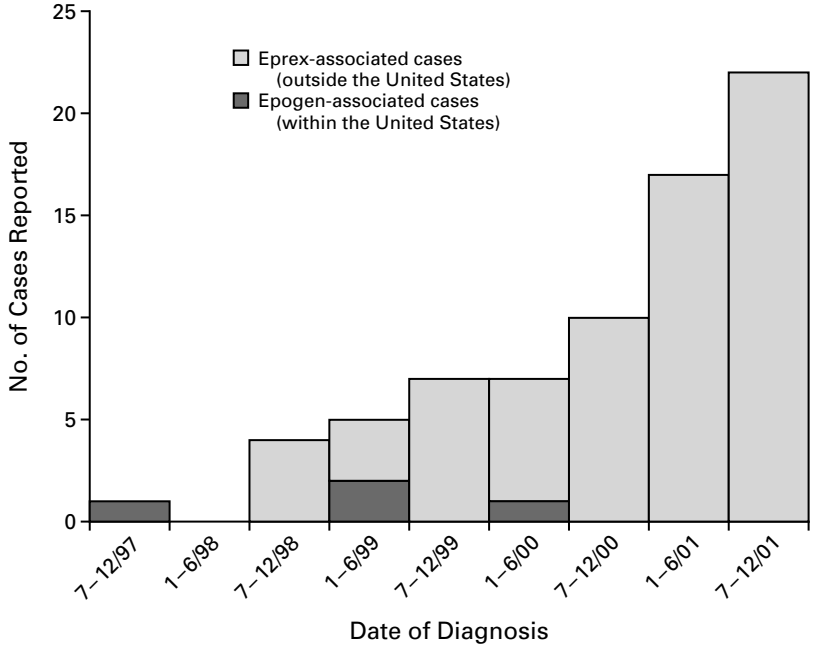

Figure 1. Pure Red-Cell Aplasia among Recipients of Epoetin According to Brand, as Reported to the Food and Drug Administration.

The date of diagnosis was not reported for nine Eprex-associated cases.

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epoetin were reported. Four patients received Epogen, none received Procrit, and 78 received Eprex (these included the patients reported by Casadevall et al.). Patients who received Eprex increased sharply in number throughout this period (Fig. 1). The distribution of Eprex increased from 16.8 million prefilled syringes and vials in 1997 to 30.9 million in 2001; corresponding figures for Epogen and Procrit combined were 23.1 million and 35.1 million in 1997 and 2001, respectively. Therefore, the amount of drug distributed appears not to account for differences among the brands in the number of cases of pure red-cell aplasia reported.

The median age of patients with pure red-cell aplasia was 61 years, and 66 percent were men. The median duration of treatment with epoetin to the time to diagnosis of pure red-cell aplasia was seven months (range, one month to five years). All patients received epoetin for anemia associated with chronic renal failure.

MedWatch, a passive-surveillance system, probably underestimates the true frequency of pure red-cell aplasia. (Information on submitting MedWatch reports is available at http://www.fda.gov/medwatch or 1-800-332-1088.) Although brands distributed in the United States appear not to be linked to recent increases in the incidence of pure red-cell aplasia associated with epoetin treatment, we share the concern of Casadevall et al. about all epoetin products and will continue to monitor such reports carefully.

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To the Editor: In his editorial (Feb. 14 issue)[1] on the adverse effects of therapy with epoetin, Bunn thoughtfully balances the low risk of development of red-cell aplasia secondary to the formation of antierythropoietin antibodies against the substantial benefit of epoetin therapy for anemia. Although we agree that the benefit of epoetin therapy outweighs the associated risks, we take issue with Bunn's statement that erythropoietin has "no clinically significant effects on nonhematopoietic cells." Many nonerythroid tissues, including endothelial cells, smooth-muscle cells, and neurons, express erythropoietin and the erythropoietin receptor. Although some of these effects are probably beneficial, such as the neuroprotective effect of epoetin,[2] others may be detrimental.

Several lines of evidence have shown that therapy with epoetin can result in hypertension, accelerated atherosclerosis, and thrombosis in patients receiving dialysis.[3] These complications were independent of the hematocrit; thus, the pathogenic mechanism was different from hypervolemia-induced or hyperviscosity-induced hypertension or thrombosis. We have recently reported an increased frequency of vascular diseases among patients with primary familial and congenital polycythemia caused by gain-of-function mutations of the erythropoietin receptor.[4,5] Development of these vascular complications was independent of either the hematocrit or the presence of common risk factors associated with the early onset of vascular diseases. In conclusion, we believe there is sufficient evidence that long-term administration of epoetin or dysregulation of the erythropoietin–erythropoietin receptor signaling pathway can be associated with clinically symptomatic vascular diseases such as those seen in patients receiving dialysis or patients with primary familial and congenital polycythemia.

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The authors reply:

To the Editor: Gershon et al. support our conclusions that Eprex is involved in the recent occurrence of pure red-cell aplasia in patients with chronic renal failure who are treated with recombinant erythropoietin. Since the publication of our paper, we have detected neutralizing antierythropoietin antibodies in 19 more patients with chronic renal failure.

Overall, we have detected neutralizing antierythropoietin antibodies in serum from 39 patients referred to our laboratory: 26 from France, 6 from the United Kingdom, 4 from Australia, 2 from Switzerland, and 1 from Canada. Of these 39 patients, 36 were receiving Eprex at the time of the onset of anemia, 2 received Neorecormon exclusively, and 1 had been receiving Eprex and was switched to Neorecormon one month before the diagnosis of anemia.

Among the 82 cases of pure red-cell aplasia reported by Gershon et al., the presence of antierythropoietin antibodies was not demonstrated in all the patients. Although the presence of neutralizing antibodies is likely, it should be demonstrated if immunosuppressive treatment is under consideration.

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The editorialist replies:

To the Editor: Sokol and Prchal take issue with my statement that erythropoietin has "no clinically significant effects on nonhematopoietic cells." In support of possible adverse effects on blood pressure, atherosclerosis, and thrombosis, they cite a thought-provoking review that focuses on in vitro and in vivo effects of epoetin, along with correspondence and an abstract describing families with mutations of the erythropoietin receptor. Several million patients have been treated with epoetin. Its efficacy and safety have been truly remarkable. Nevertheless, there is understandable concern about whether epoetin might have clinically significant adverse effects on the cardiovascular system.

Accelerated atherosclerosis was well known to be a major cause of death among patients with end-stage renal disease before epoetin therapy became available in 1986. The treatment of patients receiving dialysis with epoetin has resulted in improved cardiac function, cardiac dimensions, and exercise capacity. It is difficult to assess the effects of epoetin per se, independent of its effect on increasing red-cell mass. Besarab et al.[1] compared 618 patients receiving relatively high doses of epoetin to achieve a mean hematocrit of 42 with 615 patients receiving lower doses sufficient to maintain a mean hematocrit of 30. In these patients, there was no significant correlation between the dose of epoetin and blood pressure, thrombosis of venous-access sites, or mortality.

I am unaware of any reports of adverse cardiovascular effects when epoetin has been administered to patients with anemia who do not have renal disease. In like manner, patients with severe chronic anemias often maintain, over several decades, markedly elevated levels of endogenous erythropoietin — higher than what is achieved with subcutaneous epoetin therapy — and yet do not appear to be at increased risk for atherosclerosis, hypertension, or thrombosis. Thus, if either therapeutic or endogenous erythropoietin affects the cardiovascular system adversely, the effects are likely to be rather subtle and of questionable significance.

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1. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339:584-90.

Intensive Insulin Therapy in Critically Ill Patients

To the Editor: Van den Berghe and colleagues (Nov. 8 issue)[1] report that intensive insulin therapy reduces mortality and morbidity among patients admitted to the surgical intensive care unit. Both the authors and Evans,[2] in the accompanying editorial, suggest that strict control of glycemia is the principal factor contributing to the improved outcomes reported. However, insulin might have had a role independent of its effect on glycemia.

Severely ill patients in intensive care units have a "cytokine storm" with release of tumor necrosis factor α (TNF-α) and macrophage inhibitory factor.[3] TNF-α is also released in acute myocardial infarction; it causes endothelial dysfunction and triggers procoagulant activity and fibrin deposition. Macrophage inhibitory factor is released with both gram-negative and gram-positive sepsis, and neutralization of this factor may protect against endotoxemia and toxic shock.

Insulin has been shown to inhibit TNF-α[4]; it is also likely that the infusion of glucose and insulin inhibits macrophage inhibitory factor.[3] The improved outcomes observed in the group receiving intensive insulin therapy may have resulted primarily from the action of insulin on these cytokines, rather than from the relatively mild hyperglycemia in the conventional-treatment group. This effect of insulin could also contribute to the well-documented benefits of treating hyperglycemia in order to reduce infection. Given the practical difficulty involved in maintaining normoglycemia in critically ill patients in community hospitals and the potential dangers associated with attempts to maintain normoglycemia, it is important not to assume that these results are wholly attributable to the normalization of blood glucose levels.

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1. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
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To the Editor: Van den Berghe et al. note that all patients began to receive nutritional support the day after admission to the intensive care unit, but they do not indicate how many patients were treated with parenteral nutrition. Klein et al.[1] found that the routine use of postoperative parenteral nutrition was actually associated with greater harm than benefit. The failure of parenteral nutrition to improve outcomes in patients after surgery may be partially attributable to iatrogenic hyperglycemia. It is possible that van den Berghe et al. observed benefits with intensive insulin therapy because it prevented hyperglycemic complications related to parenteral nutrition. We wonder whether the intensive insulin regimen was beneficial in patients who did not receive parenteral nutrition. An equivalent benefit in all patients, regardless of the type of nutritional support they received, would strengthen the conclusion that intensive insulin therapy is warranted for all critically ill patients in whom hyperglycemia develops after they have undergone surgery. If the benefit is limited to patients who receive total parenteral nutrition, such therapy would be unnecessary for most other patients.

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To the Editor: There is another potential explanation for the fascinating results of the trial comparing "tight" glycemic control with "usual" glycemic control in a population composed primarily of patients who had undergone cardiac surgery. Glucose–insulin–potassium infusion[1] reduces morbidity and mortality after myocardial infarction[2] and coronary bypass.[3] Virtually all the patients in the trial conducted by van den Berghe et al. who were randomly assigned to normoglycemia were given continuous infusions of insulin and continuous nutritional support. Administering the insulin doses used in the intensive-treatment group of the study, combined with nutrition containing more than 20 kcal per kilogram of body weight per day, is likely to produce improvements in myocardial glucose utilization and inotropic performance similar to those achieved with glucose–insulin–potassium, as well as reducing the occurrence of arrhythmias. The effect of glucose–insulin–potassium on multisystem organ failure is unclear, but better cardiac function is associated with a lower risk of death from septic shock.[4] If a "glucose–insulin–potassium" effect was largely responsible for the benefit observed with intensive insulin therapy, then it might be less important to lower glucose levels into the normal range than to lower them below a particular threshold. Was there evidence of a threshold below which the glucose level was no longer associated with an increased risk of death?

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To the Editor: Patients assigned to either group in the study by van den Berghe et al. appropriately received active therapy (albeit of different degrees of intensity) to control their blood sugar.[1,2] It seems problematic, however, that consent was "obtained from the closest family member" rather than from the research subject. The use of consent from a surrogate apparently reflected the fact that patients were enrolled only when they entered the intensive care unit after surgery.

Most of the subjects had undergone cardiac surgery and presumably could have given informed consent themselves if they had been approached before the surgery, perhaps at the same time that they consented to the surgery. This method would have enabled them to exercise choice directly rather than through a surrogate.

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2. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials — a middle ground. N Engl J Med 2001;345:915-9.

The authors reply:

To the Editor: Hirsch and Coviello note that we cannot differentiate between the direct effects of infused insulin and the effects of preventing hyperglycemia, since both occurred concomitantly in our study. Besides the antiinflammatory effects evoked directly by insulin through the suppression of cytokine production or signaling,[1] favorable effects on coagulation and fibrinolysis[2] and on macrophage function,[3] partially mediated by the prevention of hyperglycemia, may also have occurred. Multivariate logistic-regression analysis revealed, however, that the daily dose of insulin and the mean blood glucose level were independent positive predictors of the risk of death. In other words, a high dose of insulin was associated with a worse outcome, and a lower blood glucose level was associated with a better outcome, suggesting that the latter had a crucial role.

Gradual transition from intravenous nutritional support to enteral nutrition resulted in the administration of similar numbers of calories and similar amounts of glucose, protein, and lipids in the patients in both treatment groups at all times. Of all patients who remained in the intensive care unit for more than five days — the group in which intensive insulin therapy was associated with reduced mortality — 60 percent received combined parenteral–enteral feeding, with up to 68 percent of nutrition administered enterally. Intensive insulin therapy reduced mortality from 18.8 percent to 10.2 percent ($P<0.05$) in the group receiving combined parenteral–enteral feeding and from 22.3 percent to 11.1 percent ($P<0.05$) in the group receiving exclusively parenteral feeding. Effects of intensive insulin therapy on morbidity were also seen regardless of the feeding regimen. Because patients receiving exclusively parenteral feeding required a higher dose of insulin in order to maintain normoglycemia than did those receiving enteral nutrition ($P=0.007$), we agree with Mazuski et al. that our findings have implications for the controversy surrounding early enteral feeding and underscore the potential risks of parenteral nutrition without concomitant strict control of blood glucose levels.

Our strategy of maintaining normoglycemia with insulin (0.04 U per kilogram of body weight per hour) during normal intake of glucose (9 g per hour) and calories (19 kcal per kilogram per day) differs from the administration of glucose–insulin–potassium solutions for improvement of cardiac performance during myocardial injury.[4,5] The goal

of using glucose–insulin–potassium solutions is to stimulate myocardial metabolization of glucose instead of fatty acids when oxygen supply is compromised. These solutions contain much greater amounts of both insulin (0.1 to 1.0 U per kilogram per hour) and glucose (30 to 80 g per hour) than we provided and are infused without targeting normoglycemia. As mentioned, our results suggest that lowering the blood glucose level, rather than administering a high dose of insulin, resulted in lower rates of complications and death. We found no identifiable threshold glucose level below which no further risk reduction occurred.

We agree with Nusbaum that obtaining informed consent from the patient is preferable to obtaining it from a surrogate whenever this is possible. Since, in our study, only a subgroup of patients would have been capable of providing informed consent before their eventual admission to the intensive care unit, we decided after extensive discussion with the institutional ethics review board to adopt the same strategy for all patients of obtaining consent from the next of kin on admission to the intensive care unit.

Finally, because we have received many requests for more information about our protocol for intensive insulin therapy, we have prepared a more detailed summary, which is available as Supplementary Appendix 1 with the text of this letter at http://www.nejm.org.

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1. Dandona P, Aljada A, Mohanty P, et al. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? J Clin Endocrinol Metab 2001;86:3257-65.
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Acetaminophen, Aspirin, and Renal Failure

To the Editor: There is strong experimental and epidemiologic evidence that the use of acetaminophen or aspirin is associated with a very small risk of analgesic nephropathy. However, only extensive and uncontrolled consumption has been proved to be dangerous. Because there is a higher risk of acute renal impairment associated with cyclooxygenase inhibition, current practice is to ban the use of nonsteroidal antiinflammatory drugs (including high-dose aspirin) in patients with chronic renal failure and to recommend instead acetaminophen or low-dose aspirin.

The case–control study by Fored et al. (Dec. 20 issue)[1] apparently contradicts this view, but the data raise the question of recruitment bias. Because patients had quite advanced chronic renal failure, it is likely that they and their physicians had known about the underlying renal disease for years. During this "lag time," it is likely that these patients used more aspirin for the prevention of cardiovascular events and used fewer nonsteroidal antiinflammatory drugs (and more acetaminophen) for pain and fever than the general population; such a treatment history would be a powerful confounding factor. Without correction for the timing of the diagnosis of renal disease and for coexisting conditions (which would be possible only in follow-up studies), the plausible hypothesis that the use of acetaminophen or aspirin is harmful in patients with renal failure remains unproved.

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To the Editor: Fored et al. found that the regular use of aspirin was associated with an increased cumulative risk of chronic renal failure from any cause. Their tables and bar graph show an increase in risk even with lifetime use in the range of 1 to 99 g. It is common practice for doctors to advise their patients to take (and to take themselves) one aspirin daily for decades for reasons unrelated to renal conditions. Even if patients take a "baby aspirin" (81 mg) daily, 1 g will be accumulated in 12.35 days, almost 30 g in one year, and 500 g in just under 17 years. This level of aspirin consumption places the user in a high-risk group, according to Figure 1 in the article by Fored et al. Persons who take one 325-mg tablet daily will accumulate aspirin four times as fast. Do the authors of this report believe we should continue to advise many of our patients to take one aspirin (whether "baby" or adult-sized) daily?

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The authors reply:

To the Editor: Contrary to Dr. Campo's assertion, protopathic bias — the possibility that the renal disease or its antecedents were responsible for the observed pattern of analgesic use — was our primary concern in the planning, analysis, and interpretation of our study. The main reason we chose to study risks in patients with early-stage disease was the assumption that drug use was less likely to be affected in these patients than in those with end-stage disease. It was, however, evident that the patients with chronic renal failure had more aches and pains than the disease-free controls. Although protopathic bias was not completely ruled out, we concluded that the observed excess risks could not be entirely explained by this bias.

First, lagged analyses, in which analgesic consumption during the most recent decade was disregarded, showed es-

sentially the same relative risks as our primary analysis. Second, on direct questioning, few of the patients with chronic renal failure reported having received any advice about changing their use of analgesics, and reanalysis excluding the patients who had received such advice did not materially alter our results. Third, similar associations with analgesic use were found among patients with insidious renal failure that had not had clinical antecedents.

Dr. Thurlow asks whether we need to reconsider the practice of prescribing low-dose aspirin prophylactically. This question is best addressed by comparing the absolute effect of aspirin use on the risk of chronic renal failure with its absolute effect on the risk of major cardiovascular events. Since the size of our study base was known, we could estimate the sizes of our risk strata on the basis of the proportion of users among our controls. Since virtually all new cases in subjects in the study base were ascertained and the subjects could be assigned to a risk stratum, we were able to estimate the incidence in each risk stratum. Then we could compute the difference in incidence as a measurement of the excess incidence among the subjects with exposure to aspirin.

Although there is a small possibility of overestimation due to protopathic bias, we estimated that the excess among regular users of aspirin was 8.9 new cases of chronic renal failure per 100,000 person-years. In comparison, 150 myocardial infarctions were prevented by aspirin therapy during the same number of person-years, according to a recent meta-analysis of randomized, controlled trials.[1] Hence, although some of the studies in that meta-analysis included subjects with hypertension and an increased baseline risk, it appears that the cardiovascular benefits of low-dose aspirin therapy far outweigh the renal hazards. Therefore, we see no good reason for changing the current practice of recommending low-dose aspirin to patients at risk for cardiovascular disease.

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Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin

To the Editor: The article by Catella-Lawson et al. (Dec. 20 issue)[1] is interesting, particularly in view of the number of patients with cardiac conditions who are candidates for both traditional nonsteroidal antiinflammatory drugs (NSAIDs) and low-dose aspirin.

One result reported by the authors seems to be in conflict with the pharmacokinetics and mechanism of action of ibuprofen and aspirin. In the parallel-group study, aspirin was given two hours before the start of a multiple-dose regimen of ibuprofen. Surprisingly, the protective effect of aspirin was not maintained in these circumstances. If we accept the idea that the mechanism underlying the effect of aspirin is an irreversible acetylation of the serine residue, then antagonism of the effect of the dose of aspirin is unlikely. The subsequent doses of ibuprofen may have modified the benefit of aspirin but should not have eliminated the benefit, since 12 hours after dosing, up to six half-lives may have passed and blood levels of ibuprofen should be minimal.[2]

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1. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809-17.
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To the Editor: Catella-Lawson and colleagues conclude that treatment with ibuprofen may limit the cardioprotective effects of aspirin in patients with an increased risk of cardiovascular events. However, the extent of ex vivo platelet cyclooxygenase inhibition does not reflect in vivo inhibition of thromboxane biosynthesis and may not be a reliable measure of the potential cardioprotective effects of drugs that target cyclooxygenase. Episodic increases in thromboxane biosynthesis, as reflected by increases in urinary 11-dehydro-thromboxane B_2 excretion,[1] have been reported in patients with unstable angina, despite more than 95 percent suppression of platelet cyclooxygenase by aspirin,[2] and can be more effectively suppressed by a nonselective inhibitor of cyclooxygenase than by aspirin.[3] Despite the lack of a demonstrable effect of rofecoxib on ex vivo thromboxane generation in patients already receiving aspirin, as reported by Catella-Lawson et al., it remains possible that the combination of a selective cyclooxygenase inhibitor and aspirin is more effective than aspirin alone for suppressing in vivo thromboxane generation. Whether greater suppression of in vivo thromboxane biosynthesis reduces the risk of cardiovascular events remains to be determined.

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1. Perneby C, Granstrom E, Beck O, Fitzgerald D, Harhen B, Hjemdahl P. Optimization of an enzyme immunoassay for 11-dehydro-thromboxane B(2) in urine: comparison with GC-MS. Thromb Res 1999;96:427-36.
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3. Cipollone F, Patrignani P, Greco A, et al. Differential suppression of thromboxane biosynthesis by indobufen and aspirin in patients with unstable angina. Circulation 1997;96:1109-16.

The authors reply:

To the Editor: Dr. Burnakis believes that interference with the action of aspirin by a multiple-dose daily regimen of ibuprofen is unexpected. However, the evidence that re-

lates plasma NSAID levels to platelet cyclooxygenase-1 inhibition is scant, and the evidence that links drug levels to the likelihood of an interaction with aspirin is nonexistent. We reported that six hours after a single dose of ibuprofen — roughly three half-lives — the inhibition of platelet cyclooxygenase-1, as reflected by serum thromboxane B_2 levels, remains substantial (81±4 percent). Inhibition might be even greater after the administration of ibuprofen three times a day for six days. It also seems plausible that inhibition may be related nonlinearly to the capacity for interference with the access of aspirin to its target serine.

Drs. McQuillan and Eikelboom misinterpret the implications of our description of the nonlinear relation between the inhibition of serum thromboxane B_2 and urinary thromboxane metabolite excretion,[1] in questioning the importance of platelet cyclooxygenase-1–derived thromboxane in patients with unstable angina. However, controlled trials have shown that daily doses of 75 mg, 324 mg, and 1300 mg of aspirin have similar effects on cardiovascular outcomes in patients with unstable angina.[2] Although such diverse regimens all completely suppress platelet cyclooxygenase-1, they are unlikely to accomplish similar degrees of inhibition of cyclooxygenase-2.

Indeed, it "remains to be determined" whether cyclooxygenase-2 inhibitors augment the efficacy of aspirin in such situations. However, it also remains plausible that they may undermine the efficacy of aspirin in patients with cardiac conditions and renoprival syndromes or may even represent an independent cardiovascular hazard. Drs. McQuillan and Eikelboom also suggest that NSAIDs might afford cardioprotection superior to that of low-dose aspirin. Again, there is no evidence to that effect.[3] A recent epidemiologic analysis of 17,000 patients did not show a cardioprotective effect of naproxen.[4] Interestingly, the relative risk of a myocardial infarction in patients taking aspirin together with ibuprofen was increased by roughly 30 percent, a finding consistent with the hypothesis advanced in our article.

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Extracranial Carotid Stenosis

To the Editor: In his review of extracranial carotid stenosis (Oct. 11 issue),[1] Sacco recommends medical therapy alone for patients over the age of 79 years who have asymptomatic carotid disease of any severity. The problem is that most, if not all, of the original studies that were used as a foundation for these guidelines arbitrarily excluded patients who were older than 80 years of age. This fact should not be viewed as implying that surgery should never be considered in people over the age of 80 years merely because they are old.

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To the Editor: I do not agree with Sacco's recommendation of carotid endarterectomy for the 64-year-old man with symptomatic carotid-artery stenosis. For every 15 patients who undergo surgery, a single stroke is prevented within five years after surgery. This means that 14 patients derive no benefit at all from surgery. The results of clinical trials cannot be applied wholesale to the real world. A recent observational study of carotid surgery reported a 30-day case fatality rate of 4.5 percent and a 30-day rate of stroke or death of 11.4 percent.[1] These findings indicate that the risk–benefit ratio of surgery is more problematic than clinical trials suggest.

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1. Chaturvedi S, Aggarwal R, Murugappan A. Results of carotid endarterectomy with prospective neurologist follow-up. Neurology 2000;55:769-72.

To the Editor: Dr. Sacco considers the role of carotid-artery stenting to be unclear. However, he does not address published data from multicenter registries that included more than 5000 patients[1] and used devices to protect the brain from the microembolization of plaque during the procedure (neuroprotection systems).[2,3] These case series reported low rates of immediate complications and favorable long-term outcomes,[4] suggesting that carotid-artery stenting can be performed with rates of periprocedural complications that are similar to or lower than those associated with surgery. The Carotid and Vertebral Artery Transluminal Angioplasty Study,[5] as noted by Dr. Sacco, reported lower rates of operative complications after stenting than after endarterectomy. Dr. Sacco advocates a surgical approach for symptomatic patients if the periprocedural risk is 6 percent or lower, as well as for asymptomatic patients if the risk is 3 percent or lower. If the risk of periprocedural complications from carotid-artery stenting meets these predefined standards, stenting should be considered an acceptable alternative to endarterectomy.

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Dr. Sacco replies:

To the Editor: The management of carotid stenosis continues to be a source of controversy. The age limit of 80 years is predicated on the findings of the Asymptomatic Carotid Atherosclerosis Study,[1] from which evidence-based guidelines are derived. I agree that, despite their chronological age, some 80-year-olds may be good candidates for surgery, but the risk–benefit ratio may not be optimal for these patients. Trials provide data derived from populations and help us make clinical decisions involving individual patients, but they may not answer all the questions. Clinical judgment is still needed when evidence is lacking.

For patients with moderate symptomatic carotid stenosis of 60 to 79 percent, surgery will significantly reduce the absolute and relative risk of stroke, especially among those with a recent history of hemispheric transient ischemic attacks. The prevention of 1 stroke for every 15 patients treated is an acceptable achievement given our less than satisfactory results with certain medical approaches. Unfortunately, we cannot predict which patients will not benefit from surgery. The risk–benefit ratio may vary depending on the level of surgical expertise and the characteristics of the patients.

I agree that carotid angioplasty with stenting is a promising procedure. Despite the favorable rates of periprocedural complications, data from case series and registries can never replace the data on safety and efficacy from randomized trials. Selection biases and the lack of systematic identification of outcomes can threaten the validity of the results and conclusions of case series. I am sure Dr. Roubin, a member of the executive committee of the Carotid Revascularization with Endarterectomy or Stent Trial, would agree that a randomized trial of this approach is needed. The evidence derived from this trial will not only change guidelines, but also undoubtedly alter the way we practice.

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1. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-8.

Overdose of Cyclic Antidepressants and the Brugada Syndrome

To the Editor: The Brugada syndrome is a rare clinical and electrocardiographic entity consisting of sudden death from cardiac causes associated with right bundle-branch block and unusual ST-segment elevation in the right precordial leads (V_1 to V_3).[1] A Brugada electrocardiographic pattern mimicked by overdose of cyclic antidepressants has been reported in rare instances.[2] To assess the prevalence of the Brugada electrocardiographic pattern and its relation to death during overdose of cyclic antidepressants, a retrospective study was carried out in our intensive care unit.

We studied 98 consecutive cases of intoxication with cyclic antidepressants in 95 patients (mean [±SD] age, 41±13 years) that occurred between January 1998 and December 2001 (Table 1). No patient had a personal or familial history of cardiac disease, and none had ingested antiarrhythmic drugs. Intoxication with cyclic antidepressants was defined by a plasma concentration greater than 1 μM per liter. All 12-lead electrocardiograms obtained at admission, during the hospital stay, and at discharge were examined.

A Brugada electrocardiographic pattern was present in 15 of 98 cases of overdose of cyclic antidepressants (15.3 percent). The Brugada electrocardiographic pattern was definite in 12 (Fig. 1) and equivocal in 3 patients. One woman admitted three times for poisoning with cyclic antidepressants and one time for poisoning with another drug had a Brugada electrocardiographic pattern during each overdose of cyclic antidepressants. The overall mortality rate was 3 percent, with one patient with the Brugada electrocardiographic pattern and one patient without it dying from refractory ventricular fibrillation. The mortality rate was 6.7 percent among patients with the Brugada electrocardiographic pattern and 2.4 percent among patients without it ($P=0.39$). The Brugada electrocardiographic pattern disappeared when plasma concentrations of cyclic antidepressants were less than 1 μM per liter. No antiarrhythmic-drug assays or electrophysiologic or genotyping studies were performed.

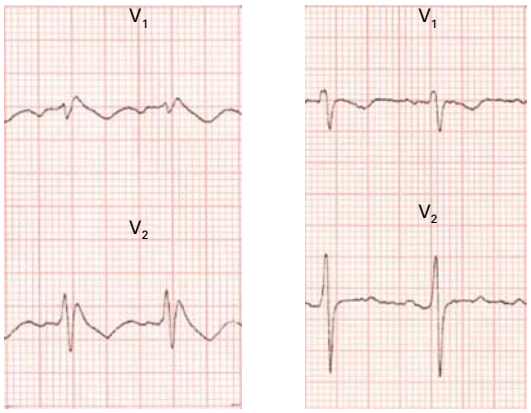
The Brugada syndrome is a cardiac disorder related to a genetically determined sodium-channel dysfunction (blockade of inward sodium current) without evidence of structural heart disease. This disease is associated with a high mortality rate in middle-aged men, resulting from ventricular fibrillation whose pathophysiology remains incompletely understood. Drugs that block sodium channels such as class IA or IC antiarrhythmic drugs are usually used to aggravate or unmask the Brugada electrocardiographic pattern in order to confirm the diagnosis.[1] Cyclic antidepressants have the ability to block cardiac sodium channels.[3]

In our study, the prevalence of the Brugada electrocardiographic pattern in patients with overdose of cyclic antidepressants exceeds the prevalence in the general population (0.05 to 0.1 percent).[1] A functional or organic disease exacerbated by cyclic antidepressants cannot be ruled out, but there was no statistically significant increase in the risk of death from cardiac causes related to the Brugada electrocardiographic pattern in the patients we studied. The Brugada electrocardiographic pattern has also been reported in cases of poisoning with neuroleptic agents, which likewise have blocking effects on sodium channels.[3] Information on the dose of neuroleptic agents is not commonly requested. Thus, combined poisoning with neuroleptic agents cannot be ruled out and renders our conclusions questionable with respect to the relation between overdose of cyclic antidepressants alone and the Brugada electrocardiographic pattern.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH CYCLIC-ANTIDEPRESSANT POISONING.*

CHARACTERISTIC	BRUGADA ELECTROCARDIOGRAPHIC PATTERN (N=15)	NO BRUGADA ELECTROCARDIOGRAPHIC PATTERN (N=83)	P VALUE
Age — yr			0.7
Mean	39.3±10	41.0±14	
Range	24–55	17–84	
Sex — M/F	1/3	1/1.5	0.22
SAPS II			0.04
Mean	42±13	32±16	
Range	25–75	1–91	
APACHE II			0.08
Mean	16.5±5.3	14.0±7.6	
Range	11–31	4–44	
Stay in the ICU — days			0.03
Mean	7.0±6.1	4.5±6.2	
Range	2–26	1–43	
Plasma cyclic-antidepressant concentration — μM/liter			0.004
Mean	4.1±2.1	2.7±1.6	
Range	1.2–8.9	1.0–9.2	
Death — no. (%)	1 (6.7)	2 (2.4)	0.39

*Plus–minus values are means ±SD and were compared with the use of the Mann–Whitney U test, chi-square test, and Fisher's exact test. A P value of less than 0.05 was considered to indicate statistical significance. SAPS II denotes Simplified Acute Physiology Score, APACHE II Acute Physiology and Chronic Health Evaluation, and ICU intensive care unit.



Clomipramine, 4.75 μM/liter

Clomipramine, <1 μM/liter

Figure 1. Electrocardiograms Recorded in a Single Patient Admitted with Cyclic-Antidepressant Poisoning.

Every physician in charge of patients with cyclic-antidepressant poisoning should be aware of the Brugada electrocardiographic pattern, which may be a marker of a high risk of death.

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