considering protocols of interhospital transfer, one must therefore balance the known benefits of percutaneous coronary intervention with our evolving understanding of the risks of exposure to traffic.

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1. Jacobs AK. Primary angioplasty for acute myocardial infarction — is it worth the wait? N Engl J Med 2003;349:798-800.

DR. STONE REPLIES: Dr. Tosteson and Mr. Greenbaum suggest that the interpretation of Peters and colleagues' analyses should be tentative, in contrast to my statement. However, my assignment was to put their results in the context of other information and thus to form a larger sense of the significance of the study. The observations of Peters et al. are based on data related to exposure to traffic and the onset of myocardial infarction; air-pollution measurements were not included. The evidence that air pollution may be responsible for the onset of myocardial infarction is compelling because of the observation that the risk of myocardial infarction was increased regardless of the means of transportation: car, public transportation, or bicycle or motorcycle. I interpreted these results in the context of supportive, short-term epidemiologic data,[1] such as those from the Determinants of Myocardial Infarction Onset Study,[2] which showed that the risk of the onset of myocardial infarction increased during the two-hour period of exposure to elevated concentrations of air-pollution particles. Mechanistic studies both in humans and in animals provide a plausible explanation for the relationship between transient changes in air pollution and sudden triggering of myocardial infarction.[1]

In their letter, Dr. Tosteson and Mr. Greenbaum mention new data suggesting that air-pollution levels just before the myocardial infarctions in the study by Peters et al. were not associated with an increased risk of myocardial infarction. As they note, however, air pollution assessed at a central monitoring site may not be a good surrogate for personal exposure in traffic. I agree that it will be critical to confirm and extend Peters and colleagues' work so that public health policies can be based on the most objective data.

In response to Dr. Lebwohl's comments: it should be emphasized that although the relative risk of the onset of acute myocardial infarction increased after exposure to traffic, the absolute risk was low. For patients with acute myocardial infarction there may be minor risks associated with exposure to traffic during transport, but these risks are outweighed by the documented benefit of mechanical reperfusion in appropriately selected and transported patients.[3]

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Carotid-Artery Stenting versus Endarterectomy

TO THE EDITOR: To compare protected carotid-artery stenting with carotid endarterectomy, Yadav et al. (Oct. 7 issue)[1] chose to study a group for which endarterectomy has been found to be only marginally better than medical therapy.[2,3] Although the population was defined as having a high risk on the basis of associated medical conditions, the patients were not at a high risk for stroke on the basis of symptoms and carotid-artery anatomy. More than 70 percent of the patients were asymptomatic, with an estimated carotid-artery stenosis of at least 80 percent of the luminal diameter. For symptomatic patients, a carotid-artery stenosis of only 50 percent was required. In such patients, the expected advantage of endarterectomy over medical therapy would be only 1 to 2 percent per year.[2,3] The absence of a medical control group is justified by the small statistical advantages previously found in a similar population.[2,3] However, because 12.2 percent of the patients who received a stent had died

or had had a stroke or myocardial infarction at one year, it is not clear that medically treated patients would have fared much worse.

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1. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.
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TO THE EDITOR: Yadav et al. claim that the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial shows that protected carotid-artery stenting is not inferior to carotid endarterectomy in high-risk patients. For what outcome are these patients at high risk? Although the patients were required to have at least one high-risk factor at the time of enrollment, the claim of high risk is not totally borne out in the 30-day outcomes. Table 1 provides a comparison between the patients included in the actual-treatment analysis in the SAPPHIRE trial and the patients who underwent carotid endarterectomy in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the ASA and Carotid Endarterectomy (ACE) trial.[1] The doubling in the 30-day composite end point of stroke, death, or myocardial infarction in the SAPPHIRE trial was due entirely to the occurrence of myocardial infarction, not stroke. In fact, the rate of stroke was lower in the SAPPHIRE trial. If indeed the SAPPHIRE trial was concerned with the treatment of patients for whom surgery posed an increased risk, why were 54.4 percent of the patients who received a stent entered into a registry rather than randomly assigned to stenting in the trial? The results of the trial still raise the question of how to treat the large proportion of patients with carotid-artery stenosis who were excluded.

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1. Barnett HJM, Meldrum HE, Eliasziw M. The appropriate use of carotid endarterectomy. CMAJ 2002;166:1169-79.

TO THE EDITOR: Yadav and colleagues' conclusion that stenting is not inferior to endarterectomy war-

Table 1. Outcomes at 30 Days in the SAPPHIRE Trial, NASCET, and the ACE Trial.*

Outcome	SAPPHIRE		NASCET and ACE	ACE
	Stenting (N=159)	Carotid Endarterectomy (N=151)	Carotid Endarterectomy (N=2670)†	Carotid Endarterectomy (N=1214)‡
	percent of patients			
Stroke	3.1	3.3	5.8	3.9
Death	0.6	2.0	1.2	1.2
Myocardial infarction	1.9	6.6	1.0	1.8
Stroke, death, or myocardial infarction	4.4	9.9	6.9	5.5

* SAPPHIRE denotes Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy, NASCET the North American Symptomatic Carotid Endarterectomy Trial, and ACE ASA and Carotid Endarterectomy.
† The patients had symptoms.
‡ The patients did not have symptoms.

rants further discussion. It is clear that the difference between the treatment groups in the composite end point is related to the higher incidence of perioperative myocardial infarction in the endarterectomy group than in the stenting group. The inclusion of myocardial infarction as an end point is controversial for many reasons.[1] Moreover, the lower incidence of myocardial infarction in the patients who underwent stenting may have been due to the use of clopidogrel. The patients who underwent endarterectomy did not receive clopidogrel. There is convincing evidence that clopidogrel in addition to aspirin reduces the risk of myocardial infarction.[2,3]

In the absence of robust data on long-term efficacy, careful selection of candidates for stenting will be crucial. However, no detailed information is given on why 413 patients who fulfilled the inclusion criteria and did not meet the exclusion criteria (55 percent of the 747 patients enrolled) were not randomly assigned to treatment. Additional information on selection procedures for randomization and reanalysis of efficacy (the primary end point without myocardial infarction) may help make these data more suitable for clinical practice and more relevant to the design of future trials.

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1. Cambria RP. Stenting for carotid-artery stenosis. N Engl J Med 2004;351:1565-7.
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TO THE EDITOR: To interpret the important results of the comparison of carotid-artery stenting with endarterectomy, reported by Yadav et al., we seek clarification regarding two issues. First, we would like to know whether the decision to stop the trial was based exclusively on poor recruitment and was unbiased by any knowledge of the interim results. Second, was the use of antiplatelet agents identical in the two groups between the 30-day and 1-year follow-up assessments (i.e., did more patients assigned to stenting continue to take clopidogrel with aspirin during this interval)?

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THE AUTHORS REPLY: Most practitioners disagree with Dr. Friedman in their assessment of the robustness of the Asymptomatic Carotid Surgery Trial and NASCET findings and refer patients with severe asymptomatic and symptomatic disease for endarterectomy. The SAPPHIRE trial was a real-world study that compared a less invasive treatment with surgery among patients who had already been referred for surgery. Medical therapy alone was not believed to be a suitable treatment for these patients, either by their primary physicians or by the multidisciplinary panel that evaluated them as part of the trial enrollment process.

In response to Drs. Tonarelli and Hart: interim analyses were not performed before the decision was made to stop the trial because of slowing recruitment. Patients who underwent stenting were required to take aspirin plus clopidogrel for two weeks after the procedure. If patients in the surgical group had received clopidogrel, the increased incidence of bleeding might have tilted the balance further in favor of stenting. We do not have data on how many patients in either group received clopidogrel at the physician's discretion.

With regard to Dr. Killestein's comments, we believe that not to include myocardial infarction as an end point in a study involving patients with cardiovascular disease would be controversial. In Table 3 of our article, we do present a "conventional" end point, without myocardial infarction, which still shows a distinct trend in favor of stenting (incidence of the end point, 5.5 percent, vs. 8.4 percent with endarterectomy). In commenting on the effect of clopidogrel on the incidence of myocardial infarction, Dr. Killestein refers to studies involving patients with acute coronary syndromes who were undergoing coronary intervention.[1,2] The patients in the SAPPHIRE trial were more akin to those in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial,[3] and two to four weeks of treatment with clopidogrel would have had a

negligible effect on their risk of periprocedural myocardial infarction or stroke.

We agree with Drs. Eliasziw and Barnett that the surgical investigators in the SAPPHIRE trial were excellent and that the rates of stroke and death after carotid endarterectomy among the high-risk patients in this trial compare favorably with the event rates after endarterectomy in trials involving low-risk patients. The criteria with respect to high surgical risk in the SAPPHIRE trial were based on well-recognized risk factors associated with surgery. A perioperative myocardial infarction has a significant adverse effect on long-term survival and is a relevant part of the primary end point in trials of carotid revascularization, just as stroke is a relevant end point in trials of coronary revascularization or thrombolysis. The registry patients were believed (by the surgeons who were treating them) to have a prohibitive, as compared with high, surgical risk and thus could not undergo randomization. An analysis of the registry patients is currently under way.

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1. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. [Errata, N Engl J Med 2001;345:1506, 1716.]
2. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. Circulation 2004;110:1202-8.
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Anti–Interleukin-12 Antibody for Active Crohn's Disease

TO THE EDITOR: Mannon et al. (Nov. 11 issue)[1] describe the safety of anti–interleukin-12 antibody (anti–interleukin-12) for the treatment of active Crohn's disease. Among the 44 recipients of anti–interleukin-12 who could be evaluated at 18 weeks, no serious infections were reported.

These results are similar to those of the original studies of infliximab for the treatment of Crohn's disease and rheumatoid arthritis, in which serious infectious complications were not identified.[2,3] The small number of patients enrolled, the exclusion of those at risk, and the limited follow-up for uncommon events are also similar. Through postmarketing surveillance, we learned that anti–tumor necrosis factor (TNF) therapy is associated with tuberculosis, listeriosis, and endemic fungal infections, as predicted by the inhibition of TNF.

Like TNF-α, interleukin-12 is important in interferon-γ production and defense against intracellular pathogens. The absence of interleukin-12 in humans has been linked to complicated infections due to mycobacteria and nontyphoidal salmonella species.[4,5] None of these infections were found in this limited study.

The potential expansion of anticytokine therapeutics reminds us that we need improved screening, preventive measures, and a longitudinal registry of patients receiving these therapies in order to determine the true prevalence of serious infections.

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TO THE EDITOR: The study reported by Mannon et al. shows the preliminary efficacy of anti–interleukin-12 in patients with active Crohn's disease. We wondered whether the title of the report should have been "Anti–Interleukin-12/23 for Active Crohn's Disease," since interleukin-12 p40 is equally impor-