

powered to allow a secondary comparison of the standard-treatment group (paclitaxel every 3 weeks) with the three experimental groups (weekly paclitaxel, docetaxel every 3 weeks, and weekly docetaxel). As we state in the article, there was a significant interaction between docetaxel and the weekly schedule with regard to both disease-free survival ($P=0.003$) and overall survival ($P=0.01$); this interaction affected the primary but not secondary comparisons. The clinical relevance and importance of the significant improvement in the group that received weekly paclitaxel in a secondary comparison are not diminished by the failure to show a difference in the primary comparisons.

Aksoy and colleagues point out that the cumulative dose of taxane given weekly as compared with every 3 weeks was substantially higher with paclitaxel (960 vs. 700 mg per square meter) than

with docetaxel (420 vs. 400 mg per square meter), implying that a benefit of weekly docetaxel may have been observed had a similar weekly dose of docetaxel (equivalent to 45 mg per square meter) been used. Patients treated with weekly docetaxel, as compared with patients treated with weekly paclitaxel, were more likely to have grade 3 or grade 4 toxic effects (45% vs. 28%), require dose modification (40% vs. 29%), and receive fewer than the 12 planned doses (25% vs. 12%), indicating that a docetaxel dose of more than the 35 mg per square meter used in our trial would not have been feasible.

Joseph A. Sparano, M.D.

Montefiore–Einstein Cancer Center
Bronx, NY 10461
jsparano@montefiore.org

Carotid Stenting versus Endarterectomy

TO THE EDITOR: Gurm and colleagues (April 10 issue)¹ conclude that carotid stenting is not inferior to carotid endarterectomy in high-risk patients. This conclusion may be misleading. First, patients were at high risk not for stroke but for surgery. Second, in the absence of controls, the best strategy could have been medical therapy alone. A pooled analysis of the Asymptomatic Carotid Atherosclerosis Study² and the Asymptomatic Carotid Surgery Trial³ shows that in patients with asymptomatic carotid artery stenosis (71% of patients randomly assigned to a study group in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [SAPPHIRE] study) who did not undergo immediate surgery, the risks after a mean follow-up of 3.16 years were 8.6% for any stroke and 14.3% for any cause of death, which are similar to the risks observed in the stenting group of the SAPPHIRE trial after 3 years of follow-up (9.0% and 18.6%, respectively). Finally, if the subjects were at high risk for surgery, which was therefore not an appropriate option for most patients, a non-inferior technique cannot be recommended either.

Clotilde Balucani, M.D.

Charlotte Cordonnier, M.D., Ph.D.

Lille University Hospital
59037 Lille, France
clotilde_balucani@hotmail.com

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TO THE EDITOR: How many patients had atrial fibrillation in the SAPPHIRE study, which compared carotid artery stenting with endarterectomy? We would expect a high prevalence of atrial fibrillation because of relevant risk factors in the study population, including older age, hypertension, coronary heart disease, heart failure, and smoking.¹ Differences in the prevalence of atrial fibrillation might have contributed to differences in the incidence of stroke. Were the use of antiplatelet agents, the intensity of medical therapy, and bleeding complications registered? How would the authors explain the rates of stroke that were higher among asymptomatic patients (10.3% in the stenting group and 9.2% in the endarterectomy group) than among symptomatic patients (6.0% in the stenting group and 8.7% in the endarterectomy group)? How would they explain the de-

creasing divergence of the survival curves at the 3-year follow-up?

Claudia Stöllberger, M.D.
Josef Finsterer, M.D., Ph.D.
Krankenanstalt Rudolfstiftung
1030 Vienna, Austria
claudia.stoellberger@chello.at

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TO THE EDITOR: Gurm et al. report long-term follow-up data from the SAPHIRE trial, which showed no significant difference between carotid artery stenting and endarterectomy in outcomes at 3 years. In their study, 14.4% of the patients in the stenting group and 29.9% of the patients in the endarterectomy group were lost to follow-up. It has been suggested that a rate of loss that is less than 5% probably leads to little bias, whereas a rate of loss that is greater than 20% potentially poses serious threats to validity.¹ Therefore, the influence of loss bias on the interpretation of these results is substantial and should be considered. Moreover, a previous report² indicated that 310 patients received the assigned treatment. When they compared carotid artery stenting with endarterectomy at 3 years, the authors calculated all the percentages on the basis of the 334 patients who were randomly assigned to a study group originally. We would like to know why the authors did not include an analysis based on patients receiving the assigned treatment.

Jin-Tai Yu, M.D.
Lan Tan, M.D.
Qingdao Municipal Hospital
Qingdao 266071, China
dr.tanlan@163.com

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THE AUTHORS REPLY: We agree with Balucani and Cordonnier that there are no data from randomized trials to support or refute the need for revascularization in addition to best medical therapy in patients with severe carotid stenosis who are at high surgical risk. As we noted in our article, the SAPHIRE trial randomly assigned only patients

who were referred by their physicians for carotid revascularization to undergo either surgery or protected stenting if a surgeon and an interventionalist thought that both procedures could be performed with an acceptable risk of procedural complications. These data cannot be extrapolated to all patients with carotid stenosis, and the need for treatment in each patient must be individualized on the basis of a careful assessment of the patient's risk of stroke with medical therapy or revascularization as well as his or her expected long-term survival.

With regard to the comments of Stöllberger and Finsterer, 29 patients in the endarterectomy group (17%) and 14 in the stenting group (8%) had a history of atrial fibrillation. In this group, two patients who underwent endarterectomy had ipsilateral strokes (on day 2 and day 87), as did two in the stenting group (on day 0 and day 182). Among patients with no history of atrial fibrillation, there was no significant difference at 3 years between stenting and surgery with regard to the cumulative incidence of death (18% and 20%, respectively), stroke (8% and 9%, respectively), or the prespecified major secondary end point (23% and 26%, respectively). The details of antithrombotic therapy during long-term follow-up were not recorded, but there were no reported major bleeding events after 30 days. We believe that the small numbers of patients and events in the subgroups of patients with asymptomatic and symptomatic disease preclude any meaningful conclusions, although we agree with the concern about possibly high rates of events among asymptomatic patients who received either treatment. We believe that the survival curves should be interpreted as being not significantly different, with the changes after 1 year indicating only three more ipsilateral strokes and one less death from a neurologic cause in the stenting group.

Yu and Tan are concerned about data being presented on an intention-to-treat basis rather than on an as-treated basis. We believe that the important safety issues in this study require an intention-to-treat analysis.¹ We also included the estimates of events using survival methods to partially correct for incomplete follow-up. The results at 3 years, however, were similar when the population was analyzed on an as-treated basis for the cumulative incidence of the major secondary end point (25% in the stenting group vs. 28% in the

endarterectomy group) and ipsilateral stroke (6% in the stenting group vs. 5% in the endarterectomy group).

Hitinder Gurm, M.D.

University of Michigan School of Medicine
Ann Arbor, MI 48109-5853

Donald E. Cutlip, M.D.

Harvard Clinical Research Institute
Boston, MA 02215
don.cutlip@hcri.harvard.edu

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Artesunate for Malaria

TO THE EDITOR: Rosenthal (April 24 issue)¹ presents a hypothetical case of malaria and states that there is “major concern” about the timeliness of artesunate availability because it is available rapidly only for hospitals that are near the 20 Centers for Disease Control and Prevention (CDC) quarantine stations. Artesunate is stocked at 8 of the 20 stations, which are located at major U.S. airports. To date, the timeliness of the provision of artesunate has been quite reasonable. Among the actual cases of the disease, on average it has taken only 7 hours (range, 3.5 to 15.5) from the time of the request for artesunate until the patient receives the first dose; 73% of the patients treated have been in hospitals that are not near CDC quarantine stations (average distance, 480 miles [772 km]; range, 66 to 1448 [106 to 2330]). To date, all patients treated according to this protocol have recovered. The CDC will continue to provide artesunate until it becomes a Food and Drug Administration (FDA)–approved, commercially available product and hospitals can maintain their own supply. Meanwhile, the current system can provide artesunate rapidly, and health care providers should be encouraged to access this medicine for the treatment of severe malaria.

Paul M. Arguin, M.D.

Centers for Disease Control and Prevention
Atlanta, GA 30333

Peter J. Weina, M.D., Ph.D.

Walter Reed Army Institute of Research
Silver Spring, MD 20910

Cindy P. Dougherty, Pharm.D.

Centers for Disease Control and Prevention
Atlanta, GA 30333

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TO THE EDITOR: I would like to make some additional comments regarding the toxic effects of artemisinin antimalarial drugs, since these effects

are briefly mentioned in Rosenthal’s article. Neurotoxic effects have been observed in animals treated with intramuscular artemisinin in oil-based formulations. However, clinical reports on such toxic effects are rare and inconclusive, despite the large pool of treated patients. The same derivatives given intramuscularly but with the use of a water-based formulation do not have toxic effects in animals.¹

A colleague and I have argued that changes in the pharmacokinetics of artemisinin due to a prolonged absorption after repeated oil-based intramuscular injections cause the observed toxic effects in animals.² Oral and intravenous injections are the most common routes of administration in humans, and with the short half-life of these drugs, the risk of toxic effects seems minimal. Even the intramuscular injections may not be of concern because of the limited number of injections.

When investigating the efficacy and toxicity of drugs, it is imperative to consider their pharmacokinetic properties.

Toufigh Gordi, Ph.D.

University at Buffalo
Buffalo, NY 14260
tgordi@buffalo.edu

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TO THE EDITOR: Rosenthal provides an excellent review of artesunate for the treatment of severe falciparum malaria. However, many physicians are unaware that the onset of symptoms may be delayed among Americans with malaria.

From 1992 to 1998, a total of 5185 cases of malaria were diagnosed in the United States. In 35% of the patients, the symptoms started more