

patients were less severely poisoned. In fact, 80 percent of our patients (121 of 152) (vs. 73 percent²) met criteria used for severe poisoning. Dr. Finnerty also proposes that three days of normobaric-oxygen therapy should be equivalent to intermittent hyperbaric-oxygen therapy, yet the rate of cognitive sequelae was 25 percent with hyperbaric-oxygen therapy in our study, whereas it was 70 percent with normobaric-oxygen therapy in the study by Scheinkestel et al.² Finally, our 132 medical transfers were carried out without adverse events.

It is not easy to compare our results with previous findings,³ because our study was different with respect to blinding, the definition of sequelae, neuropsychological testing, the patient population, and the dose and frequency of hyperbaric-oxygen treatment. Apparently overlooking our inclusion and exclusion criteria, Raphael et al. incorrectly assert that we recommend hyperbaric-oxygen therapy regardless of the cause or severity of carbon monoxide poisoning.³ They claim that the 31 percent rate of attempted suicide in our study confounds the results, because they expect cognitive function to be abnormal before carbon monoxide poisoning in patients who attempt suicide. If they are correct, the higher proportion of suicide attempts in the hyperbaric-oxygen group (36 percent, as compared with 26 percent in the normobaric-oxygen group)³ should have resulted in an increased rate of cognitive sequelae in the hyperbaric-oxygen group. However, we found a reduced rate of cognitive sequelae in the hyperbaric-oxygen group. We reanalyzed our data and found a lower, though statistically insignificant, rate of cognitive sequelae among patients who had attempted suicide (28 percent [13 of 47 patients]) than among

those who had been accidentally poisoned (39 percent [41 of 105])—the opposite of their expectation.

Dr. Isbister and colleagues correctly identify the absence of delayed-memory tests in our study. However, the tests we used detect impairments due to hypoxia. Since we found impairments with less sensitive cognitive measures, our results may underestimate cognitive dysfunction. Isbister et al. claim that base-line cognitive measures are necessary, and they appear to overlook the power of between-group comparisons in randomized clinical trials.¹ Furthermore, on the basis of comparisons of our patients with normal matched control subjects,⁴ “regression to the mean” did not bias our results. Scores for activities of daily living and other functional scores, as well as “real life” benefits, are reported and discussed in our article.

We thank Dr. Cardellach and colleagues for sharing their data that support the concept of mitochondrial dysfunction due to carbon monoxide poisoning.

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2. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust* 1999;170:203-10.
3. Raphael JC, Elkharrat D, Jars-Guincestre MC, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet* 1989;2:414-9.
4. Hopkins RO, Weaver LK, Churchill S. Neuropsychological performance in patients with carbon monoxide (CO) poisoning and demographically matched normal control subjects. *Undersea Hyper Med* 1999;26:Suppl:52. abstract.

Aspirin, Clopidogrel, or Both for Secondary Prevention of Coronary Disease

TO THE EDITOR: Gaspoz et al. (June 6 issue)¹ present an interesting perspective on the problem of escalating health care costs. Their comparison between the cost effectiveness of aspirin and that of clopidogrel is commendable, given the increasing focus by the public on the costs of newer drugs. In their analysis, the authors' assumptions about the costs of the drugs do not take into consideration future costs that would be expected to be lower for both brand-name and generic versions of clopidogrel.

Estimates of the cost of developing a new drug vary, with some figures as high as \$800 million.² The need to recoup these expenses is one of many reasons for the price of new drugs. Without the marketing of new drugs, it is doubtful whether lower-priced generic versions would become available once the patents had expired; if they did not, the public would be deprived of therapeutically superior medications. Clopidogrel has been shown to be more effective than aspirin alone in reducing the in-

cidence of cardiovascular events.³ The authors' conclusion that the use of clopidogrel is financially unattractive appears to sound a death knell for therapeutic innovation and to mark the beginning of a managed-care era for the pharmaceutical industry.

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1. Gaspoz J-M, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2002;346:1800-6.
2. Tufts Center for the Study of Drug Development pegs cost of a new prescription medicine at \$802 million. News release of the Tufts Center for the Study of Drug Development, Boston, November 30, 2001.
3. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.

TO THE EDITOR: We believe that the estimates of incremental effectiveness used by Gaspoz et al. are incorrect for each of the strategies evaluated. First, the 31 percent relative risk reduction associated with aspirin therapy is based on a meta-analysis¹ of trials performed before statins, angiotensin-converting-enzyme inhibitors, glycoprotein IIb/IIIa inhibitors, and coronary stents were used routinely after acute coronary syndromes. A more recent report from the same group suggests that there was a 27.7 percent relative risk reduction for nonfatal myocardial infarction and only a 21 percent relative risk reduction for major cardiovascular events.²

Second, it appears that the incremental effects of clopidogrel and of clopidogrel plus aspirin were underestimated. Assuming a 31 percent relative risk reduction from aspirin, an incremental 20 percent relative risk reduction associated with the addition of clopidogrel should yield a net 44.8 percent relative risk reduction, as opposed to the 37.2 percent used by Gaspoz et al. Similarly, the relative risk reduction with clopidogrel alone should be 37 percent, rather than the 33.7 percent reported. The correct formula is $RRR_{combined} = 1 - [(1 - RRR_{aspirin}) \times (1 - RRR_{aspirin+clopidogrel})]$, where RRR is the relative risk reduction; the formula used by Gaspoz et al. was $RRR_{combined} = RRR_{aspirin} + (RRR_{aspirin} \times RRR_{aspirin+clopidogrel})$.

The assumptions of efficacy and safety used in this model are taken from a short-term study involving patients treated early after the onset of an acute coronary syndrome, for a maximum of 12 months.³ The extrapolation of such results to long-term therapy is inherently flawed. The rate of adverse ischemic events is highest during the period

immediately after an acute coronary syndrome and decreases thereafter. Episodes of bleeding, on the other hand, would probably follow a more "linear" time course. Because the risks and benefits of 25 years of treatment with the combination of clopidogrel and aspirin have not been established, the cost effectiveness of this strategy is irrelevant.

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Editor's note: Drs. de Lemos and McGuire report having received speaker's honorariums from Sanofi, which manufactures clopidogrel. Dr. de Lemos reports having received speaker's honorariums from Bristol-Myers Squibb, which markets clopidogrel.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106. [Erratum, *BMJ* 1994;308:1540.]
2. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324:141.]
3. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. 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.]

TO THE EDITOR: I use the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study¹ to teach residents the importance of avoiding the use of relative risk reductions in describing treatment effects and instead using absolute risk reductions and numbers needed to treat. Treatment with clopidogrel resulted in an 8.7 percent relative risk reduction for the composite primary end point of ischemic stroke, myocardial infarction, or death from vascular causes, as compared with aspirin. At first glance, this reduction seems impressive, but closer scrutiny reveals an absolute risk reduction of only 0.9 percent and a number needed to treat of 115 (95 percent confidence interval, 58 to 8647). This huge 95 percent confidence interval, which ranges from a number needed to treat that would be worthwhile to one that would offer no advantage at all, calls into question whether clopidogrel is truly superior to aspirin. On the basis of the number needed to treat of 115, 114 patients would have to be treated for 730 days (2 years) at a cost of \$3.22 per tablet in order to prevent 1 patient from having an adverse event. The cost would be \$267,968 per ad-

verse event prevented. A Cochrane review² that included the findings of the CAPRIE trial presented data for single outcomes rather than for a cluster of clinical outcomes. According to these analyses, the differences between clopidogrel and aspirin in terms of the outcomes of total strokes and total deaths are nonsignificant. For total myocardial infarctions, the absolute risk reduction is 0.7 percent, giving a number needed to treat of 143, and the cost per myocardial infarction prevented over a two-year period is a staggering \$333,785.

Coronary heart disease is a major killer of adults in the United States. An estimated 40 million Americans are uninsured, and those who are insured are paying more but getting less. In this context, I would replace the somewhat euphemistic term “unattractive” used by Gaspoz et al. with the term “prohibitive” in describing the cost effectiveness of routine use of clopidogrel for secondary prevention of coronary heart disease.

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1. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
2. Hankey GJ, Sudlow CLM, Dunbabin DW. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. *Cochrane Database Syst Rev* 2000;2:CD001246.

TO THE EDITOR: In his commentary on the study by Gaspoz et al., Wood¹ states that he finds it “deeply troubling” that the authors interpret \$130,000 per quality-adjusted year of life for clopidogrel as an “unattractive” value for expenditure. He then cites the cost of drug development as reasonable justification for the price of the drug. Unfortunately, his link between drug pricing and drug-development costs — a link often made by pharmaceutical manufacturers — is spurious. The \$3.22 price of a 75-mg clopidogrel tablet has very little to do with the cost of developing the drug. Rather, it is what the managers at the companies that market clopidogrel (Bristol-Myers Squibb and Sanofi Pharmaceuticals) believe the market will bear for this product. What troubles me is that Wood appears to reject the fact that health value for expenditure should play any part in the argument, particularly when the quality-adjusted years of life are his. Public and private health insurance plans face budget constraints and severe pressure to curb future increases in health care expenditures. Those who make the difficult decisions for these or-

ganizations know that the incremental cost of adding clopidogrel to their formularies will force them to cut costs elsewhere, perhaps by restricting access to much more cost-effective therapies. Even if the lives saved by those treatments are not his, which ones would he choose?

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Editor's note: Dr. Ramsey reports having received a research grant from Bristol-Myers Squibb.

1. Wood AJJ. When increased therapeutic benefit comes at increased cost. *N Engl J Med* 2002;346:1819-21.

TO THE EDITOR: Wood seems to be arguing that we should be willing to pay any increase in cost, no matter how large, in return for any increase in benefit, no matter how minuscule. Such an attitude would certainly cost more lives than it would save. Forty million Americans lack health insurance and therefore lack access to even basic health care. As medical costs continue to rise, more and more employers are forced to drop health care coverage. Nobody knows how many people die because lack of insurance causes them to delay seeking medical care until it is too late, but the number is certainly larger than the number of lives saved by adding clopidogrel to aspirin therapy.

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THE AUTHORS REPLY: We disagree with Dr. Akinlade. Pharmaceutical companies should be able to achieve profits at reasonable cost-effectiveness ratios so that beneficial drugs are affordable. Future drug prices are unpredictable, and the patents on clopidogrel run until 2019.

Dr. Armstrong calculates the costs per event avoided to reach conclusions that are stronger than ours. We prefer the term “unattractive” but understand his preference for “prohibitive.”

Drs. de Lemos and McGuire raise three issues. First, our estimated 31 percent reduction in the risk of cardiovascular events with aspirin is consistent with the 30 percent reduction in the odds of nonfatal myocardial infarction among patients with previous infarction¹ and the 32 percent reduction in the odds of vascular events among patients receiving moderate doses of aspirin² in the most recent overview.

Second, we appreciate their carefulness in detecting our mathematical error and apologize for it. A corrected version of our article is now available at <http://www.nejm.org>. With the correction of this error and a similar error in estimating the benefits in reducing the risk of stroke, the use of clopidogrel alone instead of aspirin is associated with a cost-effectiveness ratio of \$110,000 per quality-adjusted year of life saved and remains unattractive except for patients with the highest risk. For the combination of clopidogrel and aspirin, the cost-effectiveness ratio changed from \$130,000 to \$61,000 per quality-adjusted year of life saved, on the basis of our original assumptions that had been purposely tilted to favor clopidogrel in order to ensure the robustness of our conclusion that clopidogrel was unattractive from the perspective of cost effectiveness despite the most favorable set of estimates. These assumptions, which were unlikely to be accurate, were that the 20 percent benefit of combination therapy for the prevention of nonfatal myocardial infarction that was found during the first year in patients with acute coronary syndromes would be maintained for 25 years and that the same benefit would apply to all cardiovascular events. However, the observed relative benefits of combination therapy declined by about 50 percent during months 9 through 12 of the trial, and the reductions in the rates of stroke, fatal myocardial infarction, and death from cardiovascular causes were much lower than 20 percent, even during the first year.³ If the relative benefit of combination therapy in terms of all events after the first year were similar to what was seen during months 9 through 12, the cost-effectiveness ratio would be about \$120,000 per quality-adjusted year of life saved — nearly identical to the \$130,000 we estimated.

Third, when the actual event-specific results reported for 12 months of combination therapy³ were applied to our original question, which was about the cost effectiveness of therapy beginning 30 days after the onset of symptomatic coronary disease, the 25-year cost-effectiveness ratio for 1 year of combination treatment was \$180,000 per quality-adjusted year of life gained. As a result, we stand by our original conclusion that the long-term use of clopidogrel, despite its apparent effectiveness, is financially unattractive for patients who can tolerate aspirin, unless its price is reduced substantially.

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DR. WOOD REPLIES: Gaspoz et al. demonstrated that the addition of clopidogrel to aspirin therapy would produce a benefit of 1,437,000 quality-adjusted years of life over a 25-year period as compared with aspirin therapy alone — hardly a “minuscule” benefit, as Dr. Yaes suggests. The cost of these years of life will fall with the price of clopidogrel, as the authors acknowledged. Dr. Ramsey takes issue with the ways in which drugs are priced. Although the pricing of drugs and the fact that 40 million Americans lack health insurance are serious issues, the fundamental issue is whether we should ration care, and if so, how that rationing should be carried out. I would argue that our expenditures for health care, which, as a fraction of the gross domestic product, are higher than those of any other developed country, could certainly support therapies that have been proved to result in substantial reductions in mortality in well-controlled clinical trials. Surely, the first therapies to be eliminated should be those that we know to be ineffective or those that have not been demonstrated to be effective. Too many such therapies are still in widespread use. If society deems it appropriate to restrict care further, it will be critical for physicians to be explicit about such restrictions in talking to their patients, who might choose to deploy their economic resources differently. Patients expect us to be frank and open about the options we recommend to them. To deny patients potentially lifesaving therapy without offering them the option of receiving it (even if it must be at their own expense) seems unethical. Reasonable people can differ in their judgments of economic value; if you doubt it, look at the variety of cars in any large parking lot.

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