Clopidogrel Plus Aspirin for Stroke Prevention

To the Editor:

We are responding to the review by Drs Albers and Amarenco about the use of clopidogrel plus aspirin for patients with cerebrovascular disease.1 We view the results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, added to all of the clopidogrel data, as more supportive of the combination of clopidogrel plus aspirin in stroke-threatened patients.

There is growing evidence to support the efficacy and safety of combination antiplatelet therapy for the prevention of vascular events. Combination therapies that inhibit platelet function by more than 1 mechanism may be more efficacious than single-agent approaches. The combination of clopidogrel with acetylsalicylic acid (ASA) has several beneficial features. Ex vivo studies have shown that clopidogrel plus ASA results in an 80% reduction in platelet aggregation using 20 μmol/L ADP as the stimulus based on light transmission aggregometry.2 This is a substantially greater reduction than with either drug alone. Other studies have also documented the enhanced antithrombotic effects of clopidogrel plus ASA.3,8 There is extensive experience with clopidogrel plus ASA in patients who receive coronary artery stents. A meta-analysis of coronary stenting in 13 955 patients found that the clopidogrel-plus-ASA combination compared with the ticlopidine-plus-ASA combination was associated with a 50% risk reduction in major adverse cardiac events and a 56% risk reduction in mortality (P=0.001 for both outcomes).4

The recently reported CURE study investigated the safety and efficacy of clopidogrel plus ASA in patients with acute coronary syndromes.5 This study of 12 562 randomized patients found that the clopidogrel-plus-ASA group showed a 20% relative risk reduction (P<0.001), and a 2.1% absolute risk reduction, in the primary outcome of nonfatal myocardial infarction, stroke, and vascular death when compared with ASA plus placebo. The CURE study was not designed to address the efficacy and safety of ASA plus clopidogrel in stroke patients. Very few patients in CURE had a prior history of stroke: 4.4% in the combination group versus 3.7% in the ASA plus placebo group. As might be expected, there were relatively few stroke outcome events in the trial (162 total: 75 in the clopidogrel-plus-ASA group and 87 in the ASA-plus-placebo group).5 The numbers are much too small to demonstrate any statistically significant differences. But the fact that there was a reduction in stroke events (relative risk reduction of 14% in favor of the clopidogrel-plus-ASA combination) may indicate some clinical benefit.

One study of another combination regimen, ASA plus extended-release diprydamole, has shown efficacy for stroke prevention. In the ESPS-2 trial of 6602 patients with ischemic strokes or transient ischemic attacks, the relative reduction in stroke risk was 23% with combination therapy compared with ASA alone.6 This study further supports the enhanced efficacy of combination therapy.

Albers and Amarenco highlight the fact that the rate of stroke in myocardial infarct patients is substantially lower than in stroke patients. Although stroke patients are at highest risk for their next atherothrombotic event to be a stroke, Sacco et al found that in 5 years of follow-up, 18% of the stroke patients died of stroke while 39% died of other cardiovascular causes.7 Thus, in the short-term following a stroke, patients have more strokes, whereas in the long-term they develop other manifestations of systemic atherothrombosis such as myocardial infarction and peripheral arterial disease. There is a large body of data showing that all patients at high risk for atherothrombotic events (mainly stroke, myocardial infarction, and vascular death) receive similar proportional reductions in vascular events from antiplatelet medications. An antiplatelet medication, or combination of medications, that benefits one high-risk group of patients generally benefits other high-risk groups in a similar way.8

A potential concern of combination antiplatelet therapy is safety, particularly bleeding. In CURE there was a 1% increase in major bleeds in the combination group, but there was no increase in intracranial hemorrhage or death. Approximately 70% of patients were receiving unfractionated or low-molecular-weight heparin at the time of randomization.8 These medications, when combined with antiplatelet agents, may increase the risk of bleeding. The use of heparins for acute stroke therapy likely has diminished based on recent studies showing a lack of efficacy for such agents.9 Almost 50% of the major bleeds in CURE occurred at either arterial puncture sites or surgical sites. Also, many were noted within the first 30 days after randomization, again implying that they were related to concomitant medications or procedures during the acute hospitalization. Acute stroke patients are much less likely to undergo such interventions.

Another important factor in the risk of bleeding is the dose of aspirin. In the CURE trial, there was a clear association between aspirin dose and the occurrence of major or life-threatening bleeding. Patients receiving aspirin in doses >200 mg/d had a risk of major bleeding of 4.0% to 4.9%, while those receiving doses of <100 mg/d had bleeding rates of 2.0% to 2.5%.10,11 These data suggest that 1 strategy for reducing bleeding complications may be combining clopidogrel with lower doses of aspirin (eg, 81 to 162 mg/d). ESPS-2 did not report a significant increase in bleeding side effects in the combination group (ASA 25 mg BID plus extended-release diprydamole 200 mg BID) compared with single-agent therapy.6 This also may support the enhanced safety of using lower doses of ASA when considering combination therapy.

As indicated by Albers and Amarenco, direct data on the efficacy and safety of clopidogrel combined with ASA in stroke patients does not exist. However, this question will be answered in the ongoing MATCH study, which is a randomized, double-blind study comparing the combination of clopidogrel and aspirin to clopidogrel alone in 7600 patients with transient ischemic attack or stroke.

In the field of vascular medicine, there is a clear trend for the use of combination therapy to prevent atherothrombotic vascular events. For patients with cerebrovascular disease who are at high risk for recurrent ischemic events, single-agent therapy may not be adequate. In such patients, consideration of combination therapy is a reasonable treatment option. Until clear data on the safety of clopidogrel plus aspirin in stroke patients emerge, the combination should be reserved for patients at high risk for atherothrombotic events. If one chooses to use clopidogrel plus aspirin, there are data to suggest that the use of ≤162 mg/d of aspirin will reduce the risk of bleeding in such patients.

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Response

We thank Drs Alberts and Easton for their thoughtful commentary and appreciate the opportunity to further clarify why we believe that the CURE study should not be extrapolated to cerebrovascular patients.

We agree that there is a sound scientific rationale for combining antiplatelet agents with different mechanisms of action and that some combinations have been shown to be safe and effective in specific clinical situations. For patients with cerebrovascular disease, several individual antiplatelet agents (aspirin, ticlopidine, extended-release dipyridamole) as well as the combination of extended-release dipyridamole/aspirin have been shown to be more effective than placebo. In addition, both ticlopidine and the combination of extended-release dipyridamole/aspirin have been shown to be more effective than aspirin, while clopidogrel demonstrated similar efficacy to aspirin among stroke patients in the CAPRIE trial. Therefore, data are available to support the use of a wide variety of different antiplatelet choices for cerebrovascular patients.

Drs Alberts and Easton point out that the CURE study was not designed to address the efficacy and safety of aspirin plus clopidogrel in stroke patients and note that 8 fewer strokes occurred in the clopidogrel-plus-aspirin group compared with the aspirin-plus-placebo group. We agree that this trend is encouraging; however, our enthusiasm is tempered by the 38% increase in major bleeding complications as well as the trend toward more fatal and life-threatening bleeding events in the combination therapy group (23 more life-threatening hemorrhages and 4 more fatal hemorrhages occurred in the combination therapy group).1 We agree that many of these hemorrhages occurred early after randomization and were related to procedures or concomitant medications. However, it is important to note that this high-risk early time period also appeared to be when the combination therapy seemed to have its impact on efficacy. We note that the cumulative hazard ratio curves for vascular outcome events remain relatively parallel after the first 3 months of follow-up. In addition, stroke patients appear to be at higher risk for bleeding on antiplatelet therapies than cardiac patients,2 which further complicates extrapolation of the bleeding rates in CURE to a cerebrovascular population.

Despite the lack of data to establish the efficacy of clopidogrel plus aspirin for preventing stroke, Alberts and Easton imply that the combination of clopidogrel plus aspirin may protect stroke patients from subsequent cardiovascular deaths. They cite data from the Northern Manhattan Stroke Study suggesting death from other cardiovascular causes is more likely than stroke-related death. The most recent publication from this study indicates that among stroke patients who die, stroke is the cause of death in 21% while other cardiovascular causes account for 27% of the deaths.3 Of importance, cardiovascular deaths occur for a wide variety of reasons. In the Northern Manhattan Stroke Study, myocardial infarction was the cause of death in only 7% of stroke patients (personal communication, Ralph Sacco, MD, 2002). This is potentially important because although the clopidogrel/aspirin combination was effective for preventing myocardial infarction in CURE, no significant benefit was seen for preventing death from other cardiovascular causes. In addition, among all participants in the CAPRIE trial, the number of “other vascular deaths” was identical in the clopidogrel and the aspirin groups. Therefore, it is unclear whether either clopidogrel alone or the combination of clopidogrel/aspirin provides a meaningful efficacy advantage over aspirin for prevention of cardiovascular deaths.

We agree that subpopulations of stroke patients can be identified who are likely to have a high recurrence risk despite single-agent antiplatelet therapy. An example is patients who suffer a stroke despite treatment with aspirin. For years, many physicians assumed that these patients would be better protected by warfarin rather than continuing aspirin therapy. However, when this strategy was tested in a randomized controlled trial, warfarin was no more effective than aspirin. In addition to uncertain efficacy, untested antithrombotic strategies may entail increased hemorrhagic risks that could outweigh any beneficial effects on vascular events. Therefore, rather than using untested combinations of antithrombotic agents, we typically focus attention on other treatable risk factors (such as optimal control of blood pressure and lipids) in high-risk patients.

Drs Alberts and Easton suggest that combinations of antiplatelet agents that benefit one high-risk group of patients generally benefit other high-risk groups in a similar way. We are less confident about this conclusion. Of note, other than for the combination of aspirin and dipyridamole, the recent Antithrombotic Trialists Collaboration report lists only 3 small studies that have compared a combination of oral antiplatelet agents with either aspirin or a control group.4 Furthermore, meta-analysis of trials of dipyridamole plus aspirin suggests a greater benefit for preventing stroke than myocardial infarction.5 Also, a test of heterogeneity in the CAPRIE study was statistically significant, suggesting that the efficacy of clopidogrel may differ among populations of patients with different vascular diseases.

We agree that combinations of clopidogrel and aspirin may prove to be beneficial in a wide variety of patient groups. We look forward to the results of ongoing trials including MATCH (testing clopidogrel plus aspirin versus clopidogrel in high-risk stroke patients), ARCH (warfarin versus clopidogrel plus aspirin in patients with aortic arch atherosclerosis), ACTIVE (clopidogrel/aspirin combination in patients with atrial fibrillation) and CHARISMA (clopidogrel plus aspirin in a large population of patients with myocardial infarction, stroke, or a combination of atherothrombotic risk factors).

In summary, we believe there are important differences between cerebrovascular and other patient groups as well as significant uncertainty regarding the safety and efficacy of the clopidogrel/aspirin combination for prevention of stroke. We advise caution regarding the use of untested combinations of antithrombotic agents.

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Blood Pressure and Clinical Outcome in Acute Ischemic Stroke

To the Editor:

We read with interest the recent report about the relationship between blood-pressure and clinical outcome in acute ischemic stroke. On the basis of an analysis of a single blood pressure value before randomization in the IST trial, the authors found that high and low initial blood pressure values were associated with a worse clinical outcome. However, many of the patients, particularly those with high blood pressure values, were probably treated with antihypertensive agents in the acute phase. A relationship between a blood pressure drop within the first 24 hours after acute stroke and worse outcome in patients with acute ischemic stroke has recently been reported. For a clinically relevant interpretation of the data from the IST trial, it is therefore crucial to differentiate whether high blood pressure levels themselves or, vice versa, the subsequent treatment with antihypertensive drugs in many of these patients, might have negatively influenced the outcome. The clinical consequences of these 2 hypotheses are completely opposite. We are concerned that many physicians will interpret the IST data as evidence to lower blood pressure levels in the acute phase if the systolic BP exceeds 150 mm Hg, which may be detrimental for their patients (in fact, we do not know). Such a misinterpretation is further promoted by the formulation of the authors that “patients with higher pressures might have a better outcome . . . if their blood pressure was actively lowered with an appropriate drug.” However, the authors should have clearly noted that the opposite might also be true in order to avoid premature clinical decisions on the basis of observational evidence. As the authors correctly state, randomized evidence is required.

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Response

Lalouschek and Lang question the cause of our finding relating blood pressure in acute ischemic stroke and subsequent outcome; specifically, they raise the possibility that active treatment for the high blood pressure might have caused a poor outcome, rather than the high blood pressure itself. We acknowledge that some drugs that lower blood pressure can be detrimental, as shown in some randomized controlled trials of β-receptor antagonists and calcium channel blockers, although this may not be true for all classes of antihypertensive agents. For example, candesartan appeared to improve outcome in one trial.

The International Stroke Trial did not record the use of drugs that lower blood pressure, so we cannot altogether discount the above suggestion. Nevertheless, it is unlikely that there was any significant or systematic use of drugs to lower blood pressure because most stroke physicians have noted the results of trials such as INWEST and BEST and are concerned that reducing blood pressure might reduce cerebral perfusion in the presence of damaged autoregulation. This assertion is supported by a published survey in which few physicians reported that they routinely lower high blood pressure. Our article did not aim to suggest that stroke physicians should actively lower high blood pressure but rather to provide further observational evidence supporting the need for one or more large trials to investigate this question further and define future management.

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