Aspirin and Newer Orally Active Antiplatelet Agents in the Treatment of the Post-Myocardial Infarction Patient

CARL J. PEPINE, MD, FACC
Gainesville, Florida

The thienopyridine derivatives, ticlopidine and clopidogrel, provide alternatives to aspirin for use in the prevention of recurrent ischemic events in the post-myocardial infarction patient. These drugs act through a different mechanism than aspirin and, as a result, have potentially different profiles of safety and efficacy. The following discusses the clinical data collected supporting the use of these drugs for secondary prevention and the unanswered questions that remain regarding their use in subpopulations of individuals at risk. Based on the available data, it may be concluded that aspirin should remain the drug of choice for the prevention of recurrent ischemic events in the majority of patients who have suffered a recent myocardial infarction.

Antithrombotic therapy is recognized to reduce the risk of subsequent ischemic events in individuals who have experienced a myocardial infarction (1). The Antithrombotic Trialists’ have estimated that the risk of secondary myocardial infarction, stroke, or vascular mortality (vascular ischemic events) is reduced by approximately 25% in individuals with a suspected acute myocardial infarction or a past history of myocardial infarction. These findings are based almost exclusively on trials that have evaluated the efficacy of aspirin (1), and the question has arisen as to whether the risk of secondary ischemic events can be further reduced with newer orally active alternative antiplatelet agents.

Ticlopidine and clopidogrel are thienopyridine derivatives that inhibit platelet aggregation through a fundamentally different mechanism than aspirin (2). While aspirin inhibits platelet aggregation by blocking the synthesis of thromboxane A2, a substance that causes both vasoconstriction and amplification of the platelet activation process, the thienopyridines inhibit platelet aggregation by blocking the binding of ADP, another substance that amplifies platelet activation. The question has therefore arisen as to whether this alternative approach to platelet inhibition might yield improved therapeutic benefit.

Information on the utility of ticlopidine in preventing recurrent coronary ischemic events is limited to the Studio della Ticlopidina nell’ Angina Instabile (STAI) trial (3). This randomized, but unblinded, trial compared the incidence of atherothrombotic events in patients with unstable angina who received only customary treatment (beta-blockers, calcium antagonists, and nitrates) against those who received both 250 mg of ticlopidine twice daily plus customary treatment. Although this trial demonstrated a significant decrease in nonfatal myocardial infarctions and vascular death in the ticlopidine-treated group, it is unclear whether the observed results represent an improvement over aspirin. Furthermore, the safety profile for ticlopidine is less favorable than that for aspirin. The use of ticlopidine has been associated with an increased incidence of very serious hematologic problems such as neutropenia (4) and thrombotic thrombocytopenic purpura (5). Thus, ticlopidine use has been reserved for those patients who are unable to tolerate aspirin.

Clopidogrel, though differing from ticlopidine only by the addition of an acetate ester, has not demonstrated hematotoxicity similar to that of ticlopidine in the 11,000+ patients in which its safety has been tested (6), suggesting increased utility in patients. However, the existing clinical data on clopidogrel (7) have generated considerable debate as to whether clopidogrel provides a superior therapeutic benefit to that of aspirin in the post–myocardial infarction patients. At the heart of this debate is the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), the largest trial yet that has directly compared the efficacy of an alternative antiplatelet agent with that of aspirin in reducing atherothrombotic events (7). The CAPRIE trial enrolled a total of over 19,000 patients, the distribution of which was evenly divided between three prospectively defined populations of patients: those who had experienced 1) a recent myocardial infarction, 2) a recent stroke, or 3) significant peripheral arterial disease. Subjects in the trial were randomly assigned to take either 325 mg of plain aspirin or 75 mg of clopidogrel once daily, and after up to 3 years (1.9 years on average) of treatment, the combined incidence of myocardial infarction, stroke, and vascular death in the aspirin- and clopidogrel-treated groups were compared. This trial showed an overall reduction in the rate of subsequent atherothrombotic events in favor of clopidogrel.
treated patients experienced either a myocardial infarction, stroke, or vascular death at a rate of 5.32% per year, while aspirin-treated patients had an event rate of 5.83% per year; a relative risk reduction of 8.7% in favor of clopidogrel ($p = 0.043$).

Although the overall result of the trial favored clopidogrel, an analysis conducted to verify the homogeneity of the response among the three populations of patients indicated that the benefit was not evenly distributed among these groups. Significant heterogeneity ($p = 0.042$) across subgroups was observed, with the majority of clopidogrel’s benefit occurring in patients that entered the trial with peripheral arterial disease. Patients who entered the trial because of a recent myocardial infarction showed no reduction in the risk of subsequent ischemic events when the clopidogrel- and aspirin-treated groups were compared. In fact, a nonsignificant relative risk increase of $-3.7\%$ (95% CI $= -22.1$ to $12.0$) was seen in the clopidogrel-treated patients. The basis for this difference is currently unknown, but the possibility exists that a selection bias may have been introduced by indication. That is, the selection of patients with a particular manifestation of atherothrombotic disease as defined in the study protocol may have introduced patients with other cofounders that ultimately affected the outcome. Although the meaning of the heterogeneity between the groups continues to be the subject of considerable debate, the data suggest that in patients with a recent myocardial infarction, clopidogrel may be no more effective than aspirin. Unfortunately, the CAPRIE trial is the only trial thus far to evaluate the effectiveness of clopidogrel in secondary prevention. Until this issue is further explored, questions will remain regarding the relative benefit of clopidogrel in the coronary artery disease patient.

If the issue of heterogeneity is ignored, and it is assumed that the overall result reflects a true benefit of clopidogrel over aspirin in all of the subpopulations of patients that were studied in CAPRIE, the clinical significance of this result deserves comment. Based on prior estimates of the efficacy of aspirin in preventing recurrent thromboembolic events (1) and the results obtained in CAPRIE, it has been estimated that in a patient population similar to that in CAPRIE, aspirin will prevent 19 major events per year for every 1,000 high-risk patients that are treated, while clopidogrel will prevent 24 major events in the same group (7). Thus, it would require switching 200 patients from aspirin to clopidogrel to see even one less event per year. If the 95% confidence interval for the overall result is used, the number of patients required to be switched might actually fall between 120 and 5,000, depending on the play of chance. This additional benefit is relatively small, and is unlikely to offset the much higher cost of clopidogrel over aspirin.

Given the relatively small benefit that the overall result of CAPRIE suggests, and the uncertainty surrounding the potential for clopidogrel to outperform aspirin in patients who have experienced a recent myocardial infarction, the decision to shift a patient who would otherwise receive aspirin must rely on other factors. The CAPRIE trial demonstrated no substantive safety benefit of either aspirin or clopidogrel. Both drugs were tolerated to essentially the same extent. The rate of withdrawal from treatment because of adverse events was the same in both groups (11.4%), and the types of adverse events were similar for both drugs (e.g., upper gastrointestinal discomfort and general bleeding disorders were the most common adverse events for both drugs). Although upper gastrointestinal effects were somewhat more common in the aspirin-treated patients, the dose of aspirin used in this trial was in excess of that recognized to be effective in secondary prevention. Thus, it is likely that the incidence of these events would have been more comparable if a lower dose of aspirin or an enteric-coated formulation had been used.

In the absence of a tangible advantage with respect to efficacy or safety, there appears to be no justification at this time for a wholesale shift in treatment strategy for the symptomatic coronary disease patient. Clopidogrel may, however, prove to be a valuable therapeutic agent in the small number of patients with a prior myocardial infarction or unstable angina who are unable to tolerate aspirin either because of anaphylactic reactions, or abnormally severe gastrointestinal irritation. Clopidogrel is also expected to be a valuable replacement for ticlopidine when used in combination with aspirin in the acute treatment of interventional patients (such as those have stent implantation), but this is unproven. The CLASSICS (CLOpidogrel ASpirin Stent International Cooperative Study) trial, a comparison of aspirin plus clopidogrel versus aspirin plus ticlopidine in the prevention of stent thrombosis, is currently in the planning stages. It is expected to provide information about the utility of combining clopidogrel with aspirin in the patient at risk of recurrent coronary thrombotic events.

Another question is whether clopidogrel used in combination with aspirin may provide a greater benefit than that achieved with either agent alone. The CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial, a comparison of nonfatal myocardial infarction and vascular death in unstable angina patients receiving clopidogrel (75 mg) plus aspirin versus aspirin alone, is also in the planning stages. It should provide information about the benefits of combining aspirin with clopidogrel in patients at risk of recurrent coronary ischemic events. However, based on the currently available information, aspirin remains the drug of choice for the majority of post-myocardial infarction patients for whom long-term antiplatelet therapy is recommended. There is no convincing evidence that clopidogrel provides any benefit with respect to efficacy, safety, cost, or availability that would justify its supplanting the use of aspirin in the treatment of the post-myocardial infarction patient.

References
1. Antiplatelet Trialists’ Collaboration. Collaborative overview of randomized trials of antiplatelet therapy—II: Prevention of death, myocardial infarction,