Therapeutic Benefit
Aspirin Revisited in Light of the Introduction of Clopidogrel

Philip B. Gorelick, MD, FACP, MPH; Gustav V.R. Born, MB, ChB, PhD; Ralph B. D’Agostino, PhD; Daniel F. Hanley, Jr, MD; Lemuel Moye, MD, PhD; Carl J. Pepine, MD

Background—Antiplatelet agents are widely recognized for their efficacy in reducing the occurrence of vascular events in patients with atherothrombotic disease. Aspirin is currently considered to be the “reference standard” antiplatelet agent and is recommended by the American Heart Association for use in patients with a wide range of manifestations of cardiovascular disease on the basis of its high benefit-to-risk and benefit-to-cost ratios. Recently, clopidogrel (Plavix, Bristol-Myers Squibb Co), another antiplatelet agent, was approved by the Food and Drug Administration for many of the same indications as aspirin.

Summary of Review—Because physicians will be faced with deciding whether to switch from the well-established practice of recommending aspirin for use in patients with atherothrombotic disease, both aspirin and clopidogrel are compared with respect to the primary factors that influence such decisions (ie, their relative efficacy, safety, cost, and convenience of use).

Conclusions—Based on the available evidence, aspirin is preferred for the majority of stroke or myocardial infarction patients at risk of recurrent atherothrombotic events. Clopidogrel may, however, provide valuable therapeutic benefit over aspirin in patients with peripheral arterial disease and in stroke or myocardial infarction patients for whom aspirin treatment is contraindicated or for whom aspirin fails to achieve the desired therapeutic effect. (Stroke. 1999;30:1716-1721.)

Key Words: aspirin n clopidogrel n decision analysis n prevention

Antiplatelet therapy is widely recognized to have the potential to reduce the incidence of stroke, heart attacks, and death from vascular causes in individuals with symptomatic atherothrombotic disease. A meta-analysis of 142 trials, which included a total of over 70,000 patients with evidence of cardiovascular disease who were at high risk for recurrent illness, found an overall 27% reduction in vascular morbidity and mortality among patients allocated to use antiplatelet drugs.1 Benefits were seen irrespective of whether participants had previously experienced or were undergoing occlusive vascular events (eg, had a past history of myocardial infarction, stroke, or transient ischemic attack or had unstable angina or suspected acute myocardial infarction) or were at high risk of having these events (eg, patients with stable angina, valvular heart disease, atrial fibrillation, peripheral vascular disease, and those having coronary or peripheral vascular procedures). Furthermore, the benefit was observed regardless of sex, age, blood pressure, or the presence of diabetes.

The majority of the data collected by the Antiplatelet Trialists’ Collaboration regarding the efficacy of antiplatelet therapy has come from clinical trials that have used aspirin. Other antiplatelet drugs have been less extensively studied. However, data from trials in which these drugs were directly compared with aspirin, as well as data from trials in which individual treatment regimens were evaluated against placebo, led the Antiplatelet Trialists to conclude in 19941 that no other antiplatelet regimen (eg, dipyridamole, sulfinpyrazone, ticlopidine, sulcotidil, or combinations of aspirin with dipyridamole or sulfinpyrazone) was more effective than aspirin alone in preventing recurrent myocardial infarction, stroke, or vascular death.

Recently, clopidogrel (Plavix, Bristol-Myers Squibb Co), another antiplatelet agent, was approved by the Food and Drug Administration (FDA) for use in secondary prevention of heart attacks and stroke.2 Clopidogrel, a thienopyridine derivative similar to ticlopidine, differs from aspirin in the mechanism by which it inhibits platelet aggregation. Aspirin inhibits platelet aggregation by irreversibly blocking the enzyme cyclooxygenase, essential for synthesis of thromboxane A2 (TXA2), a substance that both causes vasoconstriction and amplifies the platelet activation process leading to platelet aggregation.3 The thienopyridines, clopidogrel and ticlopidine, by contrast, inhibit platelet aggregation by irreversibly inhibiting the binding of adenosine diphosphate (ADP), a substance that is released in platelets.
selected studies demonstrating the effectiveness of aspirin in secondary prevention in patients with a variety of manifestations of prior cardiovascular disease

Study/Analysis | Finding
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Prior myocardial infarction | Meta-analysis of 6 clinical trials of the effectiveness of aspirin in preventing recurrent myocardial infarctions (all completed before 1981). Included >10,000 patients and doses of aspirin ranging from 300 to 1500 mg/d. Found a 16% reduction in cardiovascular death ($P<0.01$) and 21% reduction ($P<0.001$) in the combined incidence of fatal and nonfatal myocardial infarctions compared with placebo.

Unstable angina | The Veterans Administration Cooperative Study included >1200 men with unstable angina. Showed a 51% reduction ($P=0.0005$) in death or acute myocardial infarction in the aspirin group (325 mg/d) compared with placebo after 12 weeks of treatment. The effect persisted at the 1-year follow-up.

Prior stroke or transient ischemic attack | The Swedish Aspirin Low-Dose Trial (SALT) included >1200 male and female patients with transient cerebral ischemia or minor stroke. Showed an 18% reduction of stroke or death ($P=0.02$) in patients taking aspirin (75 mg/d) compared to placebo. The overall incidence of stroke, myocardial infarction, or vascular death was also significantly less (17%; $P=0.03$) in the aspirin group.

The UK-TIA Study Group, 1991 | The UK-TIA study included 2435 patients with transient cerebral ischemia or minor stroke. Compared the effectiveness of 1200 mg and 300 mg aspirin against placebo. Neither aspirin dose group was significantly different from placebo, but combined data from both aspirin groups showed an 18% reduction in the risk of stroke, myocardial infarction, or death ($P=0.01$).

Atrial fibrillation | Stroke Prevention in Atrial Fibrillation (SPAF) included >1300 patients with nonvalvular atrial fibrillation. It showed a 32% reduction ($P=0.02$) in the incidence of stroke, systemic embolism, or death in patients taking aspirin (325 mg/d) compared with placebo.

Stable angina | The Swedish Angina Pectoris Aspirin Trial (SAPAT) included >2000 patients with stable angina. It showed a 34% reduction ($P=0.003$) in the incidence of myocardial infarction and sudden death in patients treated with aspirin (75 mg/d) and sotalol (a β-blocker administered for control of angina symptoms) compared with those receiving placebo plus sotalol.

during activation and, like TXA₂, amplifies the aggregation process. Currently there are no experimental data indicating a therapeutic advantage for either mechanism of platelet inhibition in the prevention of occlusive thrombotic events. Preclinical studies suggest that both TXA₂ and ADP contribute about equally to platelet aggregation. Thus, clinical choices between aspirin and clopidogrel must be based on clinical evidence of the relative benefits and risks associated with the use of these drugs. The following analysis of the relative efficacy, safety, cost, and convenience of use of aspirin and clopidogrel is intended to provide the basis for choosing between these 2 antiplatelet agents for treatment of individual patients.

Efficacy
Numerous preclinical studies demonstrate that both aspirin and clopidogrel are effective in inhibiting platelet aggregation, and on the basis of this effect, both drugs would be expected to be effective in reducing the incidence of thrombotic events. The available clinical data support this conclusion but are less clear with respect to whether one agent is more efficacious than the other.

Aspirin
Aspirin, widely used since the beginning of this century for its antipyretic, anti-inflammatory, and analgesic properties, was first recognized in the 1950s to reduce the incidence of myocardial infarctions. Research conducted in the early 1970s uncovered the mechanism by which aspirin confers its benefits, and the first published study showing statistically significant benefits of aspirin in patients at risk of stroke, by the Canadian Cooperative Study Group, appeared in the late 1970s. Since then, multiple randomized, controlled clinical trials (Table) have shown a clinically significant decrease in cardiovascular morbidity and mortality in patients at risk of recurrent thromboembolic events.

As indicated in the Table, aspirin has been tested at a range of doses. Many of the early studies used doses of aspirin (eg, 500 mg to 1500 mg daily) comparable to those shown to be effective for antipyretic, anti-inflammatory, and analgesic effects. Recent trials, however, have used lower doses (eg, 50 mg to 325 mg daily) because they have been shown to provide maximal inhibition of the synthesis of platelet TXA₂. Although the concept of therapeutic equivalency between high- and medium-dose aspirin has been considered controversial by some investigators, the meta-analytic comparison performed by the Antiplatelet Trialists showed equivalent efficacy of high- (eg, 500 mg to 1,500 mg daily) and medium-dose (eg, 75 mg to 325 mg daily) aspirin in preventing the composite end point of nonfatal myocardial infarction,
nonfatal stroke, or vascular death. Although there is some uncertainty involved in the use of meta-analyses to arrive at an optimum dose when little data exist from studies in which doses were directly compared, the FDA now recommends the use of 50 to 325 mg of aspirin once per day for the prevention of ischemic stroke and transient ischemic attack and the use of 75 to 325 mg of aspirin once per day for the prevention of recurrent myocardial infarction (63 FR 56802 at 56817).

**Clopidogrel**

Clopidogrel, the acetate derivative of ticlopidine, has been demonstrated in preclinical studies to inhibit platelet aggregation by the same mechanism as ticlopidine but is approximately 6-fold more potent. Given the demonstrated efficacy of ticlopidine in secondary prevention (especially in individuals with preexisting cerebrovascular, cardiovascular, or peripheral vascular disease), it would be expected that clopidogrel would also prevent recurrent occlusive thrombotic events.

The clinical efficacy of clopidogrel in secondary prevention is demonstrated in the clinical trial, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE). This trial compared the efficacy of clopidogrel with that of aspirin in preventing recurrent myocardial infarction, stroke, and vascular death in 19,185 patients with either (1) a recent myocardial infarction, (2) a recent stroke, or (3) significant peripheral arterial disease. Enrollment was evenly distributed between these 3 high-risk groups, and study subjects were randomly assigned to take either 325 mg of plain aspirin or 75 mg of clopidogrel once daily. After up to 3 years (1.9 years on average) of treatment, the incidence of events (myocardial infarction, stroke, and vascular death) in the aspirin- and clopidogrel-treated groups were compared. The data from all 3 high-risk groups, though separately enrolled, were combined in this analysis based on the premise that atherothrombotic disease is the common pathology underlying all 3 conditions.

The CAPRIE trial found an event rate of 5.83 events per year in the aspirin-treated group versus 5.32 events per year in the clopidogrel-treated group (P=0.043), a difference equivalent to the occurrence of 5 additional events per 1000 patients. Although the authors concluded on the basis of these results that clopidogrel is "more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death," many questions have been raised about whether the results demonstrate clear evidence of the superiority of clopidogrel over aspirin. The major issues that have been raised include the relatively small magnitude and marginal statistical significance of the absolute difference between treatments, the apparent heterogeneity of the findings between the 3 populations of patients that were recruited into the trial, and the absence of corroborating data.

As indicated above, the CAPRIE trial showed only a small relative difference (ie, 8.7% relative risk reduction; 95% CI, 0.3 to 16.5) in outcome between the aspirin- and clopidogrel-treated groups. The absolute risk reduction of only 5 events per 1000 patients leaves open questions about whether such a difference is clinically meaningful, or in fact, reproducible. Because the results of the study have not yet been replicated, it is impossible to know whether the findings of the CAPRIE trial represent a chance statistical occurrence or a real difference between therapies. Despite the large size of CAPRIE, the possibility that some peculiarity of the design or conduct of the study may have influenced the outcome is greater than if 2 independent trials had been performed and had given the same outcome.

A secondary analysis carried out in the CAPRIE study to verify that the outcome was homogeneous found heterogeneity (P=0.042) in responsiveness among the 3 patient populations studied. By far, the largest benefit of clopidogrel occurred in the group with peripheral arterial disease. Over 75% of the therapeutic advantage of clopidogrel over aspirin occurred in those with peripheral arterial disease (ie, 62 fewer events in the clopidogrel-treated peripheral arterial disease patients out of a total difference of 82 events in the combined analysis), resulting in a 23.8% relative risk reduction in this group versus a <8% reduction in the stroke group and a slight increase in the myocardial infarction group. This raises questions about whether there may have been unique features in the peripheral arterial disease patients that would account for the more robust difference between clopidogrel and aspirin seen in this group and whether the decision to pool data from all 3 patient groups is valid.

For example, there may have been subtle selection biases occurring in the different patient populations that may have affected the results. The baseline characteristics reported for the peripheral arterial disease group showed that it contained more smokers and more patients with prior myocardial infarction (ie, prior to the qualifying event) than the other 2 groups of patients. Also, patients with peripheral arterial disease may be less aggressively treated (ie, with dietary and drug interventions) than patients with coronary artery disease. Such differences could affect outcome. Alternatively, the difference in the effectiveness of aspirin and clopidogrel in patients in CAPRIE may have arisen because of differences in disease severity or concomitance of diseases between the groups, or because of differences in the pathogenesis of the disease depending on the vascular bed in which it was primarily manifest (eg, coronary, carotid, femoral, or popliteal arteries), or simply by chance. Further research will be necessary to verify whether clopidogrel is uniquely more effective than aspirin in patients with peripheral arterial disease.

Uncertainty regarding the relative efficacies of aspirin and clopidogrel in the CAPRIE trial should not overshadow the observation that clopidogrel is at least as effective as aspirin (ie, marginally more effective) in the prevention of recurrent atherothrombotic events. Although no placebo group was possible in CAPRIE because of the ethical issues inherent in denying patients known effective treatment (ie, aspirin), it is likely that clopidogrel would have outperformed placebo had one been used. Clopidogrel was not significantly less effective than aspirin in either the overall analysis or any of the secondary analyses. Given the demonstrated ability of aspirin to prevent secondary events and the known antithrombotic effects of clopidogrel and aspirin, it is appropriate to conclude that clopidogrel is effective in the prevention of secondary thromboembolic events.
Safety
When 2 drugs are shown to have comparable efficacy, drug choice is frequently based on the relative safety of one drug over the other. The results of CAPRIE suggest that although the safety profiles of aspirin and clopidogrel differ slightly, the 2 agents are similarly tolerated by patients.

Aspirin
Aspirin is perhaps one of the most widely used drugs of all time. Over 1 trillion aspirin tablets have been consumed over the last 100 years, and conservative estimates suggest that close to 30 billion tablets are consumed every year in the United States alone. The extensive and unparalleled postmarketing experience that exists for aspirin has provided a wealth of data on which conclusions about the safety of aspirin can be based. It is widely recognized that the key side effects of aspirin include gastrointestinal discomfort, gastric erosions or ulcers, gastrointestinal bleeding, other bleeding episodes (including hemorrhagic stroke), allergic reactions, and an increase in symptomatic gout. Gastrointestinal disturbances are by far the most common, and these effects are dose and duration dependent.

The overall results of clinical trials in which several different doses of aspirin have been tested for their cardiovascular benefits indicate that although not completely eliminated, the prevalence of gastrointestinal side effects decreases with dose. For example, a direct comparison of the prevalence of gastrointestinal toxicity among patients using 300 and 1200 mg of aspirin per day in the UK-TIA trial showed that both subjective gastrointestinal complaints and gastrointestinal bleeding were more frequent at 1200 mg/d (41% had gastrointestinal discomfort and 4.8% had gastrointestinal bleeding) than at 300 mg/d (31% had gastrointestinal discomfort and 3.1% had gastrointestinal bleeding) or with placebo (26% had gastrointestinal complaints and 1.1% had gastrointestinal bleeding). Further reducing the dose of aspirin to 50 mg/d, using enteric-coated or highly buffered aspirin, or using aspirin in conjunction with products that protect the gastric lining may reduce the incidence and severity of aspirin-induced gastric toxicity.

Clopidogrel
Clopidogrel was developed as a less-toxic alternative to ticlopidine. Neutropenia or thrombocytopenia occur in between 2% and 3% of the patients who receive ticlopidine and neutropenia has been severe in approximately one third of these individuals and fatal in a number of cases. The potential for such bone marrow depression requires monitoring of bone marrow status (eg, complete blood and platelet counts) every 2 weeks during the first 3 months of treatment. Recently, ticlopidine was shown to be associated with thrombotic thrombocytopenic purpura with exposure of relatively brief duration (eg, 2 weeks or less).

Preclinical studies and the CAPRIE trial indicate that clopidogrel use is free of severe bone marrow depression. Although clopidogrel and ticlopidine were not directly compared in CAPRIE, clopidogrel-treated groups showed a lower frequency of neutropenia and thrombocytopenia (0.1% and 0.26%, respectively) than has been found in other studies with ticlopidine (2.4% and 2%, respectively). The incidence of severe neutropenia was also less with clopidogrel in CAPRIE (0.05%) than has been observed with ticlopidine (0.85%). The incidence of neutropenia in the CAPRIE trial was roughly the same as that seen with aspirin, a drug not known to cause neutropenia. Thus, the side effect of ticlopidine that has been most problematic for patients (ie, bone marrow depression) appears much less frequently with clopidogrel. Also, clopidogrel-treated patients in CAPRIE reported less diarrhea (4.46%; severe or leads to discontinuation in 0.23% to 0.42%) than has previously been reported for ticlopidine (~20%; severe or leads to discontinuation in 2% to 6%).

The CAPRIE trial further showed that when used at a dose of 75 mg/d, clopidogrel was tolerated to roughly the same extent as aspirin (325 mg/d). For example, the same percentage (11.4%) withdrew from treatment in each group because of adverse events. Also, upper gastrointestinal tract symptoms and generalized bleeding were the most frequently reported side effects for both drugs. There were, however, slight differences in the prevalence of some side effects between groups. The overall incidences of rash (6.02%) and diarrhea (4.46%) were greater in the clopidogrel group than in the aspirin group (4.61% and 3.36%, respectively), and the overall incidences of gastrointestinal discomfort (17.59%), gastrointestinal hemorrhage (2.66%), peptic ulcer (1.2%), and abnormal liver function (3.15%) were greater in the aspirin group than in the clopidogrel group (15.01%, 1.99%, 0.7%, and 2.97%, respectively). No significant difference was seen between clopidogrel and aspirin with respect to the incidence of general bleeding disorders or intracranial hemorrhage.

It is uncertain, however, how representative the safety data obtained in CAPRIE are with respect to actual usage of aspirin and clopidogrel in the broader population. For example, the CAPRIE trial used 325 mg of aspirin and 75 mg of clopidogrel. Although these doses are maximally effective, it is generally believed that using lower doses of aspirin will cause fewer side effects without compromising efficacy. Also, it is common practice to recommend the use of enteric-coated or highly buffered preparations of aspirin for long-term treatment to reduce gastrointestinal toxicity; however, plain aspirin was used in CAPRIE. It is possible that a comparison of lower-dose aspirin or an enteric-coated preparation may shift the balance of side effects to favor aspirin. It is also difficult to draw conclusions about the absolute safety advantages of clopidogrel versus aspirin (either at the dose tested or at lower, less-toxic doses), because aspirin-intolerant individuals were excluded from the trial. Depending on how the exclusion criterion “aspirin intolerance” was interpreted by the physicians participating in the trial, patients reporting past experiences with either gastrointestinal bleeding or gastrointestinal symptoms while on aspirin may have been excluded. Such a practice would have minimized any differential in the observation of gastrointestinal effects.

Outside of the experience in CAPRIE, relatively few data are available on the toxicity of clopidogrel. Other data on side effects are limited to those obtained in small studies of healthy volunteers and patients in phase 2 studies (ie, a total of <1000 participants). This is in marked contrast to the large database

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Outs...
available on aspirin safety. Important questions remain regarding what can be expected with long-term use of clopidogrel under “normal use” in the general population.

It is anticipated that individuals using antiplatelet therapy for secondary prevention of atherothrombotic events will need to continue use for the remainder of their lifetime. Aspirin, the prototype antiplatelet agent, has been in use for over 100 years, and little remains unknown about the effects associated with its long-term use in a wide variety of patient populations. By contrast, the longest exposure thus far for clopidogrel is 3 years (1.9 years on average in the CAPRIE trial),33 which has occurred in a carefully selected clinical trial population. Thus, the potential exists for side effects of clopidogrel to become evident with long-term use in a more diverse population. Also, there is limited information on the effects of clopidogrel in severe or chronic overdosage and incomplete information on the potential for interactions of clopidogrel with other medications.38 Although the data suggest that significant interactions are unlikely with such commonly used drugs as aspirin, heparin, atenolol, nifedipine, estrogen, digoxin, theophylline, or other cardiovascular or antidiabetic medications, the possibility exists for adverse interactions when in use in a larger, more heterogeneous population.

Cost
Cost is always an important consideration when deciding between alternative therapies; especially when patients must assume the burden of the cost for the rest of their lives, as is the case with antiplatelet therapy. The cost of drug treatment is, however, only one of the factors that must be considered when comparing the cost-effectiveness of alternative treatments. Consideration must also be given to the costs of primary events or side effects that occur but might have otherwise been avoided had an alternative treatment had been chosen.

When compared only on the basis of drug costs, aspirin costs less than clopidogrel. At $5.45 per quarter (based on a price of $0.06 per tablet and a treatment regimen of 1 tablet per day), aspirin provides an approximate 45-fold cost advantage over clopidogrel (based on an average wholesale price of $288 per 100 tablets and a treatment regimen of 1 tablet per day). This differential is less, however, when the costs to prevent an event or save a life are calculated. By comparing the data on event rates from CAPRIE with those from untreated groups in prior trials1 and balancing these data against the cost of drug treatment plus the cost of side effects encountered during treatment,39–42 it is estimated that the costs to prevent an event or save a life would be $8559 or $8181, respectively, for aspirin and $43 843 or $49 367, respectively, for clopidogrel. These differentials amount to a 5- to 7-fold cost advantage for aspirin over clopidogrel. These differentials are relatively unchanged, if only peripheral arterial disease patients are considered (the group demonstrating the greatest difference in reduction of morbidity and mortality). Ultimately, the cost of clopidogrel would have to be lowered to $0.30 per tablet to match aspirin on cost per event prevented and to $0.20 per tablet to match aspirin on the cost per life saved. It should be kept in mind, however, that these are estimates reflecting the event and side-effect rates associated with the treatment protocols used in CAPRIE and do not predict costs likely to be incurred at lower aspirin doses or with use in the broader population.

Cost is also an important factor in determining compliance. Although the effect of cost on compliance is complex, studies have reported that an increase in the cost of treatment reduces a person’s adherence to treatment.43 If patients deem the cost of therapy excessive, they may not have a prescription filled or may stop treatment prematurely.44 As Americans are becoming increasingly responsible for covering drug costs out-of-pocket,45 high drug costs may be prohibitive for some individuals. Such noncompliance may ultimately result in higher costs due to increased emergency room visits, hospitalizations, nursing home care and other forms of treatment, and/or premature death.

When faced with the choice of antiplatelet agents, the physician must ultimately decide whether clopidogrel provides enough extra benefit to justify asking patients to pay more than the cost of aspirin. Unless aspirin cannot be tolerated or is ineffective, the relative cost of aspirin treatment favors its use over clopidogrel. Furthermore, the over-the-counter availability of aspirin makes it a more convenient treatment option than clopidogrel.

Conclusions
When the efficacy, safety, cost, and convenience of aspirin and clopidogrel are compared, the balance of the evidence favors the use of aspirin in the prevention of recurrent thromboembolic events in stroke and myocardial infarction patients. A large base of clinical trial experience exists that when taken together demonstrates that aspirin is effective in such patients. Thus, it is difficult to recommend initially administering clopidogrel or switching from the use of aspirin in stroke or myocardial infarction patients for whom it has been effective and well tolerated. Clopidogrel does appear, however, to be a viable alternative to aspirin, and it should be considered for the stroke and myocardial infarction patients who do not benefit from the use of aspirin (eg, those who are aspirin intolerant or for whom aspirin treatment fails). Clopidogrel may also be preferred over aspirin in patients with peripheral arterial disease. This is the only patient population in the CAPRIE trial to show a clear therapeutic benefit of clopidogrel over aspirin. Although clopidogrel does not appear to be less safe than aspirin based on the currently available data, only through long-term monitoring will the potential for delayed or rare side effects with clopidogrel be evaluated. Further research should be directed toward understanding the apparent differences in efficacy of aspirin and clopidogrel in the various atherosclerotic patient populations enrolled in the CAPRIE trial. Additional research into the potential for added benefit with combination therapy in all groups of patients may also be valuable, given the complementary mechanisms of action of these drugs. Both the recent data suggesting a synergistic inhibition of platelet aggregation in individuals using both aspirin and an ADP-binding inhibitor46 and the demonstration of an added benefit in secondary stroke prevention when low-dose aspirin is used in
conjunction with dipyridamole suggest increased protection with combination therapy.

References


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