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Clinical Investigations

Antiplatelet Therapy in the Prevention of Ischemic Vascular Events: Literature Review and Evidence-Based Guidelines for Drug Selection

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Summary

Background: New antiplatelet drugs are being developed and many clinical trials evaluating the benefits of antiplatelet drugs for the secondary prevention of ischemic events in patients with atherosclerotic vascular disease have been performed.

Hypothesis: An updated systematic review and evidence-based guidelines for the appropriate selection of antiplatelet drugs may be beneficial to physicians and healthcare organizations attempting to create or update current clinical practice guidelines or clinical pathways aimed at caring for these patients.

Methods: (1) A systematic review of the recent literature on the relative efficacy and safety of aspirin, ticlopidine, and clopidogrel was undertaken; (2) an evidence-based, expert panel approach using a modified Delphi technique to create explicit guidelines for prescribing antiplatelet therapy was instituted; and (3) the recommendations of an expert panel were summarized.

Results: Consensus guidelines were developed for the utilization of aspirin, ticlopidine, or clopidogrel for the prevention of ischemic events in patients with manifestations of atherosclerotic vascular disease (prior myocardial infarction, prior ischemic stroke, or established peripheral arterial disease) who are at increased risk for recurrent ischemic events. Based on efficacy and safety, clopidogrel was recommended as the drug of choice for patients with established peripheral arterial disease; aspirin or clopidogrel should be considered in patients with prior myocardial infarction (with clopidogrel favored for patients who have had a recurrent event while on aspirin or in whom aspirin is contraindicated); aspirin or clopidogrel should be considered as first-line treatment in patients with prior ischemic (nonhemorrhagic) stroke–however, clopidogrel is the favored drug in patients in whom other antiplatelet drugs are either contraindicated or who have had recurrent events while on therapy.

Conclusions: Myocardial infarction, ischemic stroke, and peripheral arterial disease are all clinical manifestations of the same underlying disease process (atherosclerosis), with thrombus formation on the disrupted atherosclerotic plaque (atherothrombosis) being a common precipitating factor of ischemic events in patients suffering from these disorders. An evidence-based approach was used to develop a practice guideline, based on available published evidence, for the appropriate utilization of antiplatelet agents (aspirin, ticlopidine, or clopidogrel). These guidelines may be of use to multidisciplinary teams wishing to create or update clinical guidelines or clinical pathways which address the care of patients with atherosclerotic vascular disease. New antiplatelet agents such as clopidogrel may be more effective and associated with lower risk of selected adverse effects (such as gastrointestinal distress, gastrointestinal hemorrhage, and neutropenia) than those previously used to prevent thrombus formation in the setting of atherosclerotic arterial disease. Combination antiplatelet therapy is being evaluated as an option for those patients who experience recurrent events on a single antiplatelet agent.

Dr. Eric Raps is deceased.

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Introduction

Atherosclerotic vascular disease, often a generalized process involving more than one vascular bed,[1,2] is a common cause of ischemic vascular events in the United States. The number of patients discharged annually in the United States with a diagnosis of acute myocardial infarction (858,000), cerebral artery occlusion (330,000), and peripheral arterial disease (225,000) is significant.[3] These may represent only a fraction of the total number of patients at risk for, or having a history of, ischemic events who may benefit from inhibition of both formation or progression of thrombus with antiplatelet agents. For example, in adults aged ≥65 years, over 30% report living with ischemic heart disease[4] and 12.4% have evidence of peripheral arterial disease manifested by ankle/brachial systolic pressure indices <0.9.[5] Thrombosis may result from three contributing factors: exposure of thrombogenic arterial wall substrates with vascular injury, local rheology of blood flow at sites of arterial narrowing, and hemostatic factors in the blood such as catecholamines, low-density lipoprotein cholesterol, and fibrinogen.[6,7] Thrombus formation at the site of disrupted arterial atherosclerotic plaques is the underlying pathophysiology leading to ischemic events in most of these patients: injury to the endothelium, and especially disruption of the vulnerable lipid-rich plaque, results in exposure of prothrombotic tissue substrates such as "fatty gruel," collagen, smooth muscle cells, and von Willebrand's factor. The "fatty gruel" of lipid-rich plaques from the aorta, coronary arteries, carotid or other arteries[8,9] is the most thrombogenic substrate and initiates the coagulation pathway, thrombin formation, and platelet activation. Arterial stenosis narrowing, mural thrombus, or small arteries increase local shear force and platelet deposition.[6,7] Shear force-induced platelet aggregation is reduced by adenosine diphosphate (ADP) inhibition but not by aspirin.[10] Most coronary risk factors (e.g., smoking-related release of catecholamines, hyperlipidemia, or uncontrolled diabetes) increase factors in the blood that increase platelet deposition.[6,7]

By virtue of sharing this common underlying pathology (e.g., with plaque disruption in the aorta, coronary and carotid arteries), ischemic stroke, myocardial infarction, and peripheral arterial disease frequently occur in the same patient populations: coronary disease may be found in 28% of patients with cerebrovascular disease[11] and in 50–78% of patients with peripheral arterial disease.[12] There is a five- to six-fold increase in the 10-year mortality rate from cardiovascular events in patients with peripheral arterial disease compared with those without this condition.[13]

Antiplatelet agents (also known as "platelet inhibitors") are well recognized for their beneficial impact on decreasing the frequency of ischemic events related to thrombus formation at the site of atherosclerotic plaque: fatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and other vascular-related death.[14] However, it is important to distinguish these arterial thrombi from those that occur in the venous system without an underlying plaque and that are not particularly responsive to antiplatelet agents.[10]

Practice guidelines ("systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances"[15]) and clinical pathways are being developed by physicians and many different organizations to improve quality of care, reduce health care costs, and minimize unexplainable variations in medical care.[16] The intent of practice guidelines is to support clinical decision making with up-to-date medical evidence.[17] When practice guidelines form the scientific foundation of a disease management program,[18] they have been shown to improve patient outcomes.[19] Therefore, practice guidelines and clinical pathways may assist practitioners to provide optimal care for patients both prior to and following ischemic vascular events.

While aspirin has traditionally been the antiplatelet agent most commonly used for the prevention of ischemic arterial events (primarily based on a 25% odds reduction for myocardial infarction, stroke, or vascular death compared with control observed in the Antiplatelet Trialists' Collaboration analyses[20]), in recent years additional antiplatelet agents with biochemically distinct biologic effects have become available.[14,21,22] This has created a need for the systematic investigation of the appropriate selection and indications for antiplatelet drug use. We report the findings of an expert panel convened to establish evidence-based practice guidelines for the appropriate selection of antiplatelet agents for the secondary prevention of ischemic events in patients who are at high risk for such events. In addition, a systematic overview of the recent literature addressing the use of aspirin, ticlopidine, and clopidogrel is provided. This information may be used to inform multidisciplinary teams who are developing or updating evidence-based practice guidelines and clinical pathways.

Methods

The overall approach to the development of the clinical guidelines and expert recommendations is as depicted in Figure 1.

Expert Panel

An expert multidisciplinary panel of physicians in the fields of cardiology (four), neurology (two), vascular surgery (one), vascular medicine (one), and preventive medicine (one) was convened and met over two days (November 7–8, 1997).

Systematic Overview

Panel participants were provided with an evidence-based review of the literature pertaining to the use of the three currently available antiplatelet agents—aspirin, ticlopidine, and clopidogrel (an agent which has recently received FDA approval). Other antiplatelet drugs such as specific thromboxane

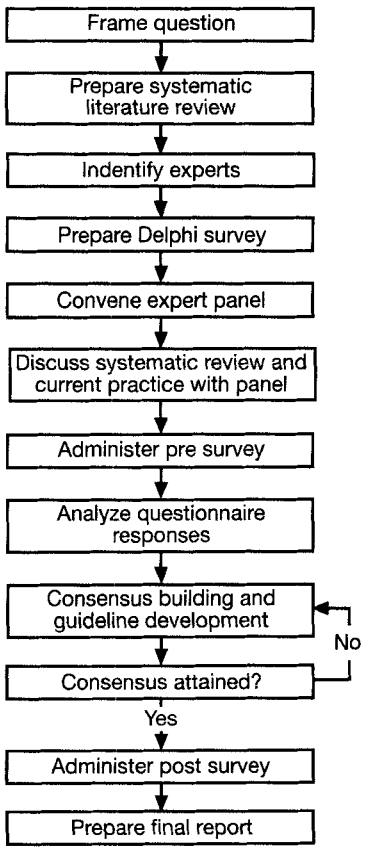

FIG. 1 Steps in guideline development.

synthase A_2 inhibitors, thromboxane receptor antagonists, combined thromboxane synthase/thromboxane receptor antagonists, and glycoprotein Ib/IIb/IIIa antagonists which remain either investigational or unavailable for long-term prophylactic use were not covered in this review. Dipyridamole was not directly included in the review since it is most commonly used in combination with other agents and is not generally considered efficacious when used as a single agent.[20]

The October 1995 supplement to *Chest*, reporting the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy, was used as a baseline source of citations and peer-reviewed information addressing the use of the antiplatelet agents aspirin and ticlopidine.[14, 21, 23, 24] In addition, to identify articles published since the *Chest* supplement, Medline, Healthstar, and Cinahl online bibliographic databases were searched for the entry months 1/95 through 10/97, and candidate articles were selected by combining search results generated with exploded MESH subject headings or keywords in the following categories: Agents (platelet aggregation inhibitors, aspirin, ticlopidine, clopidogrel), Disorders (cerebrovascular disorders or stroke, myocardial infarction, peripheral arterial diseases), and Qualifiers (Human studies, English language).

Approximately 420 new citations were retrieved with the computer search. Screening of titles and abstracts identified 85 potentially applicable primary studies (i.e., addressing one or more of the drugs of interest being used for one or more of the three disorders of interest). Review was then limited to prospective, randomized trials and meta-analyses which were then obtained and summarized, along with data from trials noted in the *Chest* supplement. Other classes of articles such as letters to the editor, commentaries, news items, and abstracts were specifically excluded. In addition, several review papers which provided updates on antiplatelet agents in general,[10, 22, 25–27] and in patients suffering from stroke[28–32] and acute myocardial infarction[33] were reviewed for potential additional citations.

Primary studies cited were assigned a "Level of Evidence" (Table I) based on the primary predefined study outcomes (not subsequent subgroup analyses) according to Cook *et al.*[34] for consistency with the schema used in the *Chest* supplement.

Data regarding patient outcomes with respect to clopidogrel were provided by review of the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE)[35] trial results as well as by additional subgroup analyses (data on file, Sanofi) of data collected during this trial.

Modified Delphi Survey

For the rapid identification of participant opinion and target areas requiring discussion to resolve variation in opinion, a modification of the Delphi survey technique[36] was used. In advance of the meeting, panelists were provided with an evidence-based review (as above) of the role of antiplatelet therapy for the primary and secondary prevention of ischemic vascular events. An anonymous survey was then administered which asked participants to rate the level of appropriateness (on a 9-point scale, with 1 being highly inappropriate and 9 being highly appropriate) for the use of aspirin, ticlopidine, or clopidogrel in a wide variety of clinical scenarios describing patients with manifestations of atherosclerotic arterial disease.[37, 38] Mean scores for the panel were then presented to the participants as a starting point for further discussion of the rel-

TABLE I Levels of evidence for literature evaluation

Level I:	Randomized trials or meta-analayses in which the lower limit of the confidence interval for the treatment effect exceeds the minimally clinically important benefit
Level II:	Randomized trials or meta-analyses in which the confidence interval for the treatment effect overlaps the minimally clinically important benefit
Level III:	Nonrandomized concurrent cohort comparisons between contemporaneous patients who did not receive antithrombotic agents
Level IV:	Nonrandomized historic cohort comparisons between current patients who received antithrombotic agents and former patients (from the same institution or from the literature) who did not
Level V:	Case series without controls

Source: Ref. 34.

ative appropriateness of indications for each of the drugs. At the conclusion of the meeting, a "postsurvey" (closely mirroring the presurvey administered at the end of Day One, but with language slightly modified to frame the clinical scenarios with reference to the potential indications that evolved during the guideline development discussions) was administered to assess whether the relative rankings and degree of agreement had changed based upon the intervening discussion.

Guideline Development

A guideline for the selection of an appropriate antiplatelet drug for the secondary prevention of ischemic events in patients with atherosclerotic arterial disease was generated after (1) discussion of the general need for, and principles of, clinical guideline development, and (2) presentations by three members of the expert panel (one for each of ischemic stroke, myocardial infarction, and peripheral arterial disease) reporting current antiplatelet usage within clinical guidelines deployed at their local institutions, as well as nationally recognized guidelines. The subsequent guidelines were formulated by (1) defining specific inclusionary and exclusionary criteria, (2) identifying the indications and relative appropriateness of drugs based on published efficacy and safety data, (3) facilitated open discussion of the literature in support of recommendations being generated, and (4) majority vote on recommendations (no recommendation was accepted with more than one opposing vote).

Cost was not included as a consideration for selecting appropriate antiplatelet agents. Formal cost–benefit analyses which consider efficacy and adverse events in the analysis would provide important information for health care organizations. During manuscript preparation, it was noted that while there are also no published data applicable to substituting or combining antiplatelet agents in the setting of recurrent ischemic events, there was a need to add a consensus recommendation to address the practical issue.

Results

Modified Delphi Survey Results

Mean pre- and postsurvey appropriateness scores for the antiplatelet drugs are displayed in Figures 2 and 3 for each of the clinical manifestations of atherosclerosis (ischemic stroke, myocardial infarction, and peripheral arterial disease) as well as each of the possible combinations. Figure 2 represents the mean scores for patients who are candidates for the use of any of the three drugs, and Figure 3 represents the mean scores for patients in whom aspirin would be contraindicated (allergic, intolerant, or contraindicated due to comorbidities such as history of gastrointestinal bleeding).

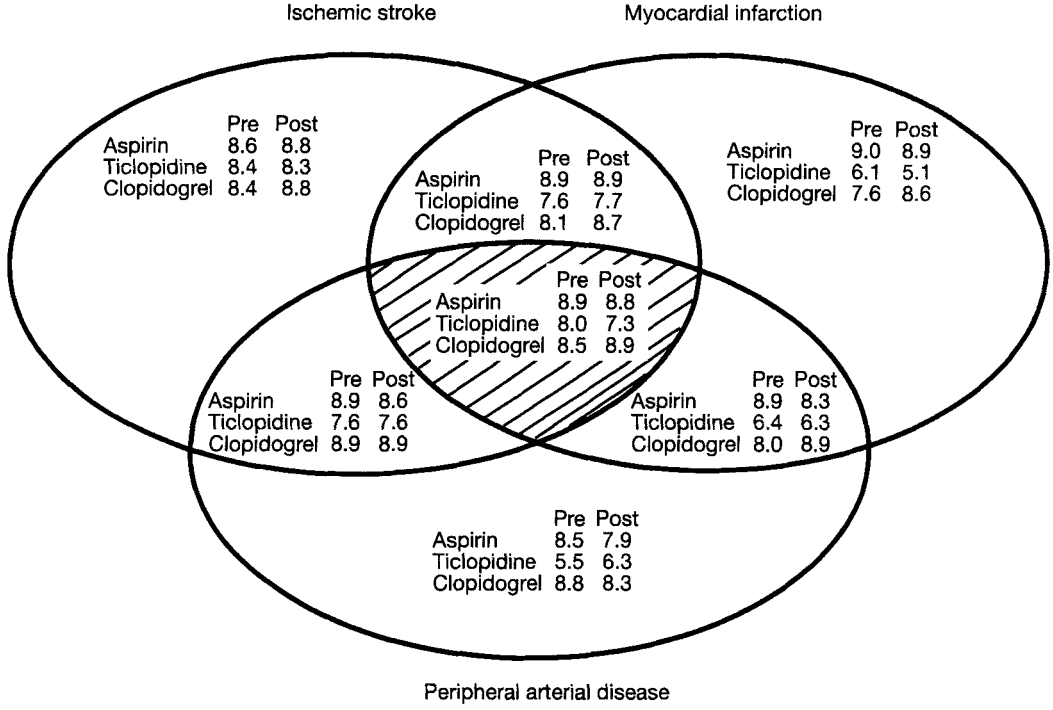

FIG. 2 Survey results for patients who are considered candidates for aspirin therapy. "Pre" indicates average of survey scores for the presurvey, "Post" indicates average of survey scores for the postsurvey. The three antiplatelet drugs were rated for appropriateness on a scale of 1–9 (1 = highly inappropriate, 9 = highly appropriate) for preventing arterial thrombosis in the setting of each of the clinical manifestations of atherosclerosis. The areas of overlap represent patients who have multiple clinical manifestations of atherosclerosis; for example, the central shaded area represents patients who have a history of nonhemorrhagic ischemic stroke, a history of myocardial infarction, and established peripheral arterial disease.

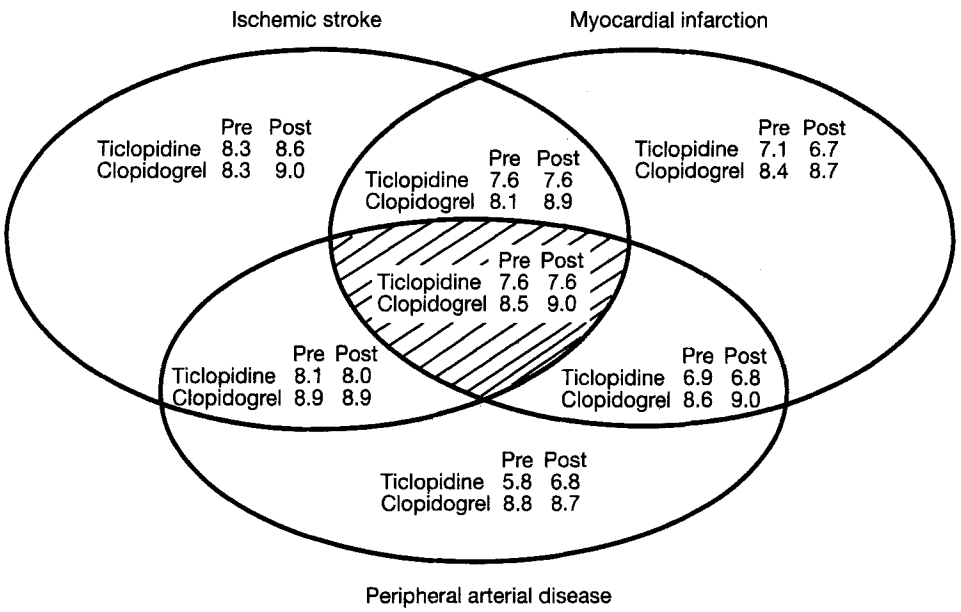

FIG. 3 Survey results for patients who are not candidates for aspirin therapy (i.e., aspirin allergic, intolerant, or otherwise contraindicated; suffered ischemic event while on aspirin therapy). "Pre" indicates average of survey scores for the presurvey, "Post" indicates average of scores for the postsurvey. The two antiplatelet drugs were rated for appropriateness on a scale of 1–9 (1 = highly inappropriate, 9 = highly appropriate) for preventing arterial thrombosis in the setting of each of the clinical manifestations of atherosclerosis. The areas of overlap represent patients who have multiple clinical manifestations of atherosclerosis; for example, the central shaded area represents patients who have a history of nonhemorrhagic ischemic stroke, a history of myocardial infarction, and established peripheral arterial disease.

Evidence-Based Guidelines

Individual guidelines were defined for patients with myocardial infarction (Fig. 4), ischemic stroke (Fig. 5), and peripheral arterial disease (Fig. 6). A summary guideline which synthesizes the recommendations (for myocardial infarction, ischemic stroke, and peripheral arterial disease) and which can be applied to any patient with identified atherosclerotic vascular disease is presented in Figure 7. Figure 8 is a consensus recommendation addressing options for the possibility of a patient who may have an ischemic event while on clopidogrel.

Overview of Evidence-Based Literature Review

Pharmacology and Clinical Considerations

Aspirin: Aspirin inhibits platelet aggregation by preventing formation of thromboxane A_2 as a result of the irreversible acetylation of platelet cyclooxygenase. While the most common dosage of aspirin studied has tended to be 325 mg,[20] thromboxane A_2 biosynthesis is inhibited within 1 h of a single oral dose of 100 mg of aspirin, whereas it takes 7–10 repeated daily doses of 30 to 50 mg to achieve the same effect.[39,40]

Table II summarizes overall findings from the Antiplatelet Trialists' Collaboration,[20,41] a large meta-analysis of more than 100,000 (> 70,000 high-risk) patients that combined the outcomes for a variety of antiplatelet drugs to demonstrate an

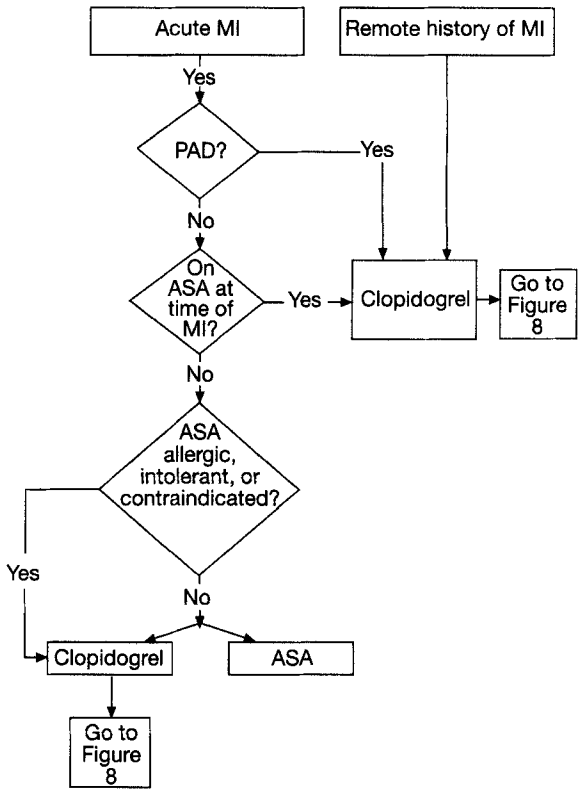

FIG. 4 Antiplatelet selection guideline for patients with history of myocardial infarction. ASA = aspirin, PAD = peripheral arterial disease, MI = myocardial infarction.

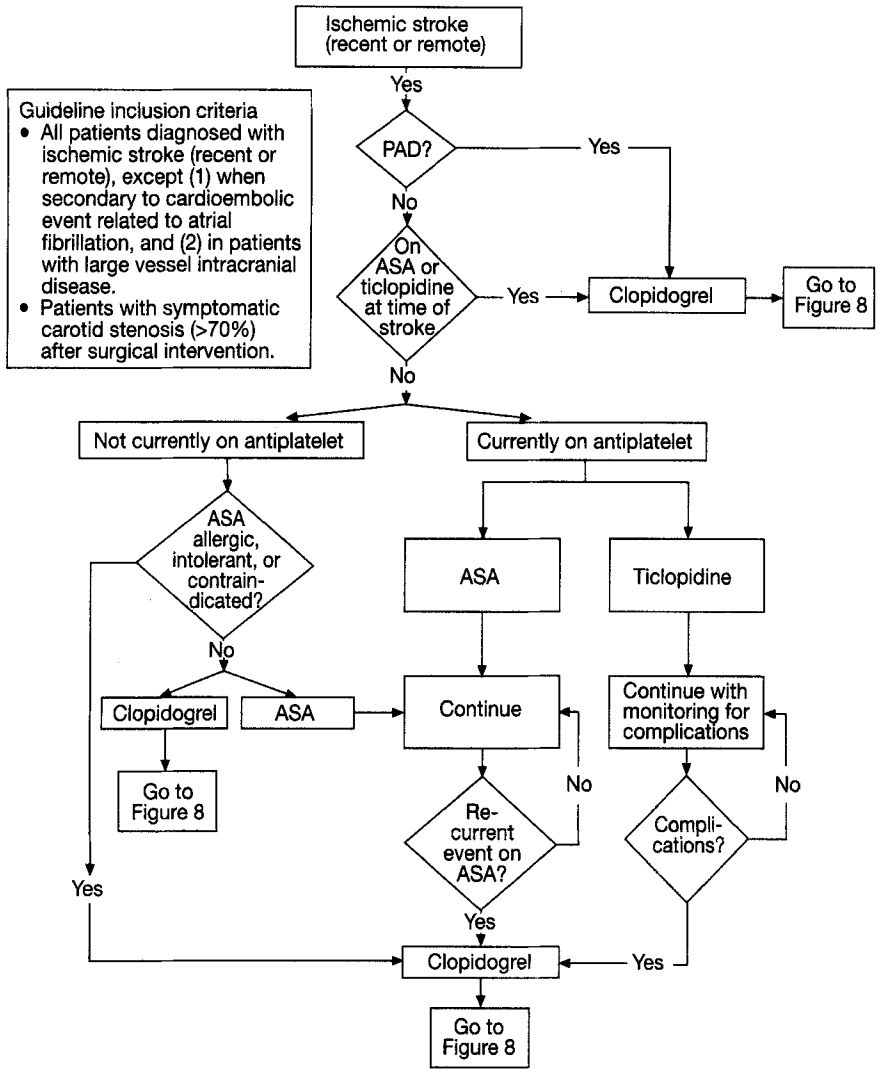

FIG. 5 Antiplatelet selection guideline for patients with a history of ischemic stroke. ASA = aspirin, PAD = peripheral arterial disease.

TABLE II Impact of antiplatelet therapy in general

Category of trial	No. of trials with data	MI, Stroke or vascular death: Antiplatelet (%)	MI, Stroke or vascular death: Adjusted controls (%)	% Odds reduction (SD)
Prior MI	11	1331/9877 (13.5)	1693/9914 (17.1)	25 (4)
Acute MI	9	992/9388 (10.6)	1348/9385 (14.4)	29 (4)
Prior stroke/ TIA	18	1076/5837 (18.4)	1301/5870 (22.2)	22 (4)
Other high risk	104	784/11,434 (6.9)	1058/11,542 (9.2)	32 (4)

Adapted from Fig. 2 of Ref. No. 20.
Abbreviations: MI = myocardial infarction, TIA = transient ischemic attack, SD = standard deviation.

overall positive impact of antiplatelet agents for the prevention of the combined outcome of myocardial infarction, stroke, or vascular death (27% odds reduction for high-risk patients). When aspirin, which was the focus of many of the studies, was analyzed separately, the odds reduction was 25% over control.

The main side effects of aspirin therapy, beyond increased risk of bleeding, are gastrointestinal, including gastric mucosal damage and ulceration. It has been estimated that patients treated with aspirin at doses of 75–325 mg/day have an approximately 1.5 to 2.0 times greater incidence of gastrointestinal bleeding than those treated with placebo.[42,43] As with all the drugs considered, there are treatment failures (recurrent ischemic events while on therapy) as well as the possibility of allergy and intolerance. Partial resistance to the effects of aspirin therapy (as measured by platelet aggregation studies) has been demonstrated in ~ 33% of an ischemic stroke patient population, with 8.2% of these patients ultimately developing complete resistance to even high doses (1300 mg/day) of aspirin.[44]

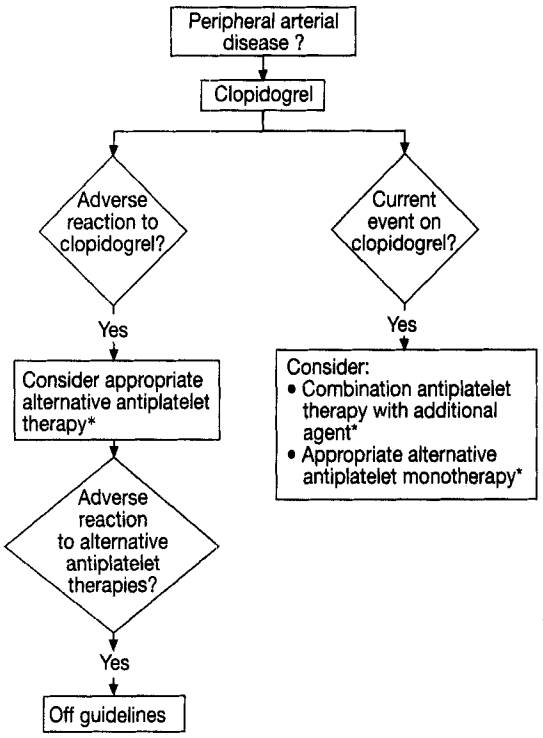

FIG. 6 Antiplatelet selection guideline for patients with peripheral arterial disease. * = If agent(s) being considered are not otherwise contraindicated.

Ticlopidine: Ticlopidine is a thienopyridine with antiplatelet activity related to specific platelet-ADP-receptor blockade and subsequent inhibition of ADP-dependent platelet aggregation[45–48] which, in the Antiplatelet Trialists' Collaboration,[41] has been associated with an overall 33% odds reduction for ischemic events. Ticlopidine is inactive in vitro but undergoes metabolic activation in the liver and exerts its maximal effect on platelet aggregation at 8 to 11 days.

Gastrointestinal symptoms are the most commonly reported side effects with the use of ticlopidine, with diarrhea occurring in approximately 12.5% of patients. Skin rashes follow as the next most common side effect and occur in approximately 5.1% of patients. Monitoring of blood counts is recommended for the first 12 weeks of therapy with ticlopidine because of concerns regarding dose-independent bone marrow depression.[49] Ticlopidine is associated with neutropenia (neutrophils < 1200/mm^3) or severe neutropenia (neutrophils < 450/mm^3) in approximately 2.4 and 0.8% of treated patients, respectively. Neither aspirin nor clopidogrel carry such cautions or recommendations for routine monitoring of blood counts, as the rates of neutropenia and severe neutropenia are 0.17 and 0.04% for aspirin and 0.1 and 0.05% for clopidogrel, respectively.[35]

Clopidogrel: Clopidogrel is a comparatively new thienopyridine agent with antiplatelet activity.[10, 22] It is chemically related to ticlopidine and, like ticlopidine, its antiplatelet activity is at a site distinctly different from that of aspirin—related to specific, irreversible, platelet-ADP-receptor blockade and subsequent inhibition of ADP-dependent platelet aggregation.[45–48] Clopidogrel, like ticlopidine, is inactive in vitro but undergoes metabolic activation in the liver; clopidogrel appears to be approximately six times more potent than ticlopidine in inhibiting human platelet aggregation induced by ADP in laboratory testing.[22] The onset of action for clopidogrel is more rapid than ticlopidine. Inhibition of platelet aggregation can be seen within 2 h of oral administration, and the maximal effect on platelet aggregation occurs at between 4 and 7 days of the usual 75 mg single daily dose (compared with ticlopidine which is dosed twice daily). Clinically, the bleeding time is doubled after approximately 7 days of repeated oral administration.[50]

Side effects associated with clopidogrel from the CAPRIE trial[35] were diarrhea (4.5 vs. 3.4% for aspirin; $p < 0.05$) and skin rash (6.0 vs. 4.6% for aspirin; $p < 0.05$). Compared with aspirin, clopidogrel was associated with significantly fewer instances of gastrointestinal hemorrhage requiring discontinuation of therapy (0.52 vs. 0.93%; $p < 0.05$).

Selected Antiplatelet Trials

The majority of studies evaluating the impact of antiplatelet drugs have focused on assessing a combined outcome, which usually encompasses the components of stroke, myocardial infarction, and cardiovascular-related death. While statistically significant differences have been shown for the combined outcomes in many studies, it has been more difficult to achieve a statistically significant assessment of the impact of each drug for each of the outcomes because of the vast numbers of patients who would need to be studied to power the trials to do so. As a result, it is difficult to separate the studies completely along well-defined, disease-specific (e.g., stroke), boundaries. Primary outcomes from selected major studies presented in the white paper provided to Expert Panel members are summarized in Tables II–V.

Subsequent randomized controlled trials such as the Second International Study of Infarct Survival (ISIS-2)[51] (n = 17,187) conclusively demonstrated the benefit of aspirin therapy in reducing mortality, reinfarction, and stroke in patients with acute myocardial infarction. Patients who received aspirin (162.5 mg daily for 30 days) had a 23% reduction in total vascular mortality, which improved to a 42% mortality reduction when aspirin was combined with streptokinase therapy (compared with 25% for streptokinase alone) ($p < 0.00001$ for all interventions).

The International Stroke Trial (IST)[52] was a randomized controlled trial (n = 19,435) of aspirin (300 mg daily), subcutaneous heparin, both, or neither in patients presenting within 48 h of a suspected acute ischemic stroke. Primary outcomes were mortality within 14 days and death or dependency at 6 months. Overall mortality at 14 days was 9.0% in both the heparin- and aspirin-treated patients (compared with 9.3 and 9.4% in the respective placebo groups; no significant difference). Recurrent (within 14 days) ischemic strokes occurred

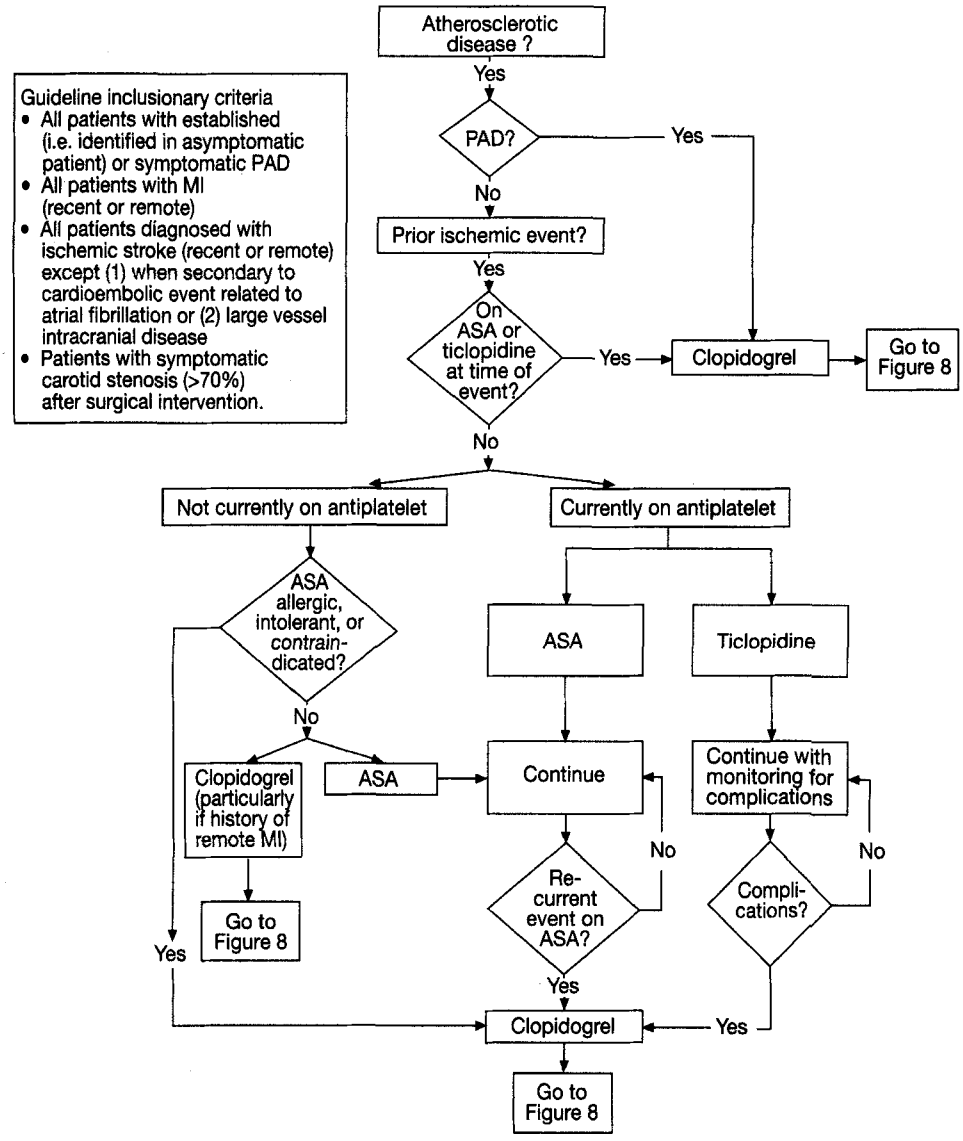

FIG. 7 Overall antiplatelet drug selection algorithm for secondary prevention of ischemic events in any patient with clinical manifestations of atherosclerosis (e.g., myocardial infarction, ischemic stroke, peripheral arterial disease). ASA = aspirin, PAD = peripheral arterial disease, MI = myocardial infarction.

in 2.8% of aspirin-treated patients versus 3.9% of placebo-treated patients ($p < 0.001$) but, while similar findings were noted for heparin-treated patients, heparin use was associated with a statistically significant increase in subsequent hemorrhagic strokes. At 6 months, there was no significant difference between heparin- and placebo-treated groups with respect to "death or dependence," but there was a trend ($p = 0.07$) favoring aspirin which became statistically significant ($p = 0.03$) after "adjustment for baseline prognosis."

The recently published Chinese Acute Stroke Trial (CAST)[53] was a randomized placebo-controlled trial (n = 21,106) of early aspirin use in the setting of acute ischemic stroke. Aspirin (160 mg daily) was initiated within 48 h of stroke onset. In this study, mortality within the first 4 weeks after stroke was 3.3% in aspirin-treated compared with 3.9% in placebo treated patients ($p = 0.04$; odds reduction of 14%). In addition, when the combined endpoint of death or recurrent nonfatal stroke was examined, there was a 12% odds reduction with aspirin treatment (5.3% with aspirin vs. 5.9% with placebo; $p = 0.03$).

The Canadian American Ticlopidine Study (CATS)[54] was a randomized, double-blind, placebo-controlled trial of ticlopidine (250 mg twice daily) for preventing the combined outcome of recurrent stroke, myocardial infarction, or vascular death in patients (n = 1,072) who had recently suffered a thromboembolic stroke. Statistically significant relative risk reductions were noted for the combined outcome as well as for stroke and stroke-related death (30.2 and 24.1%, respectively). A statistically significant relative risk reduction (23.3%; $p = 0.02$) in favor of ticlopidine for the combined out-

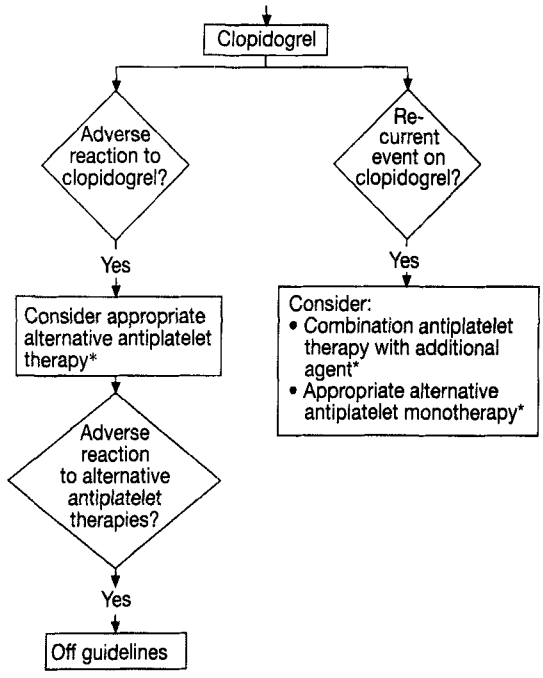

FIG. 8 Antiplatelet selection considerations for patients who have an adverse reaction or recurrent event while on clopidogrel. * = If agent(s) being considered are not otherwise contraindicated.

come was maintained on an intention-to-treat analysis. Severe side effects occurred ~ 3 times more often in the ticlopidine group than in the placebo group (8.2 vs. 2.8%; $p < 0.001$).

The Ticlopidine Aspirin Stroke Study (TASS) (n = 3,069) was a randomized trial comparing ticlopidine (250 mg twice daily) with aspirin (650 mg twice daily) for the prevention of stroke in high-risk patients (transient ischemic attack, amaurosis fugax, reversible ischemic neurologic deficit, or minor stroke within the 3 months prior to study entry).[55] At 3 years, nonfatal stroke or death had occurred in 19% of aspirin- and 17% of ticlopidine-treated patients [12% relative risk reduction in favor of ticlopidine; 95% confidence interval (CI) 2–26%], whereas the combined risk of fatal and nonfatal stroke at 3 years was 13% for aspirin and 10% for ticlopidine (21% relative risk reduction; 95% CI 4–38%). Side effects (primarily gastrointestinal) occurred more frequently in the ticlopidine- than in the aspirin-treated patients. In particular, severe neutropenia developed in 13 of 1,529 (0.9%) ticlopidine-treated patients but in none of the aspirin-treated patients. The authors concluded that ticlopidine may be more effective than aspirin in preventing recurrent stroke, but that it was associated with an increased incidence of adverse effects.

The Swedish Ticlopidine Multicenter Study (STIMS)[56] was a multicenter, randomized, double-blind, placebo-controlled trial examining the effect of ticlopidine (250 mg twice daily) for the prevention of the combined endpoints of fatal or nonfatal myocardial infarction, stroke, and transient ischemic attack in patients (n = 687) with intermittent claudication. A statistically significant benefit in favor of ticlopidine was noted for the combined endpoints (22.4 vs. 13.8%; relative risk reduction = 38.4%; $p = 0.017$); however, statistical significance was not maintained when an intention-to-treat analysis was performed (29.0 vs. 25.7%; $p = 0.24$). Overall mortality was lower in the ticlopidine group (18.5 vs. 26.1%; relative risk reduction 29.1%; $p = 0.015$), although there were more side effects (particularly gastrointestinal/diarrhea) associated with ticlopidine use.

The CAPRIE trial[35] was a large phase III randomized, blinded, multicenter, multinational, clinical trial (n = 19,185) conducted to evaluate the same types of outcomes that have been extensively evaluated for aspirin and (less so) for ticlopidine. The efficacy for reducing the combined outcome of myocardial infarction, ischemic stroke, or vascular death was examined in patients assigned to either clopidogrel (75 mg/day) or the comparison therapy which itself is efficacious, aspirin (325 mg/day), for up to 3 years. Clopidogrel was found to have a statistically significant benefit compared with aspirin in terms of annual risk (5.32 vs. 5.83%; $p = 0.043$) and overall relative risk reduction (8.7%; 95% CI 0.3–16.5).[35] In addition, there was a 23.8% relative risk reduction ($p = 0.0028$) for patients qualifying for the study due to the presence of peripheral arterial disease and a nonsignificant 7.3% relative risk reduction for patients with ischemic stroke ($p = 0.26$). In patients enrolled with myocardial infarction there was a nonstatistically significant trend favoring aspirin (RRR –3.7%, 95% CI –22.1–12), although subsequent subgroup analyses of patients with myocardial infarction (irrespective of selection group) favored clopidogrel: a 7.6% relative risk reduction for the primary outcome cluster in patients with any history of myocardial infarction (not statistically significant) and a significant 19.2% ($p = 0.008$) overall relative risk reduction when the outcome of myocardial infarction was considered alone.[57]

As previously noted, clopidogrel compared favorably with aspirin with regard to bleeding complications and gastrointestinal upset, but was not associated with the increased potential for neutropenia seen with ticlopidine.

Additional selected trials addressing the use of specific antiplatelet agents for treating patients with stroke are summarized in Table III. Similarly, Tables IV and V summarize data for selected trials addressing patients with myocardial infarction and peripheral arterial disease, respectively.

Primary Prevention

While this review is focused on secondary prevention, it is also important to note that the use of antiplatelet drugs for primary prevention is considerably less well defined and, with the exception of preventing coronary thrombosis, this may mostly be based upon extrapolation of the data from studies of secondary prevention. The definition of patients at risk for ischemic events is evolving from strictly primary versus secondary prevention and also includes subclinical markers of disease such as diminished ankle/brachial pressure index,[58] although it is unclear what the role is for antiplatelet drugs in treating patients in relation to these markers.

Primary prevention of stroke with aspirin has not yet been shown to be as effective as secondary prevention. The Asymp-

TABLE III Selected outcomes of selected studies of antiplatelet drugs for patients with stroke

Trial / year[a] (Ref. No.)	Design[b]	N[c]	Antiplatelet / patient population	Comparison(s)	Selected outcome(s)	Result(s)
CAPRIE 1997 (35)	RCT (I)	19,185	Clopidogrel 75 mg q.d. Peripheral arterial disease, recent stroke, recent MI	ASA 325 mg q.d.	Ischemic stroke, MI, or vascular death	All patients: RRR 8.7% (p = 0.043) PAD patients: RRR 23.8% (p = 0.0028)
					Stroke	RRR 7.3% (p = 0.26)
					GIH	0.52% vs. 0.93% (p < 0.05)
CAST 1997 (53)	RCT (I)	21,106	ASA 160 mg q.d. within 48 h	Placebo	Mortality	3.3 vs. 3.9%; OR 14%; p = 0.004
					Death or non-fatal stroke	5.3 vs. 5.9%; OR 12%; p = 0.03
IST 1997 (52)	RCT (II)	19,435	ASA 300 mg q.d. within 48 h	Subcut. heparin	Mortality at 14 days	9.0 vs. 9.4%; NSD
				Subcut. heparin +ASA	Recurrent stroke	2.8 vs. 3.9%; p < 0.001
				Neither	Death or dependence at 6 mo	NSD; p = 0.07
ESPS-2 1996 (74)	RCT (I)	6,062	ASA 25 mg b.i.d., dipyridamole 200 mg b.i.d., ASA + dipyridamole TIA or completed ischemic stroke within 3 mo	Placebo	Mortality	NSD
					Recurrent stroke	ASA RRR 18% (p = 0.013) Dipyridamole RRR 16% (p = 0.039) ASA+dipyridamole RRR 37% (p < 0.001)
MAST-I 1995 (75)	RCT (II)	622	ASA 300 mg within 6 h	Untreated	Mortality	OR 2.7 (1.7–4.3) streptokinase OR 0.9 (0.6–1.3) ASA+ streptokinase
				Streptokinase		
				ASA+streptokinase		
SALT 1991 (76)	RCT (I)	1,360	ASA 75 mg q.d. 1–4 mo after cerebrovascular event		Mortality	18% RRR
					Stroke	18% RRR
					Bleeding event	7.2% vs. 3.2%; p = 0.001
UK-TIA 1991 (77)	RCT (II)	2,435	ASA 300 mg q.d., ASA 600 mg b.i.d	Placebo	Mortality	15% RRR (−3–29%)
					UGIB	3.3x↑ w/ 300 mg; 6.4x↑ w/ 1200 mg
CATS 1989 (54)	RCT (I)	1,072	Ticlopidine 250 mg b.i.d. Recent thromboembolic stroke	Placebo	Stroke, MI, vascular death	RRR 30.2%
					As above, but intent-to-treat	RRR 23.3%; p = 0.02
					Stroke, stroke-related death	RRR 24.1%
					"Severe" side effects	8.2 vs. 2.8%
TASS 1989 (55)	RCT (II)	3,069	Ticlopidine 250 mg b.i.d. TIA, amaurosis fugax, RIND, minor stroke, within 3 mo	ASA 650 mg b.i.d.	Nonfatal stroke, death	17 vs. 19%; RRR 12%; −2–26%
					Fatal stroke, non-fatal stroke	10 vs. 13%; RRR 21%; 4–38%
					Severe neutropenia	13/1529 vs. 0/1540

[a] Year of publication.
[b] Level of evidence in parentheses.
[c] Total number of patients enrolled in trial.
Abbreviations: ASA = aspirin, b.i.d. = twice daily, GIH = gastrointestinal hemorrhage, MI = myocardial infarction, mo = months, q.d. = daily, NSD = no statistically significant difference, RCT = randomized controlled trial, RRR = relative risk reduction, subcut = subcutaneous, TIA = transient ischemic attack, UGIB = upper gastrointestinal bleeding, RIND = reversible ischemic neurologic deficit.

tomatic Cervical Bruit Study Group noted a lack of effect for aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing[59] (Level II), and the Asymptomatic Carotid Atherosclerosis Study (ACAS)[60–62] (n = 1,662) has continued to provide evidence that surgical intervention—even in the setting of asymptomatic carotid narrowing—may be more effective than medical therapy. The ACAS estimated the 5-year cumulative rate of stroke ipsilateral to the treated carotid artery, or 30-day perioperative stroke or death, as 11.0% for patients receiving aspirin therapy (325 mg daily) alone versus 5.1% for combined aspirin and surgical therapy (p = 0.004).

TABLE IV Outcomes of selected studies of antiplatelet drugs for patients with cardiac disease

Trial / year[a] (Ref. No.)	Design[b]	N[c]	Antiplatelet / patient population	Comparison(s)	Selected outcome(s)	Result(s)
CAPRIE 1997 (35)	RCT (I)	19,185	Clopidogrel 75 mg q.d. Patients with history of ischemic stroke, MI, or PAD	ASA 325 mg q.d.	Ischemic stroke, MI, or vascular death MI (all patients) GIH	All patients: RRR 8.7% (p = 0.043) PAD patients: RRR 23.8% (p = 0.0028) RRR 19.2% (p = 0.008) 0.52% vs. 0.93% (p < 0.05)
Ishikawa *et al.*, 1997 (67)	RCT (I)	1,083	ASA 50 mg + ticlopidine 250 mg b.i.d.	ASA 50 mg + dypyridamole 50 mg t.i.d.	Nonfatal or fatal MI, sudden death, or death due to CHF	3.1 vs. 7.3%; OR 0.4; 0.23–0.71
Juul-Moller *et al.*, 1992 (78)	RCT (I)	2,035	ASA, 75 mg q.d. Angina only	Placebo	CVD, MI CVA	RRR 33.6 (12–55) RRR 25.1 (§–67)
Balsano *et al.*, 1990 (68)	RCT (I)	652	Ticlopidine 250 mg b.i.d. Unstable angina	Conventional therapy	Vascular death, nonfatal MI	7.3% v 13.6%; RRR 46.3%; p = 0.009
ISIS-2 1988 (51)	RCT (I)	17,187	ASA 162.5 mg q.d. × 30 days Patients with acute MI	Streptokinase Streptokinase+ aspirin	Vascular death	RRR 23% (ASA alone, p < 0.0001) RRR 25% (streptokinase alone, p < 0.00001) RRR 42% (streptokinase + ASA, p < 0.00001)
Klimt *et al.*, 1986 (79)	RCT (I)	3,128	ASA, 330 mg, Persantine® 75 mg q.d. 1–4 mo after MI	Placebo	CVD, MI	RRR 23.8 (6–42)
AMISRG 1980 (80)	RCT (II)	4,524	ASA, 500 mg b.i.d. 25 mo after MI	Placebo	CVD, MI	RRR 4.7 (§–19)
CDPRG 1980 (81)	RCT (II)	1,529	ASA, 324 mg t.i.d. >5 years after MI	Placebo	CVD, MI	RRR 21.5 (§–50)
Breddin *et al.*, 1980 (82)	RCT (II)	626	ASA, 500 mg t.i.d. 30–42 days after MI	Placebo	CVD, MI	RRR 36.8 (§–76)

[a] Year of publication.

[b] Level of evidence in parentheses.

[c] Total number of patients enrolled in trial.

Abbreviations: PAD = peripheral artery disease, CHF = congestive heart failure, OR = odds ratio, CVD = cardiovascular death, t.i.d. = three times daily, CVA = cardiovascular accident, § = negative number. Other abbreviations as in Table III.

A randomized 6-year trial of prophylactic daily aspirin (500 mg soluble or 300 mg enteric coated) in British male doctors[63] (n = 5,139) failed to demonstrate a statistically significant decrease in mortality or incidence of nonfatal vascular events (myocardial infarction or death) in healthy subjects.

Preliminary review of data from the Worcester Heart Attack Study (n = 2,114) has indicated that aspirin use is associated with an "increased likelihood that an infarct will be of the small, non-Q-wave variety."[64] Aspirin users suffering acute myocardial infarction were more likely to have had non-Q-wave myocardial infarctions than non-aspirin users (65 vs. 49%; odds ratio 1.91; p < 0.001) and, similarly, aspirin users were more likely to sustain a "small myocardial infarction" (based on peak creatinine kinase values) than nonusers (30 vs. 22%; odds ratio 1.57; p < 0.001).

A prospective study of aspirin use (at least once per week) and primary prevention of cardiovascular disease in women (Nurses Study,[65] n = 87,678) examined the association between aspirin use and first-ever myocardial infarction, stroke, or cardiovascular death. Women who regularly took aspirin were found to have a cardiovascular risk factor-adjusted relative risk for first myocardial infarction of 0.75 (95% CI 0.58–0.99; p = 0.04). Risk differences for stroke and cardiovascular death were not statistically significant. The aspirin

TABLE V Outcomes of selected studies of antiplatelet drugs for patients with peripheral arterial disease

Trial / year[a] (Ref. No.)	Design[b]	N[c]	Antiplatelet / patient population	Comparison(s)	Selected outcome(s)	Result(s)
CAPRIE 1997 (35)	RCT (I)	19,185	Clopidogrel 75 mg q.d. Patients with history of stroke, history of MI, or PAD	ASA 325 mg q.d.	Ischemic stroke, MI, or vascular death	All patients: RRR 8.7% (p = 0.043) PAD patients: RRR 23.8% (p = 0.0028)
					GIH	0.52% vs. 0.93% (p < 0.05)
Ciocon *et al.* 1997 (83)	RCT (II)	90	ASA 325 mg q.d.	Pentoxyfylline 400 mg t.i.d.	Pain, activity, ankle/ brachial BP ratios at 6 weeks	NSD, NSD, NSD
					Walking distance to absolute claudication	2 vs. 1.2 miles; p < 0.05
Minar *et al.* 1995 (84)	RCT (II)	216	ASA 1000 mg q.d. × 24 mo Patients status-post femoral-popliteal percutaneous transluminal angioplasty	ASA 100 mg q.d. × 24 mo	Vessel patency	NSD
					Discontinuance of therapy	30 vs. 11; p < 0.01
STIMS 1990 (56)	RCT (I)	687	Ticlopidine 250 mg b.i.d. Patients with intermittent claudication	Placebo	Fatal or nonfatal MI, stroke, TIA	22.4 vs. 13.8%; RRR 38.4%; p = 0.017 (ITT 29.0 vs. 25.7%; p = 0.24)
					Mortality	18.5 vs. 26.1%; RRR 29.1%; p = 0.015
Balsano *et al.* 1989 (85)	RCT (II)	151	Ticlopidine 250 mg b.i.d. × 21mo Patients with intermittent claudication	Placebo	Exercise tolerance at 3 mo	SD
					Ankle-arm BP ratios at 3 mo	SD
Arcan *et al.* 1988 (86)	RCT (I)	169	Ticlopidine 250 mg b.i.d. × 21 mo Patients with intermittent claudication	Placebo	Pain-free walking distance	p = 0.03
					Total walking distance > 50% of baseline	39 vs. 29; p = 0.04

[a] Year of publication.

[b] Level of evidence in parentheses.

[c] Total number of patients enrolled in trial.

Abbreviations: BP = blood pressure; ITT = intention to treat analysis, PAD = peripheral artery disease. Other abbreviations as in Table III.

component of the Physician's Health Study[66] demonstrated similar but more convincing findings for men (n = 22,071), the relative risk for first myocardial infarction in this study being 0.56 (95% CI 0.45–0.70; p < 0.00001).

No studies have directly compared the use of ticlopidine with aspirin in the treatment of acute myocardial infarction, although two randomized controlled trials[67,68] have made use of ticlopidine for treating patients at increased risk for myocardial infarction. In both studies, a beneficial effect was noted but caution should be exercised in extrapolating comparisons to aspirin data.

The acute coronary stent patency rate is significantly improved with the combination of ticlopidine (250 mg twice daily) and aspirin (100 mg daily) antiplatelet therapy (p < 0.001), and this combination has been shown to be more effective than aspirin alone (0.8 vs. 5.4% reocclusion; p < 0.001).[69] In one randomized control trial, hemorrhagic complications were eliminated and there was an 87% relative risk reduction for peripheral arterial events within 30 days of stenting in patients receiving combined ticlopidine-aspirin antiplatelet therapy compared with the customary anticoagulant therapy.[70]

While antiplatelet therapy clearly has an important role in the treatment of patients with manifestations of atherosclerotic arterial disease, it should be noted that there are multiple other risk factors which are important to address as part of a comprehensive coordinated program of care. These include the use of tobacco, hypercholesterolemia, hypertension, and diabetes.[71–73]

Summary of Expert Panel Conclusions and Recommendations

1. Stroke, peripheral arterial disease, and myocardial infarction are clinical manifestations of a single, usually generalized, disease process (atherosclerosis).

2. Antiplatelet therapy is recommended to prevent arterial thrombosis and ischemic vascular events in patients with established atherosclerosis regardless of disease origin.

3. All patients with a history of myocardial infarction should be on antiplatelet agents. In patients with an acute myocardial infarction, aspirin or clopidogrel could be used; however, treatment with clopidogrel should be the initial consideration in patients with a history of remote myocardial infarction.

4. Antiplatelet therapy has a role in the treatment of patients with ischemic stroke, except in the case of cardioembolic disease related to atrial fibrillation (when anticoagulant therapy is preferable) or symptomatic carotid stenosis > 70% (when surgical intervention followed by antiplatelet therapy should be considered[24]).

5. All patients with symptomatic and/or established peripheral arterial disease should be on antiplatelet agents, with clopidogrel the preferred agent.

6. Antiplatelet therapy for secondary prevention in patients with atherosclerosis should be considered as part of a comprehensive program of care which should also address smoking cessation, cholesterol reduction, blood pressure control, exercise, and blood sugar control (for patients with diabetes).

7. Clopidogrel may be used in patients who are aspirin allergic, aspirin intolerant, have had a recurrent ischemic event while on aspirin, demonstrate aspirin resistance, or in whom aspirin is otherwise contraindicated. Aspirin would be the preferred agent in patients with an adverse event or intolerance to clopidogrel.

8. The role for antiplatelet therapy in primary prevention is not clearly defined—recommendations would currently require extrapolation from data for secondary prevention.

9. Further studies will be required to define the role, if any, for combination antiplatelet therapy.

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