

Oral Antiplatelet Therapy in Cerebrovascular Disease, Coronary Artery Disease, and Peripheral Arterial Disease

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ATHEROTHROMBOSIS REFERS TO the formation of thrombus superimposed on preexisting atherosclerosis.¹ This common pathophysiologic process results in morbid or fatal clinical ischemic events affecting the cerebral, coronary, or peripheral arterial circulation. Because the platelet is a pivotal mediator in the initiation and propagation of thrombus formation, antiplatelet drugs have emerged as key agents for prevention of recurrent ischemic events. However, there is controversy regarding choice of oral antiplatelet therapy in patients with vascular diseases (ie, ischemic stroke, coronary artery disease [CAD], and peripheral arterial disease [PAD]). While it has been established that aspirin prevents recurrent atherothrombotic events across a wide range of high-risk patients (relative risk reduction of approximately 25%),² it is less clear if other antiplatelet agents, such as clopidogrel or dipyridamole, alone or added to aspirin, are more effective.

This uncertainty is reflected in clinical practice: neurologists prefer to use aspirin combined with dipyridamole for patients with transient ischemic attacks (TIAs) or ischemic strokes³; car-

Context Atherothrombosis is a pathophysiologic process that results in clinical ischemic events affecting the cerebral, coronary, and peripheral arterial circulation. Antiplatelet agents, used alone or in combination, are effective in preventing recurrent vascular events among individuals with established vascular disease.

Objective To summarize the current state of evidence regarding oral antiplatelet treatment in patients with cerebrovascular disease, coronary artery disease (CAD), and peripheral arterial disease.

Evidence Acquisition Using the key terms *acute coronary syndrome, atherothrombosis, ischemic stroke, myocardial infarction, MI, peripheral arterial disease, TIA, transient ischemic attack, unstable angina, aspirin, ticlopidine, dipyridamole, and clopidogrel*, we searched the MEDLINE database as well as the trial register of the Cochrane Groups to identify studies published from 1960 to August 2004. We manually searched journals and abstract booklets; scrutinized reference lists of trials and review articles; and reviewed meta-analyses, scientific statements, and guidelines from official societies.

Evidence Synthesis Appropriate oral first-line antiplatelet therapy is aspirin for individuals with ST-segment elevation myocardial infarction; aspirin or clopidogrel for those with TIA or stroke, chronic stable angina, or peripheral arterial disease; and aspirin combined with clopidogrel for those with non-ST-segment elevation acute coronary syndrome. Aspirin combined with dipyridamole is a possible alternative for patients who experience a first episode of TIA or stroke in the absence of clinically apparent CAD. Although ticlopidine has been shown to be of benefit in various vascular conditions, its adverse-effect profile has limited its use.

Conclusions Aspirin, ticlopidine, clopidogrel, aspirin combined with clopidogrel, and aspirin combined with dipyridamole are effective in preventing recurrent vascular events among various subgroups of patients with vascular disease. Current clinical trial evidence favors the use of aspirin or clopidogrel as first-line agents for the majority of patients with vascular disease. Clinical trials evaluating combination antiplatelet therapies will direct future practice.

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diologists use aspirin, clopidogrel, or their combination for patients with CAD; and there are few data regarding optimal antiplatelet treatment choices

in patients with PAD. This heterogeneity in clinical practice suggests that clinicians believe that each vascular condition is different,⁴ despite evi-

See also pp 1875 and 1885.

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Table 1. Proportional Effects of Antiplatelet Therapy on Vascular Events Compared With Controls, Subdivided by Disease Categories*

Disease Category	No. of Trials	Antiplatelet Agents	Vascular Events, No. (%)†		Odds Reduction, % (95% CI)	P Value
			Antiplatelet	Control‡		
TIA/stroke	21	Aspirin, ticlopidine, dipyridamole, aspirin + dipyridamole	2045/11493 (17.8)	2464/11527 (21.4)	22 (15.2 to 27.5)	<.001
CAD§	46	Aspirin, ticlopidine, dipyridamole, aspirin + dipyridamole	2695/23587 (11.4)	3622/23672 (15.3)	29 (25.1 to 32.9)	<.001
PAD	42	Aspirin, ticlopidine, dipyridamole, aspirin + dipyridamole, picotamide	280/4844 (5.8)	347/4862 (7.1)	23 (7.9 to 35.5)	<.004

Abbreviations: CAD, coronary artery disease; CI, confidence interval; PAD, peripheral arterial disease; TIA, transient ischemic attack.

*Modified from the results of Antithrombotic Trialists' Collaboration.²

†Include ischemic strokes, MI, vascular death.

‡Derived by Antithrombotic Trialists' Collaboration.²

§Includes acute myocardial infarction (N=19302; odds reduction, 30% [10.4% vs 14.2%, $P<.001$]), previous myocardial infarction (n=20006; odds reduction, 25% [13.5% vs 17.0%, $P<.001$]), unstable angina (n=5031; odds reduction, 46% [8.0% vs 13.3%, $P<.001$]), and stable angina/CAD (n=2920; odds reduction, 33% [9.9% vs 14.1%, $P<.001$]).

dence from epidemiologic studies and findings at necropsy that atherothrombosis and atherosclerosis are systemic diseases.⁵⁻⁷ To address this apparent paradox between clinical practice and the general understanding of atherothrombosis, clinical trials have been initiated to compare various combinations of antiplatelet agents (including aspirin with clopidogrel or aspirin with dipyridamole) vs each other or vs monotherapy (aspirin or clopidogrel) in a wide variety of patients.

The purpose of this critical review is to summarize the current state of evidence regarding antiplatelet treatment in patients with cerebrovascular disease, CAD, and PAD, and to provide reasonable recommendations for clinical practice at this time.

METHODS

We sought to identify all studies that (1) were published between 1960 and August 2004; (2) were randomized; (3) recruited patients with established vascular disease (ie, TIA, ischemic stroke, CAD, and PAD); (4) compared an antiplatelet regimen (defined as a drug whose primary effect is to inhibit platelet activation, aggregation, or both) with placebo or one antiplatelet regimen with another; and (5) assessed treatment for at least 10 days. To do this, combinations of key words related to antiplatelet agents (eg, *aspirin, ticlopidine, dipyridamole, clopidogrel*), and vascular disease (eg, *acute coronary syndrome, atherothrombosis, ischemic stroke, myocardial infarction MI, peripheral arterial disease, transient ischemic attack TIA, unstable angina*) were used to search the

MEDLINE database and trial registers of the Cochrane Groups. Journals and abstract booklets were manually searched, and reference lists of trials and review articles were scrutinized to ensure that no important studies were missed. Meta-analyses and scientific statements or guidelines from official societies (eg, the American College of Cardiology) were also reviewed. Oral glycoprotein IIb/IIIa antagonists were not included in our literature search because clinical trials in patients with CAD have reported increased mortality.⁸⁻¹⁰ In addition to reviewing published randomized controlled trials identified in our literature search, we also critically examined a diverse array of studies including prospective cohort studies, mechanistic studies, meta-analyses, systematic overviews, and scientific statements from official societies. Data extraction was performed by one of the authors (H.T.).

RESULTS

We identified 111 trials, among which 22 enrolled patients with TIA or stroke (n=30619), 47 enrolled patients with CAD (n=59821), and 42 enrolled patients with PAD (n=9214).

TIA or Stroke

Aspirin. Numerous trials have examined the efficacy of antiplatelet drugs, primarily aspirin for prevention of vascular events in patients with a prior TIA or stroke.¹¹⁻¹⁶ Although many were small and inconclusive, the Antiplatelet Trialists' Collaboration (ATC) individual patient data meta-analysis reported that among more than 23000 patients (from 21 randomized controlled trials), an-

tiplatelet therapy (usually aspirin) compared with placebo or untreated control continued for a mean of 29 months was associated with a 22% reduction in the odds of recurrent ischemic stroke, myocardial infarction (MI), or vascular death (17.8% vs 21.4%, $P<.001$) (TABLE 1).

Ticlopidine and Clopidogrel. Ticlopidine, a thienopyridine that blocks adenosine diphosphate-mediated platelet aggregation, has been evaluated in 2 large randomized controlled trials involving patients with TIA and stroke.^{17,18} In the first trial, among 1072 patients with TIA or stroke, ticlopidine (500 mg/d) compared with placebo or untreated control reduced the risk of stroke, MI, or vascular death by 23% (11.3% vs 14.0%, $P=.02$) after 2 years of follow up.¹⁷ In the second trial, among 3069 patients with TIA or minor stroke, ticlopidine compared with aspirin (1300 mg/d) reduced the risk of nonfatal stroke or death by 12% (17% vs 19%, $P=.05$) and the risk of fatal and nonfatal stroke by 21% (10% vs 13%, $P=.02$) after 3 years of follow up.¹⁸ However, frequent adverse effects, such as diarrhea and rash (25%), and serious hematologic adverse effects, including neutropenia (1%-2%) and thrombocytopenic thrombotic purpura (0.025%-0.05%), have been reported.¹⁸⁻²⁰

The Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial compared clopidogrel (75 mg/d) with aspirin (325 mg/d) for the long-term prevention of recurrent atherothrombotic vascular events in 19185 patients, including 6431 with prior ischemic stroke. Among all pa-

tients, clopidogrel reduced the risk of stroke, MI, or vascular death by 8.7% (95% confidence interval [CI], 0.3 to 16.5; $P=.04$) (TABLE 2). For the subgroup of patients with prior ischemic stroke, the relative risk reduction (RRR) was similar and not statistically different from the overall result. The safety profile of clopidogrel was comparable with that of aspirin.^{21,22}

Recently, the results of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) randomized trial were published. Aspirin (75 mg) added to clopidogrel (75 mg) was compared with clopidogrel alone among 7599 patients with recent TIA or ischemic stroke.²³ The combination of aspirin and clopidogrel did not significantly lower the incidence of ischemic strokes, MI, or vascular death (15.7% vs 16.7%; RRR, 6.4%; 95% CI, -4.6 to 16.3; $P=.24$) but was associated with an increase in the risk of major (2% vs 1%, $P<.001$) and life-

threatening bleeding (2.6% vs 1.3%; absolute risk increase, 1.3%; 95% CI, 0.64 to 1.9; $P<.001$).

Dipyridamole. The combination of aspirin with dipyridamole has been compared with aspirin monotherapy for stroke prevention among patients with TIA or stroke in several clinical trials.²⁴⁻²⁶ Dipyridamole is a pyridopyrimidine derivative that vasodilates coronary microvessels and inhibits platelet activation by increasing levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate. The European Stroke Prevention Study 2 (ESPS-2) evaluated this antiplatelet agent for stroke prevention in patients with TIA or stroke in the preceding 3 months.²⁴ The study randomly assigned 6602 patients into 1 of 4 treatment groups: low-dose aspirin (25 mg twice daily) alone ($n=1649$); extended-release dipyridamole (ER-DP) (200 mg twice daily) alone ($n=1654$); aspirin combined with ER-DP (same doses) ($n=1650$); or placebo ($n=1649$). Patients were followed up for 2 years to

determine the effects of these drugs on the rate of stroke and death from any cause. Compared with placebo, each of the active treatments significantly reduced the incidence of stroke (aspirin vs placebo: 12.5% vs 15%; RRR, 18.1%; $P=.01$; ER-DP vs placebo: 12.7% vs 15%; RRR, 16.3%; $P=.04$; aspirin combined with ER-DP: 9.5% vs 15%; RRR, 37.0%; $P<.001$) (TABLE 3). No significant reduction in MI or mortality was observed, although the risk reduction in ischemic events defined as stroke, MI, and sudden death confirmed the benefit of ER-DP added to aspirin. The 18% risk reduction observed with low-dose aspirin compared with placebo was consistent with the benefit observed in earlier studies of low-dose aspirin (75 mg) in patients with stroke.²⁷ The ESPS-2 trial was the first study to show an independent statistically significant reduction in stroke risk in patients treated with ER-DP. Compared with placebo, the combination of aspirin and ER-DP was reported to be twice as effective for stroke prevention as either drug alone, indicating an additive benefit; the combination was also more effective than aspirin or ER-DP given alone (Table 3).

When the results of ESPS-2 trial are analyzed together with additional trials included in the meta-analysis by the ATC,² 10 404 patients with preexisting symptomatic atherosclerotic disease from 25 trials comparing aspirin combined with dipyridamole vs aspirin alone were combined and the addition of dipyridamole to aspirin was associated with a nonsignificant 6% risk reduction in serious vascular events (nonfatal stroke, MI, vascular deaths)

Table 2. Results of CAPRIE Study: Treatment Effect on Outcome by Subgroup*

Patient Subgroup	No. of Events/ Patient-Years at Risk		Absolute Risk Reduction, %	Relative Risk Reduction, % (95% CI)
	Clopidogrel	Aspirin		
Ischemic stroke	433/6054	461/5979	0.56	7.3 (-5.7 to 18.7)
MI	291/5787	283/5843	-0.19‡	-3.7 (-22.1 to 12.0)
PAD	215/5795	277/5797	1.15	23.8 (8.9 to 36.2)§
All patients	939/17 636	1021/17 519	0.51	8.7 (0.3 to 16.5)

Abbreviations: CI, confidence interval; MI, myocardial infarction; PAD, peripheral arterial disease.

*N = 19 185, including n = 6431 with prior ischemic stroke.²¹

†Ischemic stroke, myocardial infarction, or vascular death.

‡When the additional 2144 patients with prior MI are included in this analysis, the relative risk reduction = 7.4 (95% CI, -5.2 to 18.6), which is consistent with the overall treatment effect.

§In the PAD subgroup, the average event rate per year in the clopidogrel group was 3.7% compared with 4.9% in the aspirin group ($P=.003$), and the relative risk reduction was significantly greater compared with that of patients without PAD.

||The test of heterogeneity for the risk reductions across the 3 subgroups was significant at $P=.04$, suggesting that the benefit of clopidogrel may not be identical across the subgroups.

Table 3. Results of ESPS-2 study*

Stroke (Fatal or Nonfatal)	Low-Dose Aspirin vs Placebo	ER-DP vs Placebo	Low-Dose Aspirin + ER-DP vs Placebo	Low-Dose Aspirin + ER-DP vs Aspirin Alone	Low-Dose Aspirin + ER-DP vs ER-DP Alone
No. of stroke events/ No. entered	206/1649 vs 250/1649	211/1654 vs 250/1649	157/1650 vs 250/1649	157/1650 vs 206/1649	157/1650 vs 211/1654
Absolute risk reduction, %	2.5	2.3	5.5	3.0	3.2
Relative risk reduction, %	18.1	16.3	37.0	23.1	24.7
P value	.01	.04	<.001	.006	.002

Abbreviation: ER-DP, extended-release dipyridamole.

*From Diener et al.²⁴

(11.8% vs 12.4%; odds ratio, 0.95; 95% CI, 0.86 to 1.05; $P=.32$).² The apparent reduction in nonfatal stroke was derived mainly from the ESPS-2 study²⁴ and was not consistent with the findings for nonfatal stroke or nonfatal MI or vascular death in other studies. Possible reasons for this difference include the use of ER-DP in the ESPS-2 study vs short-acting dipyridamole in the other studies, differences in patient characteristics, or the play of chance, as no systematic biases were apparent in this trial. The extended-release form of dipyridamole has been studied in the ESPS-2 clinical trial only and replication of its effectiveness is warranted before widespread use of this antiplatelet preparation rather than aspirin or clopidogrel is advocated.

A more recent meta-analysis by De Schryver et al²⁸ included randomized trials of individuals who were within 6 months after presentation of arterial vascular disease and who were treated for at least 1 month.²⁸ Starting therapy consisted of dipyridamole (in any dose) alone or added to another antiplatelet drug compared with placebo or antiplatelet drug(s) other than dipyridamole. Dipyridamole alone or in combination with another antiplatelet agent compared with placebo reduced vascular events such as nonfatal stroke or nonfatal MI (dipyridamole vs placebo: RRR, 0.90; 95% CI, 0.83 to 0.98; aspirin combined with dipyridamole vs aspirin alone: RRR, 0.90; 95% CI, 0.80 to 1.00).²⁸ There was no evidence that dipyridamole alone was more efficacious than aspirin.

To resolve some of the controversy regarding the effectiveness of aspirin and dipyridamole, this combination is currently being evaluated in ongoing clinical trials, such as the European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) (n=4500; ER-DP [400 mg/d] added to aspirin [any dose between 30 and 325 mg/d] vs aspirin alone) for patients who have experienced a TIA or minor ischemic stroke, and the Prevention Regimen for Effectively Avoiding Second Strokes (ProFESS) trial (n=15 500; clopido-

grel added to aspirin vs ER-DP added to aspirin) for patients with ischemic TIA or stroke. Results from these studies will clarify the role of combined aspirin and ER-DP compared with other antiplatelet combinations.

Coronary Artery Disease

The pathophysiological spectrum of CAD includes stable angina, unstable angina, ST-segment elevation MI (STEMI), and non-ST-segment elevation MI (NSTEMI). Patients with CAD who become unstable by virtue of developing a change in the pattern of angina are classified as having acute coronary syndrome (ACS) and include patients with unstable angina, STEMI, and NSTEMI.

STEMI ACS. Aspirin. Initial randomized trials conducted in the 1970s and early 1980s did not consistently demonstrate a benefit of aspirin compared with placebo in patients with acute MI.²⁹⁻³² However, these were relatively small and likely underpowered. The Second International Study of Infarct Survival (ISIS-2) trial randomly assigned 17 187 patients presenting within 24 hours of onset of suspected acute MI to receive streptokinase, aspirin 162.5 mg/d for 30 days, both, or neither.³³ At the end of 5 weeks, aspirin reduced the risk of death by 23% and nonfatal MI or stroke by 49% and 46%, respectively, with no increase in major or intracranial bleeding. The survival benefits of aspirin in patients with acute MI were also seen in patients receiving concomitant heparin therapy and were additive to the benefits of streptokinase. A recently published long-term follow-up of patients randomized in the ISIS-2 trial demonstrated that the benefits of aspirin remained evident even after 10 years.³⁴

The efficacy of aspirin as an adjunct to thrombolytic therapy and for the long-term management of patients with MI treated has recently been summarized by the ATC.² Among more than 19 000 patients randomized in 15 trials, antiplatelet therapy (primarily aspirin) compared with placebo or untreated control and continued for a

mean of 1 month after the acute event was associated with a 30% reduction in the odds of stroke, recurrent MI, or vascular death (10.4% vs 14.2%, $P<.001$). Among more than 20 000 patients with a history of MI randomized in 12 trials, antiplatelet therapy (again, primarily aspirin) compared with placebo or untreated control and continued for a mean of 27 months was associated with a 25% reduction in the odds of stroke, recurrent MI, or vascular death (13.5% vs 17%, $P<.001$).

Clopidogrel and Ticlopidine. No studies have compared clopidogrel or ticlopidine with placebo or untreated control as an adjunct to thrombolytic therapy for the acute treatment of patients with STEMI ACS. The combination of clopidogrel with aspirin compared with aspirin alone is currently being evaluated in the Clopidogrel Metoprolol Myocardial Infarction Trial (COMMIT) (n=30 000) and the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study (n=2200).

As mentioned before, the CAPRIE trial²¹ of 19 185 patients with a history of symptomatic atherosclerosis included 6302 with prior MI. When all patients with prior MI, including those from the stroke and PAD subgroups, were considered together (n=8446), the risk reduction with clopidogrel vs aspirin was similar to the overall treatment effect (RRR, 7.4%; 95% CI, -5.2 to 18.6) (Table 2). Clopidogrel compared with aspirin was associated with a significantly lower risk of gastrointestinal bleeding (2.0% vs 2.7%; $P<.002$), although the overall safety profile of clopidogrel was comparable to that of aspirin.^{21,22}

NSTEMI ACS. Aspirin. Randomized trials have demonstrated the benefits of aspirin compared with placebo or untreated control for the management of patients with NSTEMI ACS.³⁵⁻⁴¹ Aspirin (75-1300 mg/d) reduced the risk of MI by about 50% at 2 years^{37-39,41} and progression to severe angina requiring cardiac catheterization by 30% at 1 year.⁴⁰

The ATC meta-analysis of antiplatelet therapy (primarily aspirin) in more

than 5000 patients with unstable angina reported a 46% reduction in the odds of stroke, MI, or vascular death with antiplatelet therapy (primarily aspirin) vs placebo or untreated control (8.0% vs 13.3%, $P < .001$) (Table 1).

Clopidogrel and Ticlopidine. No studies have compared clopidogrel with placebo/control (in the absence of aspirin) in patients with NSTEMI ACS. One open-label study of 652 patients with unstable angina demonstrated that ticlopidine compared with control reduced the risk of death or MI by 46% at 6 months ($P = .009$).⁴²

The Clopidogrel in Unstable Angina to Prevent Recurrent Events in Patients with Acute Coronary Syndromes Without ST-Segment Elevation (CURE) study of 12562 patients demonstrated that the combination of clopidogrel (300-mg loading dose followed by 75 mg/d) and aspirin (75-325 mg/d) was superior to

aspirin alone (75-325 mg/d) in preventing stroke, MI, and vascular death (RRR, 0.80; 95% CI, 0.72 to 0.90; $P < .001$).⁴³ The combination of clopidogrel and aspirin was associated with an increased risk of major bleeding (3.7% vs 2.7%; RRR, 1.38; 95% CI, 1.13 to 1.67; $P = .001$) but no significant excess in life-threatening bleeding (2.1% vs 1.8%, $P = .13$). The incidence of bleeding with clopidogrel was lower in patients receiving an aspirin dose of less than 100 mg/d compared with those receiving higher doses.⁴⁴

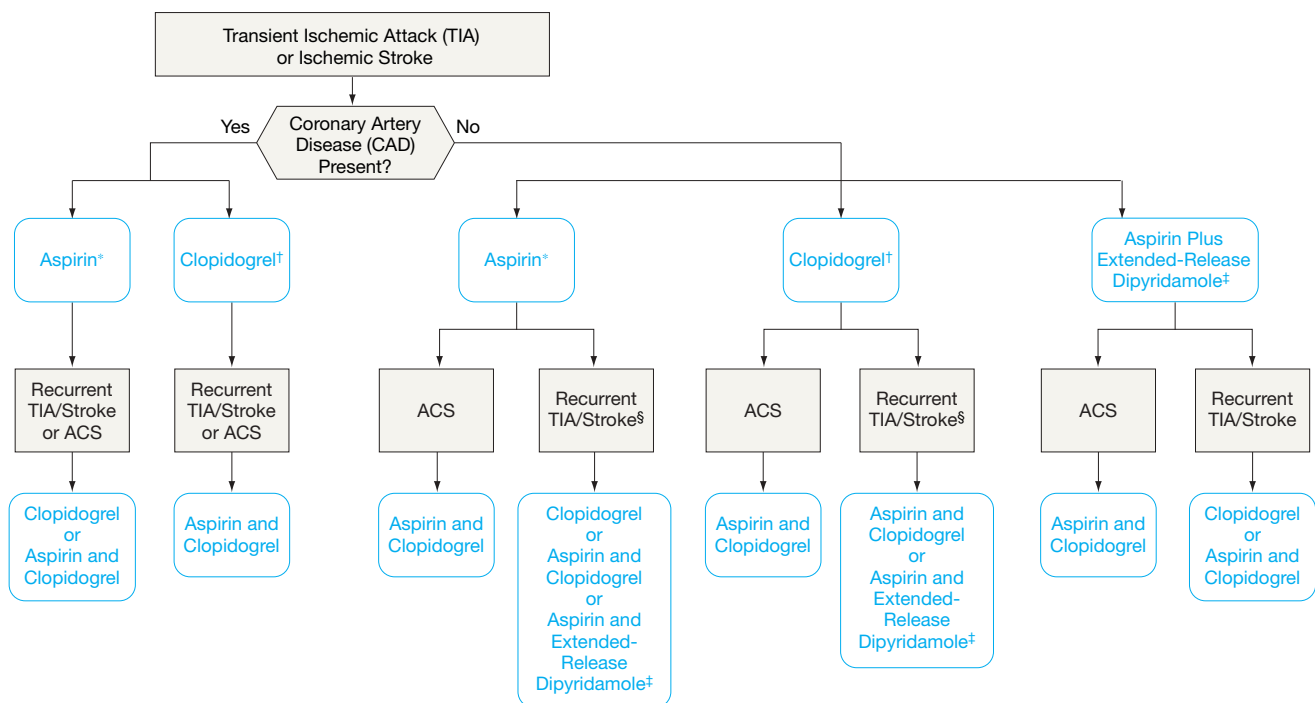
Chronic Stable Angina

Aspirin. Randomized trials have demonstrated the benefits of aspirin compared with placebo or untreated control for the management of patients with stable angina. The Swedish Angina Pectoris Aspirin Trial (SAPAT) randomly assigned 2035 patients with stable angina to receive 75 mg of aspirin daily or pla-

cebo.⁴⁵ The SAPAT investigators reported a 34% reduction in MI and sudden death (95% CI, 24% to 49%; $P = .003$). The meta-analysis of antiplatelet therapy (primarily aspirin) by the ATC group included 2920 patients with stable angina and reported a 33% reduction in the odds of serious vascular events (stroke, MI, or vascular death) with antiplatelet therapy vs placebo or untreated control (9.9% vs 14.1%, $P < .001$)² (Table 1). Taken together in patients with CAD, antiplatelet therapy (primarily aspirin) is associated with a 29% reduction in the odds of serious vascular events (11.4% vs 15.3%, $P < .001$) (Table 1).

Percutaneous Coronary Intervention. Percutaneous coronary intervention involves the use of 1 or more revascularization devices designed to remove (eg, rotational atherectomy), ablate (eg, excimer laser angioplasty), or scaffold (eg, stents) atherosclerotic plaque.⁴⁶ This

Figure 1. Recommended Initial Antiplatelet Therapy for Patients With Transient Ischemic Attack or Ischemic Stroke and Subsequent Therapy for Recurrent Ischemic Events



Abbreviations: ACS indicates acute coronary syndrome; TIA, transient ischemic attack.

*Per the Antithrombotic Trialists' Collaboration.²

†Per the CAPRIE Steering Committee.²¹

‡Per Diener et al²⁴ and De Schryver et al.²⁸

§Without coronary artery disease.

results in local vascular trauma, exposing highly thrombogenic subendothelium to the circulating blood and leading to local thrombus formation. The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Percutaneous Coronary Intervention 2001⁴⁷ recommend that aspirin 80 to 325 mg be given at least 2 hours prior to the procedure in combination with either ticlopidine or clopidogrel for at least 72 hours prior to the procedure when possible. Because of its more favorable safety profile, clopidogrel should be used in preference to ticlopidine. Aspirin should be continued indefinitely, and per the results of the Percutaneous Coronary Intervention-Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) study⁴⁸ and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial,⁴⁹ clopidogrel should be continued for approximately 12 months, and possibly longer, depending on physicians' estimates of their patients' risk.

Peripheral Arterial Disease

Aspirin. No individual randomized controlled trial has conclusively dem-

onstrated that aspirin reduces cardiovascular events among patients with PAD. The ATC meta-analysis of antiplatelet therapy (primarily aspirin) in more than 9000 patients with PAD demonstrated a 23% reduction in the odds of serious vascular events (5.8% vs 7.1%, $P < .004$), with similar benefits observed among patients with intermittent claudication, those having peripheral grafts, and those who have undergone peripheral angioplasty² (Table 1).

Ticlopidine. Ticlopidine has been reported to reduce cardiovascular and thrombotic events in patients with intermittent claudication. The Swedish Ticlopidine Multicenter Study enrolled 687 patients and compared ticlopidine (250 mg twice daily) with placebo. A significant 34% reduction in coronary and cerebrovascular events (25.7% vs 29.0%; RRR, 0.66; 95% CI, 0.45 to 0.96) was observed.⁵⁰ Despite these results, potential adverse effects associated with ticlopidine, in particular neutropenia and thrombotic thrombocytopenic purpura, have limited its use.

Clopidogrel. In addition to the overall benefit of clopidogrel among pa-

tients with a history of symptomatic atherosclerosis in the CAPRIE study, clopidogrel was associated with a risk reduction of approximately 24% (95% CI, 8.9 to 36.2; $P = .003$) compared with aspirin in a subgroup analysis of more than 6000 patients with PAD.²¹ Compared with the MI and ischemic stroke subgroups, the risk reduction was significantly higher (Table 2). Furthermore, a test of heterogeneity of the 3 treatment effects for clopidogrel was statistically significant ($P = .04$), suggesting that the true benefit of clopidogrel vs aspirin might be much greater in patients with PAD. Based on these results, clopidogrel was approved in 1997 by the US Food and Drug Administration for the reduction of ischemic events in patients with PAD.

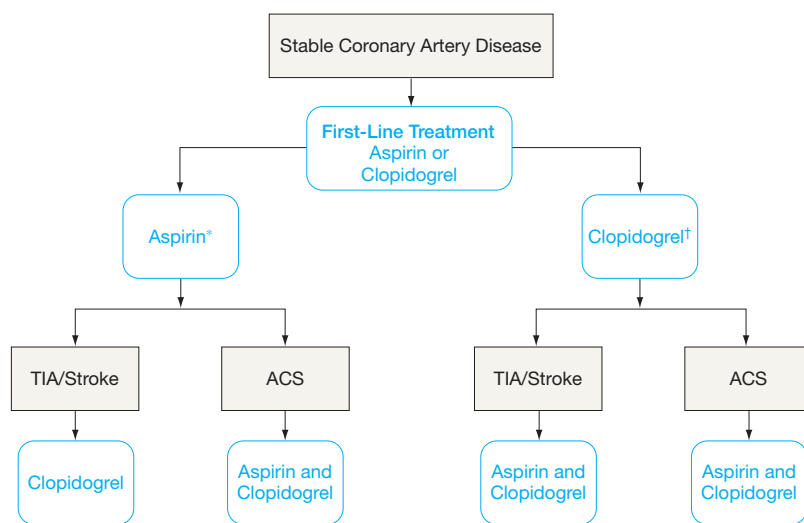
SUMMARY AND PERSPECTIVE

TIA or Stroke

The weight of current evidence supports the use of aspirin or clopidogrel as first-line therapy after a first episode of TIA or stroke. Clopidogrel may be preferred in patients with aspirin intolerance. Extended-release dipyridamole (400 mg/d) combined with aspirin (50 mg/d) is a possible alternative. However, the evidence supporting its use comes from a single trial,⁴ and its routine use in patients with concomitant symptomatic CAD is questionable. For patients who develop recurrent TIA or stroke while taking aspirin, options for changes in therapy include the use of clopidogrel alone or aspirin combined with ER-DP in the absence of CAD.²³ In patients who develop recurrent TIA or stroke while taking clopidogrel, an option for second-line therapy can be aspirin combined with ER-DP; for patients who develop ACS, aspirin combined with clopidogrel should be used (FIGURE 1).

The limiting factor in recommending more widespread use of dipyridamole is its potential to cause coronary vasodilatation resulting in increased blood flow to nonstenosed coronary arteries and possible myocardial ischemia during exercise. Current ACC/AHA guidelines (2002) recommend that dipyri-

Figure 2. Recommended Initial Antiplatelet Therapy for Patients With Stable Coronary Artery Disease and Subsequent Therapy for Recurrent Ischemic Events



Abbreviations: ACS indicates acute coronary syndrome; TIA, transient ischemic attack.

*Per the Antithrombotic Trialists' Collaboration.²

†Per the CAPRIE Steering Committee.²¹

damole not be used in patients with stable angina.⁵¹ However, this recommendation was based on short-acting dipyridamole.⁵² No increase in cardiac events has been observed with the use of ER-DP in patients with prior ACS.⁵³ Given that other effective options exist for patients with clinically apparent CAD who experience TIA or stroke, the combination of ER-DP with aspirin should be avoided until this issue is resolved by current clinical trials.

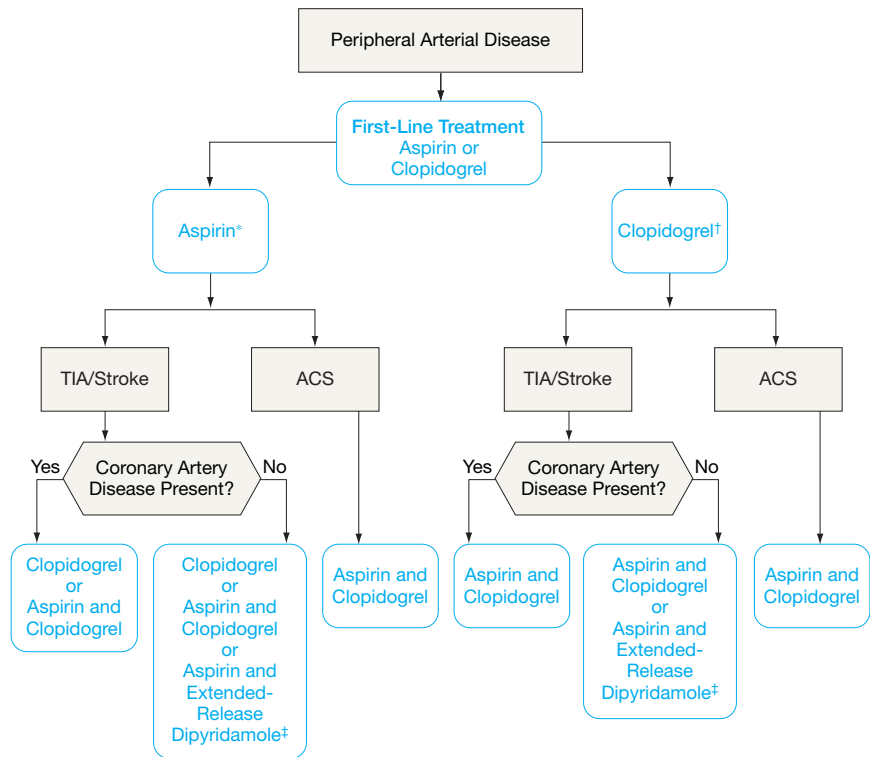
Coronary Artery Disease

In patients with chronic stable angina, there are increasing numbers of oral antiplatelet therapies that have been proven to be effective for acute or long-term therapy. Aspirin is the mainstay of treatment in this population of patients as it is effective, relatively safe, and inexpensive. Aspirin should be started as soon as the diagnosis is suspected and continued indefinitely. Among patients who have recently undergone coronary artery stenting, aspirin and clopidogrel should be given in combination for up to a year.^{48,49}

STEMI ACS. The ACC/AHA guidelines for the management of patients with acute MI (1999) recommend that aspirin (160-325 mg/d) be given on day 1 of AMI and continued indefinitely in all patients.⁵⁴ Clopidogrel or another oral antiplatelet agent, such as ticlopidine, is recommended as an alternative to aspirin only when there is a contraindication or intolerance to aspirin (FIGURE 2).

NSTEMI ACS. For patients with unstable angina and NSTEMI, the combination of aspirin and clopidogrel should be started as soon as possible after presentation in the absence of contraindications. This recommendation is reasonable since clopidogrel reduces the risk of ischemic events irrespective of whether an early interventional strategy is used and the majority of bleeding episodes are reversible. Aspirin should be continued indefinitely and clopidogrel should be continued for up to 9 to 12 months⁵⁵ and possibly longer, depending on the physician's estimate of the patient's risk.

Figure 3. Recommended Initial Antiplatelet Therapy for Patients With Peripheral Arterial Disease and Subsequent Therapy for Recurrent Ischemic Events



Abbreviations: ACS indicates acute coronary syndrome; TIA, transient ischemic attack.

*Per the Antithrombotic Trialists' Collaboration.²

†Per the CAPRIE Steering Committee.²¹

‡Per Diener et al²⁴ and De Schryver et al.²⁸

Peripheral Arterial Disease

Patients with symptomatic PAD are at high risk of vascular death due to coronary or cerebrovascular causes.⁵⁵ Therefore, in addition to modification of cardiovascular risk factor(s), aggressive antiplatelet therapy should be considered. Based on available evidence, the first-line oral antiplatelet therapy should be aspirin (160-325 mg/d) or clopidogrel (75 mg/d), and clopidogrel is recommended when aspirin is contraindicated or not tolerated. Combination antiplatelet therapy with aspirin and clopidogrel should be initiated if a patient experiences a recurrent vascular event while receiving monotherapy. Given the high proportion of patients with PAD who have coexisting CAD,²¹ aspirin combined with ER-DP should be avoided when such a patient experiences a TIA or stroke until more ef-

ficacy and safety data of this combination in high-risk vascular patients has been accrued (FIGURE 3).

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Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content: Tran, Anand.
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