# Aggregating the Evidence for Antiplatelet Drugs:

## A review of recent clinical trials



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This monograph was written by Niteesh K. Choudhry, M.D., Ph.D., Assistant Professor of Medicine, Harvard Medical School, with consultative input from Jerry Avorn, M.D., Michael A. Fischer, M.D., M.S., Leslie Jackowski, M.B.B.S., and William H. Shrank, M.D., M.S.H.S.

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**These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.**



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## Introduction

Antiplatelet drugs are widely-used for the primary and secondary prevention of myocardial infarction (MI), stroke and other cardiovascular events. Several antiplatelet agents, with different mechanisms of action, are commercially available. The oldest is aspirin; more recently, it was joined by clopidogrel (Plavix), and in 2009 by prasugrel (Effient).

Aspirin irreversibly binds to cyclooxygenase 1 and is the most widely used antiplatelet drug. Evidence supporting its efficacy in a variety of clinical settings has existed for more than two decades. Clopidogrel (Plavix), which irreversibly blocks the adenoside diphosphate (ADP) receptor, has been increasingly used since the publication of the **Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)** trial in 1996. Several large randomized controlled trials have evaluated clopidogrel as an alternative or as an adjunct to aspirin. The interpretation and clinical application of these studies can be challenging because dual antiplatelet therapy increases the risk of bleeding, necessitating a careful risk-benefit analysis. Dipyridamole, an antiplatelet agent that has been used for many decades, has recently returned to prominence in its extended-release form combined with aspirin (marketed as Aggrenox) for the management of patients after stroke. Most recently, the US Food and Drug Administration (FDA) approved the use of prasugrel (Effient) for the treatment of patients with acute coronary syndromes who have undergone coronary stent insertion. Prasugrel, which works in a similar manner to clopidogrel, appears to be highly effective but is also associated with a substantial bleeding risk.

Choosing the right antiplatelet therapy requires an understanding of the benefits and risks of specific regimens and their role in different clinical settings. In addition, clopidogrel and combination aspirin and extended-release dipyridamole (ASA-ERDP) cost substantially more than aspirin (pennies per day for aspirin, vs. approximately $156 per month for Plavix 75mg daily). In 2008, sales of clopidogrel were $8.6 billion, making it the second best-selling drug in the world, after atorvastatin (Lipitor). A substantial proportion of this use is in situations where clinical trials have found aspirin to be an equally effective, safer, and substantially less expensive alternative.[1] Therefore, the rational use of antiplatelet agents has important economic as well as clinical implications.

This document provides practice- relevant information about the comparative efficacy, safety and cost of use of antiplatelet agents. **This extensive and sometimes confusing literature is organized by disease state below**.

## Acute coronary syndromes

The acute coronary syndromes (ACS) represent a spectrum of clinical conditions including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation MI (STEMI). Many patients with an ACS undergo percutaneous intervention (PCI). Several large-scale randomized trials have assessed the role of antiplatelet agents for these patients in preventing adverse cardiovascular events.

### Benefits of antiplatelet therapy

#### *Aspirin*

The use of aspirin in the acute management of MI has been evaluated in 15 trials including about 19,000 patients. Together, these trials convincingly show that giving aspirin to acute MI patients in hospital and continuing treatment for an average of 1 month reduces the risk of re-infarction, stroke, or cardiovascular death by 30%.[2] Aspirin also reduces the risk of a major vascular event by 46% when given acutely to patients with unstable angina.[2]

#### *Clopidogrel*

While no trials have evaluated clopidogrel as an alternative to aspirin for patients with ACS, the combination of aspirin and clopidogrel (versus aspirin alone) has been studied (see Table 1).

The **Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)** trial enrolled patients with NSTEMI or UA and randomized them to clopidogrel (300 mg load then 75 mg daily) or placebo, with all patients receiving aspirin (75 mg to 325 mg daily).[3] The patients continued to receive their assigned therapy for up to one year after discharge (mean 9 months). Patients in

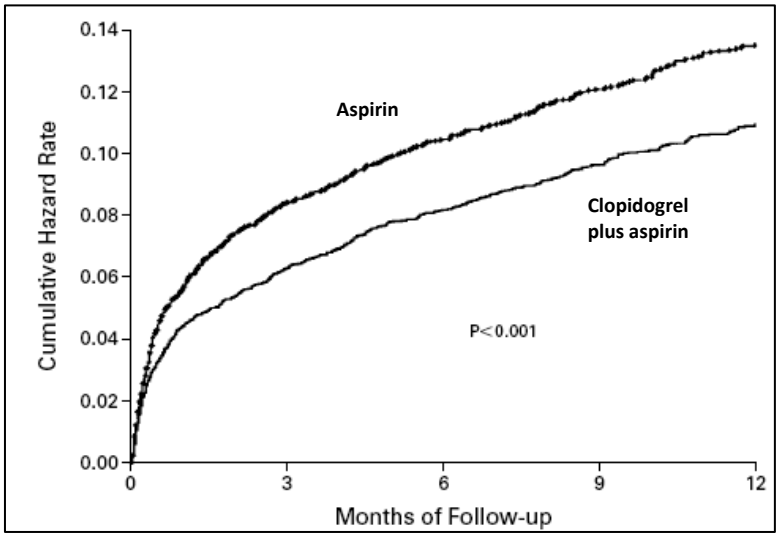


**Figure 1: Rates of the primary outcome (death from CV causes, nonfatal MI, or stroke) for patients treated with aspirin plus clopidogrel ("Clopidogrel") and aspirin plus placebo ("Placebo").**

the dual antiplatelet group had a significantly lower risk of death from cardiovascular causes, non-fatal MI, and non-fatal stroke (9.3% vs. 11.4% in patients receiving aspirin alone); as a result, dual therapy is recommended for such patients. There is little evidence to support the use of dual antiplatelet therapy beyond 1 year.

**TABLE 1: Key trials comparing aspirin plus clopidogrel versus aspirin alone for patients with acute coronary syndromes.**

| Trial Name | Who was enrolled? | What was studied and for how long? | What was the primary outcome? | What were the main results? | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Prevention of vascular events | | | Risk of major bleeding | | |
| | | | | Aspirin alone | Clopidogrel plus aspirin | Absolute difference | Aspirin alone | Clopidogrel plus aspirin | Absolute difference |
| **CURE** (NEJM 2001) | NSTEMI/UA (n=12,562) | clopidogrel + aspirin v. aspirin alone (for 3-12 months) | Death from cardiovascular causes, non-fatal MI, non-fatal stroke | 11.4% | 9.3% | 2.1% | 2.7% | 3.7% | 1% |
| **CLARITY-TIMI 28** (NEJM 2005) | STEMI (n=3,491) | clopidogrel + aspirin v. aspirin alone (until angiography, day 8 or hospital discharge) | Occluded infarct-related artery on angiography, death, or recurrent MI | 21% | 15% | 6% | 1.3% | 1.1% | not significant |
| **COMMIT** (Lancet 2005) | STEMI (n=45,852) | clopidogrel + aspirin v. aspirin alone (until discharge or up to 4 weeks in hospital) | Death, re-infarction or stroke | 10.1% | 9.2% | 0.9% | 0.58% | 0.55% | not significant |

A 2,658 patient sub-study of the CURE trial, **Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events in Patients Undergoing Percutaneous Coronary Intervention (PCI-CURE),** compared dual antiplatelet therapy with clopidogrel and aspirin to aspirin alone for ACS patients undergoing PCI.[4] Patients were pretreated with their assigned regimen for a median of 6 days before PCI and all subjects received open-label clopidogrel for 4 weeks before returning to their randomized study drug. The group that received clopidogrel and aspirin had a 30% lower relative rate of cardiovascular events than patients given aspirin alone.

The **Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)** and **Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)** trials evaluated patients hospitalized for STEMI and found that clopidogrel-aspirin therapy administered in hospital was superior to aspirin alone in preventing major vascular events (see Table 1).[5, 6] While the trials differed in important ways, such as the proportion of patients who underwent PCI both found that the combination of clopidogrel and aspirin was superior to aspirin alone in STEMI patients. In CLARITY, the benefit of dual therapy was also observed in the subgroup of patients who underwent PCI.[7]

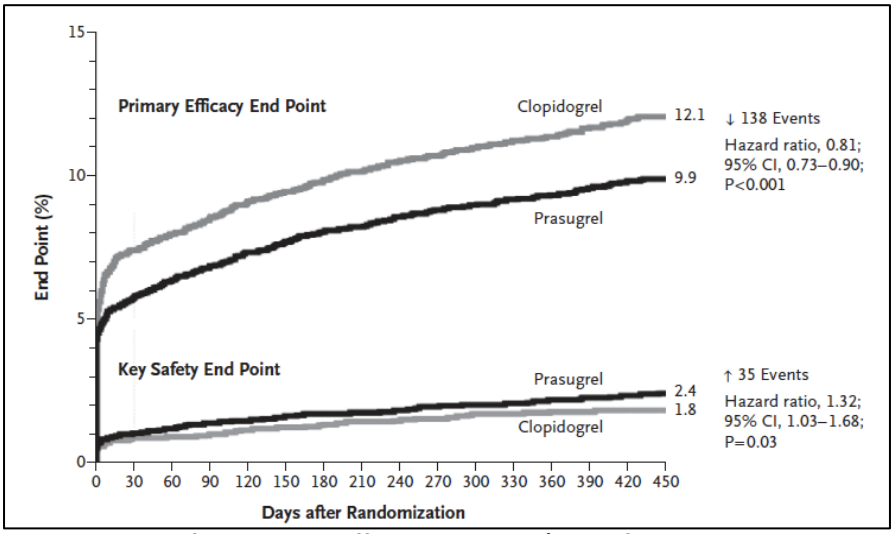


**Figure 2: Rates of the primary efficacy end point (death from CV causes, nonfatal MI, or nonfatal stroke) (top) and for the key safety end point (major bleeding not related to coronary-artery bypass grafting) (bottom) for patients treated with prasugrel and clopidogrel in the TRITON-TIMI 38 study.**

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Unfortunately, these trials were extremely short and there is no other evidence supporting the use of combination therapy for STEMI patients after discharge. Nevertheless, as recommended by the current American Heart Association/American College of Cardiology guidelines,[8] it is probable that like NSTEMI/UA patients, STEMI patients will also benefit if therapy is continued for at least one year.

### *Prasugrel*

The **Trials to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-thrombolysis in Myocardial Infarction (TRITON-TIMI 38)** study[9], published in mid-2009, evaluated a drug newly approved by the FDA, prasugrel (Effient). The trial randomized 13,608 patients with acute coronary syndrome (UA, NSTEMI, or STEMI) scheduled for PCI to receive prasugrel (as a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (as a 300-mg loading dose and a 75-mg daily maintenance dose). All patients also received aspirin (75 to 162 mg daily) and patients were followed up for 6 to 15 months (median follow-up 14.5 months).

The study's primary efficacy end point was death from cardiovascular causes, nonfatal MI, or nonfatal stroke. This endpoint occurred significantly less frequently in patients receiving prasugrel (9.9% v. 12.1%). The main finding was

due to the difference in non-fatal MI (7.3% v. 9.5%), although all-cause mortality did not differ between groups. The added benefit of prasugrel was much smaller in several important subgroups: patients with a history of stroke or transient ischemic attack before enrollment, the elderly (age ≥75 years), and those with weight of less than 60 kg.

As discussed in greater detail below, the benefits of prasugrel must be weighed against its risks. Nevertheless, the trial demonstrates the potential value of this novel agent and suggests that the appropriate duration of dual antiplatelet therapy for patients undergoing PCI after MI might be as long as 15 months.[10]

## Risks of antiplatelet therapy

Predictably, all antiplatelet agents increase the risk of gastrointestinal and intracranial bleeding, even when aspirin is used at low doses.[11] This risk increases with higher doses of aspirin. For example, in the CURE trial, the risk of major bleeding (disabling bleeding or bleeding requiring transfusion of at least 2 units) in patients treated with aspirin was less than 2% at daily doses < 100 mg, 2.8% at 100-200 mg, and 3.7% at > 200 mg per day.[12]

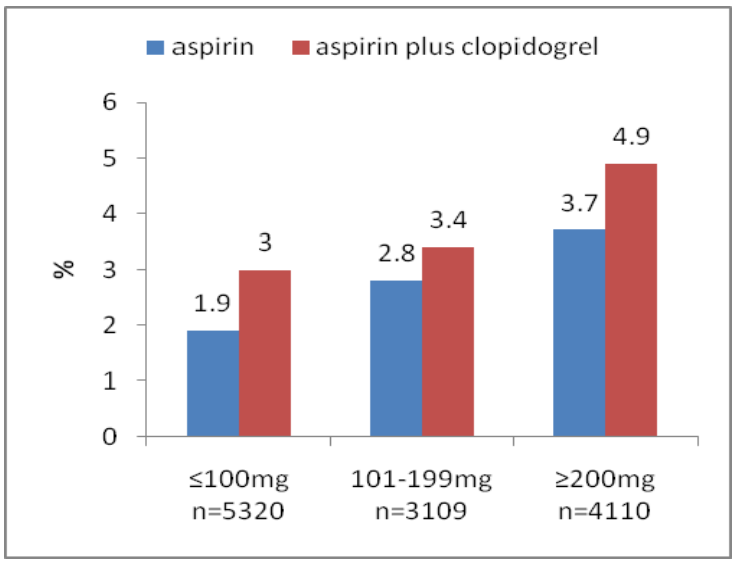



**Figure 3: Rates of major bleeding observed in the CURE trial for patients treated with aspirin alone and aspirin plus clopidogrel broken down by aspirin dosage. Adapted from: Peters RJ, Mehta SR, Fox KA, et al. Circulation 2003; 108: 1682-7.**

While the bleeding risks from combined aspirin and clopidogrel in the short-term COMMIT and CLARITY trials were similar to those of patients treated with aspirin alone, longer-term trials have found that dual antiplatelet therapy causes a higher risk of bleeding than antiplatelet monotherapy.[13]

In CURE, clopidogrel plus aspirin caused a higher incidence of major bleeding than aspirin alone (3.7% v. 2.7% over a mean follow-up of 9 months). This included bleeding that required transfusion (2.8% v. 2.2%), although there was no increase in the risk of life-threatening bleeding (2.2% v. 1.8%) or hemorrhagic stroke (0.1% v. 0.1%) with dual antiplatelet therapy when compared to aspirin alone.[3]

In TRITON-TIMI 38, the combination of prasugrel and aspirin caused a higher risk of major bleeding than clopidogrel plus aspirin (2.4% v. 1.8%, p=0.03). In the 3 subgroups of patients in whom the efficacy of prasugrel is lower (patients with a history of stroke or transient ischemic attack before enrollment, age ≥75 years, or those whose weight is under 60 kg), absolute levels of bleeding were also greater, resulting in less net clinical benefit or in clinical harm.[9] Therefore, for these patients, its advantage is not documented; if the drug is used, a reduced dose (5 mg daily rather than the usual 10 mg per day) should be considered, although it is unknown whether prasugrel is more effective than clopidogrel at this dose.

**BOTTOM LINE:** Several antiplatelet regimens have demonstrated efficacy in reducing cardiovascular events in patients with acute coronary syndromes. More potent regimens are more effective at preventing recurrent events but are also more likely to cause bleeding. Dual therapy with clopidogrel and aspirin for at least one year is the currently recommended treatment for all ACS patients. For many ACS patients who have undergone PCI, a recent trial suggests that prasugrel and aspirin for 15 months is likely the appropriate choice. However, the benefit-risk relationship did not demonstrate an advantage in patients with low body weight, age ≥ 75 years, or who have a history of stroke or transient ischemic attack.

## Recent or remote MI

### Benefits of antiplatelet therapy

In patients with prior MI (i.e., not acutely during an event), aspirin reduces the risk of subsequent vascular events by more than 25%.[2]

The CAPRIE trial compared clopidogrel as an alternative to aspirin for patients with recent, but not acute, MI.[14] It enrolled more than 19,000 patients who had a recent MI (within 35 days), a recent stroke (> 1 week and < 6 months), or peripheral vascular disease (intermittent claudication or a history of surgically repaired claudication). Patients were randomized to receive either clopidogrel (75 mg daily) or aspirin (325 mg daily) for almost 2 years. Clopidogrel was superior to aspirin for the prevention of ischemic stroke, MI, or vascular death, but the magnitude of this effect was very small (0.5% absolute reduction in risk, 8.7% relative reduction in risk).

The CAPRIE investigators then evaluated the post-MI subgroup separately, and in this group of patients found that clopidogrel was equivalent to aspirin. Therefore, the routine use of clopidogrel for all post-MI patients is not

recommended.[15] Several high-risk subgroups of patients enrolled in CAPRIE (e.g., those with a history of bypass surgery, a prior stroke or MI, arterial disease in two or more areas, diabetes, or high cholesterol) showed a particular benefit from clopidogrel compared to aspirin.[16] However, these analyses were post-hoc (i.e., not pre-planned) and therefore these associations may be due to statistical chance. Nevertheless, the use of clopidogrel is reasonable in these subgroups and in patients who are aspirin intolerant.

The **Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)** trial provides data about the use of dual antiplatelet therapy for patients with a history of MI but no recent infarction.[17] In this trial, more than 15,000 patients with symptomatic vascular disease or multiple risk factors for vascular disease were randomized to clopidogrel (75 mg daily) plus aspirin (75-162 mg daily) or aspirin alone (75-162 mg daily). Combination antiplatelet therapy was not better than aspirin alone and resulted in a higher rate of bleeding (see below). The subgroup of patients with symptomatic vascular disease showed a slight benefit from combination therapy vs. aspirin alone, but this result was of only borderline statistical significance.

Viewed in light of the COMMIT and CLARITY trials, these data suggest that patients with STEMI should be started on dual antiplatelet therapy acutely in hospital, but there may be little advantage in initiating dual therapy in patients with a history of MI who are not already taking both clopidogrel and aspirin.

## Risks of antiplatelet therapy

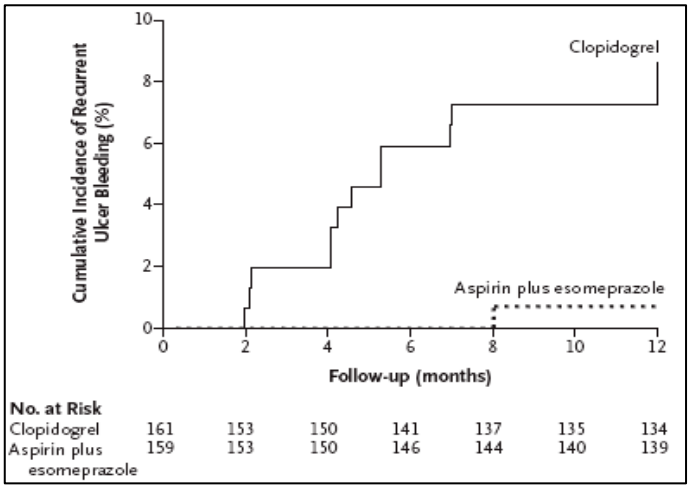



**Figure 4: –Incidence of recurrent ulcer bleeding in patients with aspirin associated gastrointestinal bleeding who were subsequently treated with clopidogrel or aspirin alone.**



The risk of serious bleeding has been reported to be minimally lower with clopidogrel than with aspirin, but this may be a dose effect. In the CAPRIE trial, the risk of intracranial hemorrhage was 0.35% in patients receiving clopidogrel and 0.49% in patients receiving aspirin, but this was not a statistically significant difference.[14] Similarly, the risk of gastrointestinal hemorrhage in clopidogrel-treated patients was 1.99% vs. 2.66% in aspirin-treated patients. This difference was statistically significant. However, aspirin-treated patients in the CAPRIE trial

received 325 mg of aspirin, a dose higher than is commonly used in current practice. It is therefore unknown whether clopidogrel is safer than lower doses of aspirin.

Based on CAPRIE trial, the American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines for the management of patients with acute ST-segment elevation MI recommend using aspirin for most patients and clopidogrel for patients who cannot take aspirin because of major gastrointestinal intolerance.[15] However, a recent trial of patients who developed ulcer bleeding while taking aspirin found that the combination of aspirin plus a proton pump inhibitor (esomeprazole) was significantly more effective than clopidogrel at reducing the risk of re-bleeding (8.6% in the clopidogrel group v. 0.7% in the aspirin plus esomeprazole group).[18]

**BOTTOM LINE:** Most patients with a history of MI (but not an acute MI) should be treated with aspirin alone. Clopidogrel alone should be used in case of aspirin allergy or in high-risk patients (those with a history of bypass surgery, multiple MIs, a prior stroke, arterial disease in two or more areas, diabetes, or high cholesterol). For patients who have a GI bleed while on aspirin, adding a proton-pump inhibitor is more effective in preventing another bleed than using clopidogrel instead of aspirin.

## Stable angina

### Benefits of Antiplatelet Therapy

Aspirin clearly benefits patients with stable angina. In 7 trials of 2,920 patients, aspirin caused a 33% reduction in the risk of stroke, MI, or vascular death.[2]

There is no evidence on the comparative value of clopidogrel vs. aspirin in patients with stable angina who have not had a recent MI, stroke, or who do not have PVD.

As noted above, the CHARISMA trial enrolled a variety of patients including those with stable angina and found no advantage of clopidogrel plus aspirin compared to aspirin alone.[17] Consistent with this, the current AHA/ACC guidelines for stable angina recommend that stable angina patients be treated with aspirin alone. Clopidogrel monotherapy should be used in patients with a contraindication to aspirin.

### Risks of Antiplatelet Therapy

The side-effects of antiplatelet therapies do not differ by clinical indication: patients with stable angina appear to face the same risk of bleeding as other patients who receive long-term antiplatelet therapy.

**BOTTOM LINE:** Patients with stable angina should be treated with aspirin unless a contraindication exists, in which case clopidogrel monotherapy is a reasonable option. Aspirin plus a PPI is better for preventing GI hemorrhage than is clopidogrel.

## Elective PCI

### Benefits of Antiplatelet Therapy

Among the studies that have evaluated the use of antiplatelet therapy for patients after elective PCI, the most notable is **Clopidogrel for the Reduction of Events During Observation (CREDO)**. It randomized 2,116 patients undergoing elective PCI (with bare metal stent or balloon angioplasty) to receive clopidogrel for 1 month or 12 months. All patients received aspirin.[19] Patients randomized to take clopidogrel for 12 months had a 27% relative reduction in the combined risk of death, MI, or stroke (absolute reduction of 3%, p=0.02) compared to those randomized to one month of use. A higher proportion of patients randomized to longer-term clopidogrel had major bleeding (8.8% v. 6.7%), although this difference did not reach statistical significance.

The AHA/ACC have extensively reviewed the use of clopidogrel plus aspirin in patients undergoing coronary stenting.[20] These groups recommend that after stent insertion, "[f]or all post-PCI stented patients receiving a [drug-eluting stent], clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding. For post-PCI patients receiving a [bare-metal stent], clopidogrel should be given for a minimum of 1 month and ideally up to12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).

Whether clopidogrel should be continued for longer than 12 months has not been established and there is ongoing debate about whether the benefits of prolonged antiplatelet therapy outweigh its risks. An important post-stent complication is the occurrence of late stent thrombosis. Its risk factors include:

- stenting of small vessels;
- multiple lesions;

- long stents;
- overlapping stents;
- ostial or bifurcation lesions;
- prior brachytherapy;
- suboptimal stent result;
- low ejection fraction;
- advanced age;
- diabetes mellitus;
- renal failure;
- ACS; and
- premature discontinuation of antiplatelet agents.

Decisions about the duration of clopidogrel use beyond a year in PCI patients should generally be made in consultation with a cardiologist.

### Risks of Antiplatelet Therapy

As noted above, patients treated with dual antiplatelet therapy for a year or more are at higher bleeding risk than patients treated with aspirin (or clopidogrel) alone. A recent meta-analysis which combined data from CREDO with other long-term dual antiplatelet trials (CURE, CHARISMA, and **MATCH (Management of Atherothrombosis with Clopidogrel in High-risk Patients)**) found that prolonged dual antiplatelet therapy was associated with a 80% increase in the relative risk of bleeding relative to monotherapy.[13] In light of these risks, the AHA/ACC currently recommend that dual therapy be continued for at least a year only in patients who are not at extremely high-risk of bleeding.

**BOTTOM LINE:** Patients who have undergone elective PCI should ideally receive clopidogrel plus aspirin for at least one year. A shorter-duration of treatment should be considered for patients at high-risk of bleeding. Whether or not to continue dual antiplatelet therapy beyond one year for patients at high-risk of late-stent thrombosis remains unclear.

## Stroke

### Benefits of antiplatelet therapy

#### *Monotherapy*

The use of aspirin in the acute management of ischemic stroke has been evaluated in trials of over 40,000 patients. In these patients, aspirin reduces the odds of a subsequent major vascular event by 11%.[2] The benefit of aspirin for

patients with a history of stroke or transient ischemic attack is also well established.[2]

The comparative value of clopidogrel vs. aspirin for patients with recent ischemic stroke was evaluated in the CAPRIE trial.[14] While the overall trial results support the use of clopidogrel over aspirin, in patients with stroke, clopidogrel was not significantly superior to aspirin and therefore its use is not generally recommended. The exception to this may be patients in high-risk subgroups (i.e., those with a history of bypass surgery, events involving multiple vascular beds, a history of more than one ischemic event, diabetes, or high cholesterol) who may benefit from clopidogrel.

The **European Stroke Prevention Study 2 (ESPS2)**[21] enrolled patients with ischemic stroke or TIA within the previous 3 months and found that both aspirin and dipyridamole as monotherapy were significantly better than placebo in preventing recurrent stroke.

### *Dual Therapy*

A variety of trials have compared aspirin or clopidogrel as monotherapy with either aspirin plus clopidogrel or aspirin plus dipyridamole.

**Table 2: Major studies compared antiplatelet monotherapy and combined therapy for patients with stroke.**

| Trial Name | Who was enrolled? | What was studied? | What was the primary efficacy outcome? | What were the main results? | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Prevention of vascular events | | | Risk of major bleeding | | |
| | | | | Monotherapy | Dual Therapy | Absolute difference | Monotherapy | Dual Therapy | Absolute difference |
| **MATCH** (Lancet 2004) | stroke or TIA within previous 3 months who also had ≥1 of prior stroke, prior MI, angina, DM, or symptomatic PVD (n=7,559) | **MONOTHERAPY**: clopidogrel **DUAL THERAPY:** aspirin + clopidogrel | ischemic stroke, MI, vascular death, re-hospitalization for acute ischemic event | 16.7% | 15.7% | Not significant | 1% | 2% | 1% |
| **CHARISMA** (NEJM 2006) | stroke or TIA within the previous 5 years (n=4,478)[1] | **MONOTHERAPY**: aspirin **DUAL THERAPY:** aspirin + clopidogrel | MI, stroke or death | 7.3%[2] | 6.8% | Not significant | 1.3% | 2.1% | 0.8% |
| **ESPS2** (J Neurol Sci 1996) | stroke or TIA within previous 3 months (n=3,299)[3] | **MONOTHERAPY**: aspirin **DUAL THERAPY:** aspirin + modified release dipyridamole | stroke | 12.9% | 9.9% | 3.3% | 0.1%[4] | 0.1% | Not significant |
| **ESPRIT** (Lancet 2006) | transient ischemic attack or a non-disabling ischemic stroke in the prior 6 months (n=2,739) | **MONOTHERAPY**: aspirin **DUAL THERAPY:** aspirin + dipyridamole | death from all vascular causes, non-fatal stroke, non-fatal MI[4] | 12.6% | 10.9% | 1.7% (borderline non-significant) | 3.9% | 2.6% | 1.3% (borderline non-significant) |
| **PRoFESS** (NEJM 2008) | ischemic stroke within 90 days of randomization (n=20,332) | **MONOTHERAPY**: clopidogrel **DUAL THERAPY:** aspirin + dipyridamole | stroke | 8.8% | 9.0% | Not significant | 3.6% | 4.1% | 0.5% |

[1]Patients with prior stroke or transient ischemic attack (TIA) only; [2]Overall trial results; [3]Patients treated with aspirin alone or aspirin plus dipyridamole only; [3]Major bleeding events were not reported; these rates reflect bleeding at any site, and any severity; [4]The study's primary outcome also included major bleeding complication.

In the MATCH trial, patients with a recent stroke or transient ischemic attack (TIA) who had a prior stroke, prior MI, angina, DM, or symptomatic peripheral arterial disease were randomized to clopidogrel 75 mg daily alone or in combination with aspirin 75 mg daily. It found that dual therapy was not superior to clopidogrel alone.[22]

Similarly, the CHARISMA trial, described above, included patients with a history of stroke or TIA within the past 5 years. It did not find any benefit of dual antiplatelet therapy compared to aspirin alone.[17] Although a post-hoc analysis

of patients enrolled in CHARISMA with ischemic stroke did reveal a significantly lower rate of ischemic events in patients treated with aspirin-clopidogrel than aspirin alone (8.7% v 10.4%, p=0.03), there were numerous such analyses that were not pre-planned at the start of the study, increasing the likelihood of an apparently significant finding occurring by chance alone. Therefore, in the context of the MATCH trial results, combining clopidogrel and aspirin for patients with a history of stroke or transient ischemic attack is not recommended.

The combination of aspirin and dipyridamole (Aggrenox) was compared to aspirin alone in ESPS2.[21] Aspirin plus dipyridamole significantly reduced the risk of recurrent stroke (relative risk reduction 23.1%, p=0.006) but only had a smaller impact on the composite end-point of stroke or death (relative risk reduction 12.9%, p=0.056).

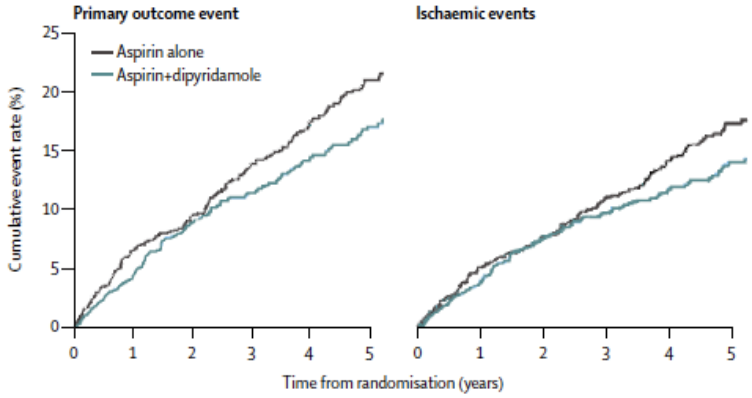



**Figure 5: –Rates of primary events (composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or a major bleeding complication) (left panel) or ischemic events (right panel) for patients treated with aspirin + dipyridamole and aspirin alone in the ESPRIT trial.**

Reproduced with permission from Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367: 1665-73.

More recently, the **European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT)**[23] randomized patients with a TIA or a non-disabling ischemic stroke in the prior 6 months to receive dipyridamole (200 mg twice daily, 83% used an extended-release formulation) plus aspirin (30 to 325 mg daily, mean dose 75 mg) or aspirin alone (30 to 325 mg daily, mean dose 75 mg). Patients taking combination therapy were less likely to have the primary outcome (a composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or a major bleeding complication) than patients treated with aspirin alone (13% v. 16%, $p < 0.05$), but the reduction in vascular events only reached modest statistical significance. Major bleeding complications occurred less frequently in patients treated with dipyridamole plus aspirin than aspirin alone, although these differences were not statistically significant.

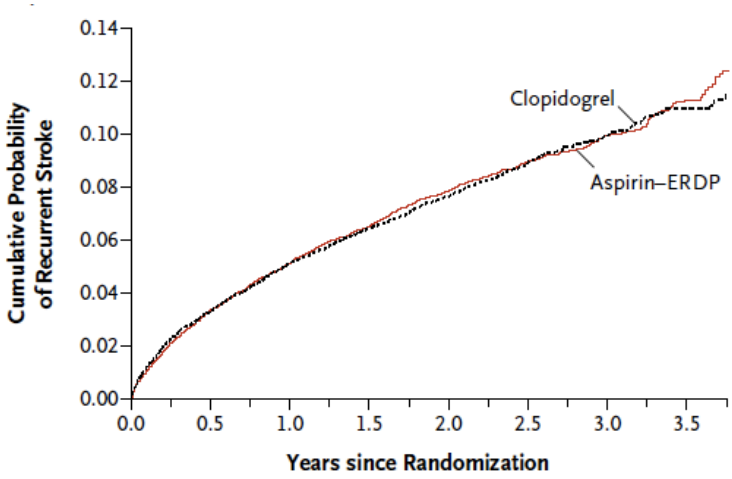



**Figure 6: From Rates of recurrence of stroke in patients in the PRoFESS trial treated with aspirin plus extended-release dipyridamole and clopidogrel.**



The **Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)** study[24] was the first trial to directly compare a twice-daily combination of aspirin 25 mg and extended-release dipyridamole 200 mg with 75 mg of clopidogrel daily for patients with a recent ischemic stroke. It found that the two treatments were equivalent in the prevention of recurrent stroke.

## Risks of antiplatelet therapy

In both the MATCH and CHARISMA trials, combining clopidogrel with aspirin caused higher rates of bleeding than aspirin monotherapy. Aspirin plus dipyridamole did not significantly increase the risk of bleeding is ESPS2; in ESPRIT, with a higher dose of aspirin, bleeding rates with aspirin-dipyridamole were increased, although the difference did not reach statistical significance (hazard ratio 0.67, 95% confidence interval 0.44 to 1.03).

In PRoFESS, patients in both treatment groups had similar rates of major bleeding, although rates of major hemorrhage were higher with aspirin-

dipyridamole than clopidogrel, including intracranial hemorrhage (hazard ratio, 1.42; 95% CI, 1.11 to 1.83)

**BOTTOM LINE:** Clopidogrel or combined aspirin-dipyridamole both appear effective for the prevention of recurrent vascular events in patients with recent stroke, although aspirin-dipyridamole might cause a slightly higher risk of bleeding. Clopidogrel should be particularly considered in high-risk stroke patients (bypass surgery, events involving multiple vascular beds, two or more ischemic events, diabetes, or high cholesterol), and in patients with aspirin allergy. Aspirin monotherapy is recommended for patients with a more remote history of stroke.

## Peripheral artery disease (PAD)

### Benefits of Antiplatelet Therapy

When given to patients with peripheral artery disease (PAD), aspirin reduces the odds of major vascular events by 23%.[2]

CAPRIE evaluated clopidogrel vs. aspirin in a pre-specified subgroup of patients with peripheral artery disease. Patients with intermittent claudication or who had undergone surgical revascularization or amputation clearly benefited from clopidogrel as compared to aspirin (see Figure 7).[14]

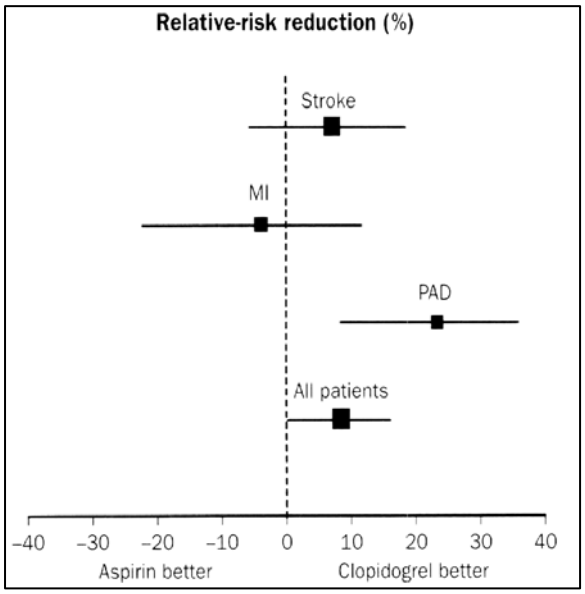



**Figure 7: Rates of recurrent vascular events in the CAPRIE trial broken down by inclusion criteria.**

Reproduced with permission from A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996; 348: 1329-39.

The use of dual antiplatelet therapy in patients with PAD was assessed in the CHARISMA trial and was found not to be superior to aspirin alone.[17] The lack of benefit from dual therapy was confirmed in a post-hoc subgroup analysis restricted to patients with symptomatic PAD.[25]

### Risks of antiplatelet therapy

The recommendation to use antiplatelet monotherapy for patients with PAD is reinforced by the risks associated with the risks of long-term dual antiplatelet therapy.

**BOTTOM LINE:** Antiplatelet monotherapy for PAD with clopidogrel is more effective than aspirin. Aspirin plus clopidogrel in combination is not superior to aspirin alone, and is associated with more side-effects.

## Cardiovascular risk factors but no known vascular disease

### Benefits of Antiplatelet Therapy

Six clinical trials involving more than 51,000 men and 44,000 women have evaluated the role of aspirin for the primary prevention of vascular disease (i.e., in patients who have not yet had a cardiovascular event). The results of a 2006 meta-analysis of these trials are summarized below.[26] It found that men appear to derive benefit from aspirin from a reduction in MI risk, whereas women derive benefit from a reduction in ischemic strokes. Aspirin was not found to reduce mortality in either men or women.

**Table 3: Meta-analysis results of randomized trials evaluating aspirin for primary prevention.[26]**

| Outcome | Odds ratio (95% confidence interval) from aspirin v. placebo | |
|---|---|---|
| | Men | Women |
| **All cardiovascular events** | **0.86 (0.78-0.94)** | **0.88 (0.79-0.99)** |
| Ischemic strokes | 1.00 (0.72-1.41) | 0.83 (0.70-0.97) |
| Myocardial infarction | 0.68 (0.54-0.86) | 1.01 (0.84-1.21) |
| Cardiovascular mortality | 0.99 (0.86-1.14) | 0.90 (0.64-1.28) |

A second meta-analyses of these trials was published in 2009 confirmed the relatively small benefits associated with aspirin when used for primary prevention,[27] especially in light of the risks associated with therapy (discussed below).

**Table 4: Recent studies of aspirin for primary prevention in patients with diabetes.**

| Trial Name | Who was enrolled? | What was studied and for how long? | What was the primary outcome? | What were the main results? | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Prevention of vascular events | | | Risk of major bleeding | | |
| | | | | Aspirin | Placebo | Absolute difference | Aspirin | Placebo | Absolute difference |
| **POPADAD (BMJ 2008)** | DM and an ankle-brachial index of ≤ 0.99 but no symptomatic cardiovascular disease (n=1,276) | aspirin 100 mg daily v. placebo (median follow-up 6.7 years) | fatal or non-fatal MI, fatal or non-fatal stroke or above ankle amputation for limb ischemia | 18.2% | 18.3% | not significant | 4.4% | 4.9% | not significant |
| **JPAD (BMJ 2008)** | DM but no symptomatic cardiovascular disease (n=2,539) | aspirin 81 or 100 mg daily v. placebo (median follow-up 4.4 years) | any atherosclerotic event* | 5.4% | 6.7% | not significant | 0.003 | 0 | not significant |

* death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis)

Further controversy about aspirin's role in primary prevention arose in 2008 with the publication of the **Prevention of Progression of Arterial Disease and Diabetes (POPADAD)**[28] and **Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD)**[29] studies (see Table 4). Both evaluated patients with diabetes, which is often considered to be a coronary artery disease "risk equivalent"; aspirin has generally been recommended for most patients with diabetes, including those without known vascular disease. While in JPAD, deaths from MI or stroke were significantly reduced in the low-dose aspirin group (1 death vs. 10 deaths, p = 0.0037), neither trial found reductions in vascular events or mortality.

No trials have evaluated clopidogrel monotherapy for the primary prevention of vascular events. CHARISMA, which evaluated dual antiplatelet therapy in patients with multiple vascular risk factors,[17] found no additional benefit of combining clopidogrel and aspirin compared to aspirin alone.

## Risks of Antiplatelet Therapy

The meta-analyses of the 6 trials evaluating aspirin for primary prevention confirm the risks associated with even low-dose aspirin. In these trials, aspirin increased the risk of bleeding in both women (odds ratio 1.68; 95% CI, 1.13-2.52) and men (odds ratio 1.72; 95% CI, 1.35-2.20).[26] Thus, the harms of aspirin may outweigh the benefits for many low-risk primary prevention patients.[27]

Consistent with this, the 2009 United States Preventive Services Task Force (USPSTF) guidelines on aspirin use for primary prevention recommends an explicit assessment of a patient's cardiovascular risk before prescribing aspirin for primary prevention. Several tools are available to assist in such risk assessment (e.g., **www.med-decisions.com**). A summary of the 2009 USPSTF guidelines is presented in Figure 8.

**BOTTOM LINE:** Because of the bleeding risk caused by antiplatelet therapy, aspirin should be prescribed for primary prevention only in patients for whom the benefits of therapy outweigh their harms. Some patients who receive aspirin for primary prevention (e.g. low-risk diabetes) may derive less benefit than traditionally believed.

Figure 8: 2009 USPSTF guidelines for the use of aspirin to prevent cardiovascular disease


## ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR DISEASE
## CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

| Population | Men Age 45-79 Years | Women Age 55-79 Years | Men Age < 45 Years | Women Age < 55 Years | Men & Women Age ≥ 80 Years |
|---|---|---|---|---|---|
| Recommendation | Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage | Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage | Do not encourage aspirin use for MI prevention | Do not encourage aspirin use for stroke prevention | No Recommendation |
| | GRADE: A | | GRADE: D | | GRADE: I (Insufficient Evidence) |

**How to Use This Recommendation**

Shared decision making is strongly encouraged with individuals whose risk is close to (either above or below) the estimates of 10-year risk levels indicated below. As the potential CVD benefit increases above harms, the recommendation to take aspirin should become stronger.

To determine whether the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage, both 10-year CVD risk and age must be considered.

| Risk level at which CVD events prevented (benefit) exceeds GI harms | | | |
|---|---|---|---|
| Men | | Women | |
| 10-year CHD risk | | 10-year stroke risk | |
| Age 45 – 59 years | ≥ 4% | Age 55 – 59 years | ≥ 3% |
| Age 60 – 69 years | ≥ 9% | Age 60 – 69 years | ≥ 6% |
| Age 70 – 79 years | ≥ 12% | Age 70 – 79 years | ≥ 11% |

**The table above applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers.**
NSAID use and history of GI ulcers raise the risk of serious GI bleeding considerably and should be considered in determining the balance of benefits and harms.
NSAID use combined with aspirin use approximately quadruples the risk of serious GI bleeding compared to the risk with aspirin use alone.
The rate of serious bleeding in aspirin users is approximately 2 – 3 times higher in patients with a history of GI ulcers.

**Risk Assessment**

**For MEN:** Risk factors for CHD include age, diabetes, total cholesterol level, HDL level, blood pressure, and smoking.
**CHD risk estimation tool:** http://healthlink.mcw.edu/article/923521437.html

**For WOMEN:** Risk factors for ischemic stroke include age, high blood pressure, diabetes, smoking, history of CVD, atrial fibrillation, and left ventricular hypertrophy.
**Stroke risk estimation tool:** http://www.westernstroke.org/PersonalStrokeRisk1.xls

**Relevant Recommendations from the USPSTF**

The USPSTF has made recommendations on screening for abdominal aortic aneurysm, carotid artery stenosis, coronary heart disease, high blood pressure, lipid disorders, and peripheral arterial disease. These recommendations are available at www.preventiveservices.ahrq.gov.

For the full recommendation statement and supporting documents, please go to: www.preventiveservices.ahrq.gov. Abbreviations: CHD = coronary heart disease, CVD = cardiovascular disease,

## Benefits of Antiplatelet Therapy

Several scoring systems, such as the $CHADS_2$ scale, can help identify which AF patients are at high risk of stroke. In the absence of contraindications, warfarin is the standard therapy for thromboembolism prophylaxis is such high-risk patients, and can reduce the risk of stroke by an impressive two-thirds.[30]

While less effective than warfarin, aspirin does reduce the relative risk of stroke by about 21% in AF patients (about one-third of the risk reduction that warfarin provides).[30] The combination of clopidogrel and aspirin was compared with warfarin in the **Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W)** trial.[31] This trial randomized 6,700 patients with AF at increased risk of stroke to receive either warfarin (for a target INR goal of 2.0 to 3.0) or clopidogrel (75 mg per day) plus aspirin (75-100 mg per day). The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. Rates of major hemorrhage were similar in the two groups although patients treated with clopidogrel plus aspirin had significantly more minor bleeding episodes.

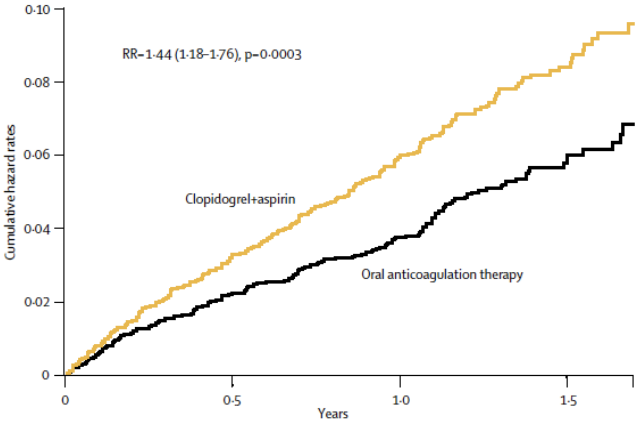



**Figure 9: Rates of the primary outcome (stroke, non-CNS systemic embolus, myocardial infarction, or vascular death) for patients treated with clopidogrel plus aspirin and warfarin in the ACTIVE W trial.**

Reproduced with permission from Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367: 1903-12.

Despite this data, patient preference, bleeding risk and other factors sometimes may make the use of warfarin less attractive. The use of dual antiplatelet therapy with clopidogrel and aspirin in such patients was recently evaluated in the **Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A)** study.[32] This trial enrolled more than 7,500 patients with atrial fibrillation at increased risk of stroke in whom warfarin was felt to be "unsuitable" (because of bleeding risk, a physician's judgment, or patient preference). Patients were randomized to clopidogrel plus aspirin or aspirin alone. The rate of major vascular events was substantially reduced with dual

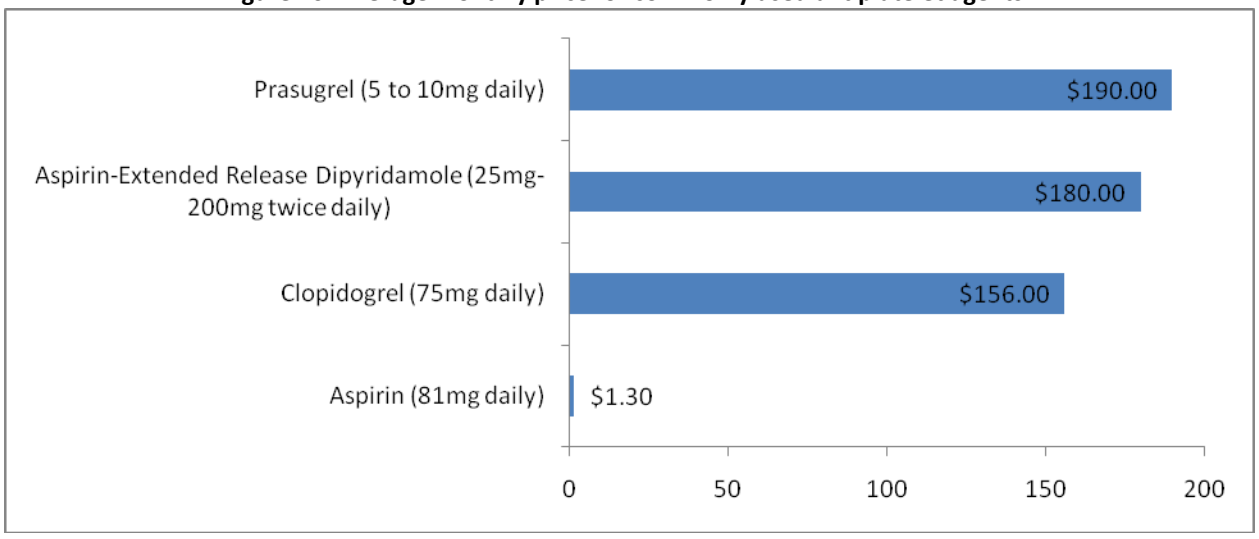
antiplatelet therapy (6.8% v. 7.5% per year, p=0.01) primarily due to a reduction in the rate of stroke (2.4% per year for patients treated with dual therapy and 3.3% per year in patients treated with aspirin alone). While dual therapy did not significantly lower rates of myocardial infarction, rates of major bleeding were increased (2.0% v. 1.3% per year, p<0.001).

**BOTTOM LINE:** In the absence of a contraindication, warfarin is the most effective therapy to prevent atrial fibrillation-associated stroke in medium- or high-risk patients, lowering the stroke risk by two-thirds. Dual antiplatelet therapy appears to be more effective than aspirin monotherapy in those patients for whom warfarin is unsuitable, but also increases the risk of bleeding.

## Costs

While the evidence provides relatively clear evidence about the choice of antiplatelet evidence in various clinical situations, there are substantial price differences between different agents. These differences are particularly relevant when choosing between agents that are probably equally effective or equally safe.

**Figure 10: Average monthly price for commonly used antiplatelet agents.**




Prices from www.drugstore.com

## Miscellaneous clinical issues

### Aspirin dose

The optimal dose of aspirin will maximize preventive efficacy and minimize bleeding risk. Several trials comparing lower dose (< 75 mg daily) with higher dose (≥ 75 mg daily) have not found any difference in efficacy.[2] Similarly, in CURE, aspirin at doses ≤ 100 mg was as effective as higher doses (both in patients treated with clopidogrel and those who received placebo).[12] Therefore, doses of aspirin between 81 and 162 mg daily are generally recommended.[33, 34]

### Do NSAIDs interact with aspirin?

In vivo studies have found that administering some non-steroidal anti-inflammatory drugs along with aspirin antagonizes aspirin's capacity to inhibit platelet activity.[35] Several clinical studies have been performed that suggest that patients taking ibuprofen and aspirin together on a consistent basis may be at higher risk of cardiovascular events than patients taking aspirin alone[36, 37] or aspirin and other NSAIDs.[36] As a consequence, the AHA-ACC recommends against the use of ibuprofen in patients taking aspirin.[15]

### Other Side Effects

Ticlopidine (Ticlid), an ADP-receptor antagonist that is chemically similar to clopidogrel, causes thrombotic thrombocytopenic purpura (TTP).[38] Because of this and dose-related neutropenia, ticlopidine is rarely used. No cases of TTP were observed in patients who received clopidogrel in the CAPRIE trial or other early trials of clopidogrel. Subsequently, post-marketing surveillance has identified 11 cases of TTP among the more than 3 million people who have used this drug.[38] Therefore, while clopidogrel may rarely cause TTP, this side effect is very rare, and generally occurs within the first two weeks after initiating therapy.[38]

### Aspirin and Clopidogrel resistance

Platelet-dependent thrombosis can occur despite treatment with aspirin[39] and clopidogrel.[40] These phenomenon has been termed "aspirin resistance" and "clopidogrel resistance," and may be the result of a variety of causes including poor adherence, inadequate dosage, and coexisting medical

conditions. It is also apparent that genetic factors play a major role in resistance.[41]

The responsible genetic variant for clopidogrel resistance occurs in an enzyme responsible for the metabolism of the drug. Clopidogrel is a pro-drug that requires activation by specific hepatic cytochrome P-450 (CYP) enzymes. Studies have shown that carriers of the specific alleles of CYP2C19 and CYP3A4 have a diminished response to the effects of clopidogrel.[41-47]

There is some tentative evidence that the concomitant use of a proton-pump inhibitor might decrease the platelet inhibitory effect of clopidogrel, because both drugs are metabolized by CYP2C19.[41] Two retrospective studies have found rates of re-hospitalization for ACS patients treated with clopidogrel and a PPI to be increased by about 25%.[48, 49] Of note, the subgroup of patients in one of these studies who received pantoprazole, which does not inhibit CYP 2C19, did not have a higher rate of adverse cardiovascular events.[49] One prospective study showed that PPIs did not affect clinical response to clopidogrel.[46] Most recently, a large retrospective trial found using advanced analytic techniques found a slightly increased risk of MI or death in older patients initiating both clopidogrel and a PPI although the risk was unlikely to be of major clinical relevance.[50]

Given these conflicting findings, the clinical significance of a PPI-clopidogrel interaction remains unclear. No prospective randomized controlled trial has shown that a PPI used in conjunction with clopidogrel causes an increased risk of adverse cardiovascular outcomes. **A prudent strategy while awaiting more definitive data would be to limit the use of PPIs to those clopidogrel-treated patients at the highest risk of adverse gastrointestinal events**.

## Putting it all together

The trial literature is complex because different studies have enrolled varying types of patients and measured different outcomes. However, a review of the literature suggests the following strategy:

| Condition | Recommended Treatment | Evidence |
|---|---|---|
| **Acute coronary syndromes [Unstable angina, non-ST-segment elevation MI (NSTEMI), and ST-segment elevation MI (STEMI)]** | CLOPIDOGREL + ASPIRIN for at least 1 year. PRASUGREL + ASPIRIN for 15 months may be a superior alternative for some non-elderly ACS patients who have undergone PCI. | CURE, COMMIT, CLARITY, CHARISMA, CAPRIE, TRITON |
| **Past MI** | CLOPIDOGREL for high-risk patients*, ASPIRIN for all others | CHARISMA, CAPRIE |
| **Stable angina** | ASPIRIN | Antiplatelet Trialists Collaboration, CHARISMA |
| **Elective PCI** | CLOPIDOGREL + ASPIRIN for at least a year | CREDO |
| **Stroke** | CLOPIDOGREL or ASPIRIN + DIPYRIDAMOLE | MATCH, CHARISMA, ESPS2, ESPRIT, PRoFESS |
| **Peripheral artery disease** | CLOPIDOGREL | CHARISMA, CAPRIE |
| **Primary prevention** | ASPIRIN only for patients in whom benefits outweigh risks | POPADAD, JPAD, USPSTF |

***High risk patients:** history of coronary artery disease, stroke, or TIA, **and** any of the following: bypass surgery, events involving multiple vascular beds, two or more ischemic events, diabetes, or high cholesterol.

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