



Anti-platelet therapy:

aspirin or clopidogrel (Plavix)?

...or both?

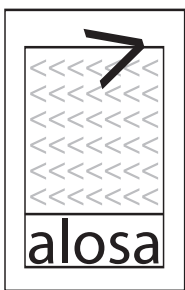
...or neither?

... and what about
dipyridamole-aspirin
(Aggrenox) and the new
prasugrel (Effient)?

Which is right for which patients?

Since the discovery that low-dose aspirin can reduce the risk of heart attack, anti-platelet agents have become an increasingly important tool for preventing cardiovascular events. While aspirin is the most widely used and best studied anti-platelet agent, the use of clopidogrel (Plavix) and combination dipyridamole-aspirin (Aggrenox) have increased substantially in recent years, and a 2007 study introduced a new agent, prasugrel (Effient). Heavy marketing to physicians and direct-to-consumer advertising have made Plavix the second best-selling drug in the world. But how do the efficacy and safety of these newer drugs compare to aspirin? At a much higher cost (\$160 per month for clopidogrel and \$180 per month for dipyridamole-aspirin), when should these drugs routinely be used to replace aspirin at \$1.30 per month?

A number of large randomized controlled trials have evaluated various antiplatelet regimens, and have produced widely varying results for different clinical conditions. The major studies are reviewed below, along with their implications for practice.



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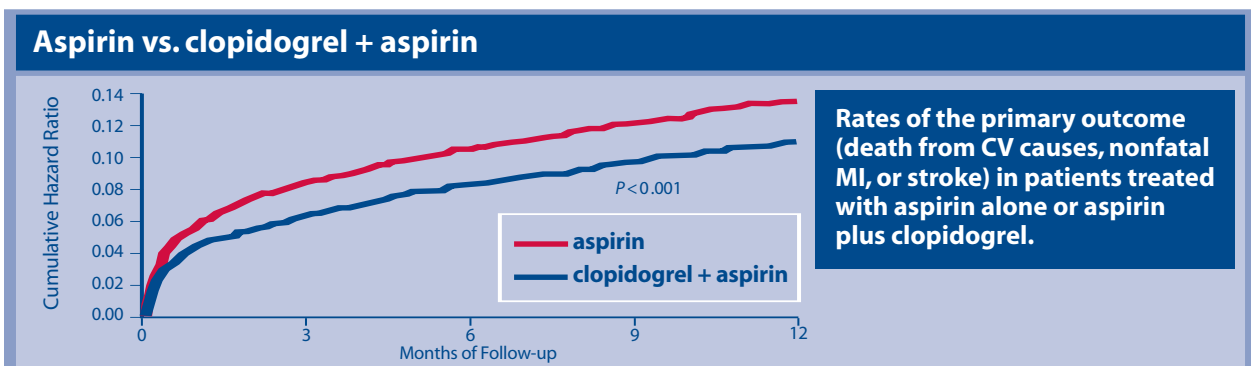
Balanced data about medications



Acute coronary events and interventions

Acute coronary syndromes (ACS): The **CURE**, **COMMIT**, and **CLARITY** trials showed that the combination of clopidogrel and aspirin is more effective than aspirin alone for patients with unstable angina or who have had a myocardial infarction (both non-ST-segment elevation MI (“NSTEMI”) and ST-elevation MI (“STEMI”)).^{1,2,3} Combining aspirin and clopidogrel does not appear to increase the risk of bleeding in the short-term, but longer-term trials all found substantially higher risks of bleeding with this dual therapy⁴; therefore, the combination should be used with caution in patients for whom the benefits of this approach do not clearly outweigh their risks.

Figure 1. Aspirin alone vs. clopidogrel + aspirin in ACS without ST-elevation in the CURE trial.



Reproduced with permission from Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *NEJM* 2001;345:494-502. Copyright © 2009 Massachusetts Medical Society. All rights reserved.

A new antiplatelet agent, prasugrel (Effient), when combined with aspirin was recently found to be superior to clopidogrel combined with aspirin in ACS patients who underwent percutaneous coronary intervention (PCI) (rate of primary study end point: 9.9% v. 12.1%, $p < 0.001$).⁵ The combination of prasugrel and aspirin also caused a higher risk of major bleeding than clopidogrel plus aspirin (2.4% v. 1.8%, $p = 0.03$). However, some patients, such as those with a low body weight, age ≥ 75 , or a history of stroke, appeared to benefit less and had higher risks of bleeding; these subgroups are less likely to benefit from this new combination.

Elective percutaneous coronary intervention (PCI): Dual antiplatelet therapy with clopidogrel and aspirin is the standard of care for patients undergoing elective PCI. A common duration of treatment is up to 12 months⁶ though the upper limit of duration has not been defined. There is ongoing debate about whether the benefits of prolonged antiplatelet therapy outweigh its risks.

In patients with ACS or elective PCI, there is good evidence for use of clopidogrel + aspirin for at least 1 year. Prasugrel + aspirin for 15 months may be a better alternative for some ACS patients who have undergone PCI, but the benefit-risk profile is worse with this drug for some patient groups, including those who are older or weigh less.

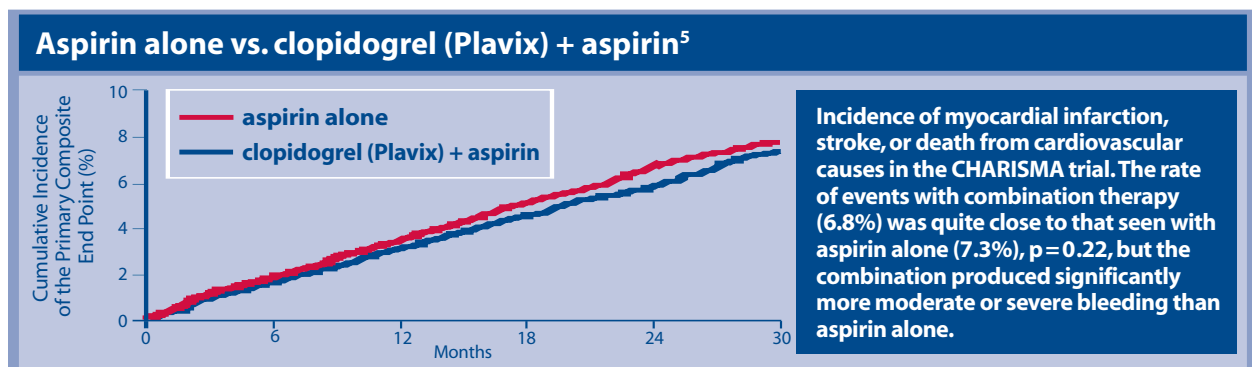


Stable coronary artery disease

The value of dual antiplatelet therapy is less clear for patients with stable coronary artery disease (including those with stable angina and a history of MI).

In the **CHARISMA** trial⁷ of patients with symptomatic vascular disease (including a history of MI and stable angina) or multiple risk factors, combining clopidogrel with aspirin produced vascular outcomes that were equivalent to those seen with aspirin alone. 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 and must be interpreted cautiously in light of the higher rate of bleeding these patients experienced (see below).

Figure 2. Aspirin vs. clopidogrel + aspirin in the CHARISMA study.



Adapted from Figure 1 in Bhatt DL, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* Apr 20 2006; 354(16):1706-1717.

The **CAPRIE** trial found only minimal differences between aspirin and clopidogrel in patients with recent, but not acute, MI.^{8,9}

However, there were some subgroups of patients in the CAPRIE trial who seemed to benefit more from clopidogrel than from aspirin, though many of these subgroups were defined after the study was completed. Clopidogrel (Plavix) may be a reasonable choice in such patients: those with a 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.¹⁰

There is little evidence to support the routine use of clopidogrel for most post-MI patients whose infarcts are not recent.⁹ In most patients with stable coronary artery disease, it is reasonable to reserve clopidogrel for high-risk patients, and use aspirin for all others.



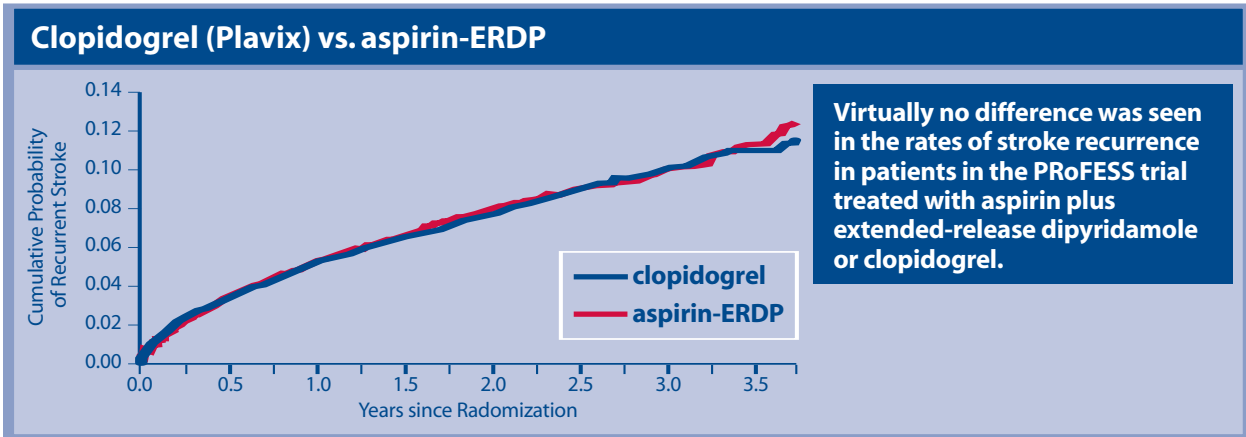
Stroke

For patients who have had a stroke or a transient ischemic attack, several trials have compared aspirin or clopidogrel alone with an aspirin-clopidogrel or aspirin-dipyridamole combination.^{7,11-14} Here is a summary of their results:

Table 1. Antiplatelet agents for stroke prevention.

Dual Therapy with:	EFFICACY	BLEEDING	Compared to:
Aspirin plus clopidogrel	equal to	more than	Aspirin alone
	equal to	more than	Clopidogrel alone
Aspirin plus dipyridamole	better than	equal to	Aspirin alone
	equal to	more than	Clopidogrel alone

Figure 3. Clopidogrel vs. aspirin-extended release dipyridamole (ERDP) in stroke prevention.



Reproduced with permission from Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *NEJM* 2008; 359: 1238-51. Copyright © 2009 Massachusetts Medical Society. All rights reserved.

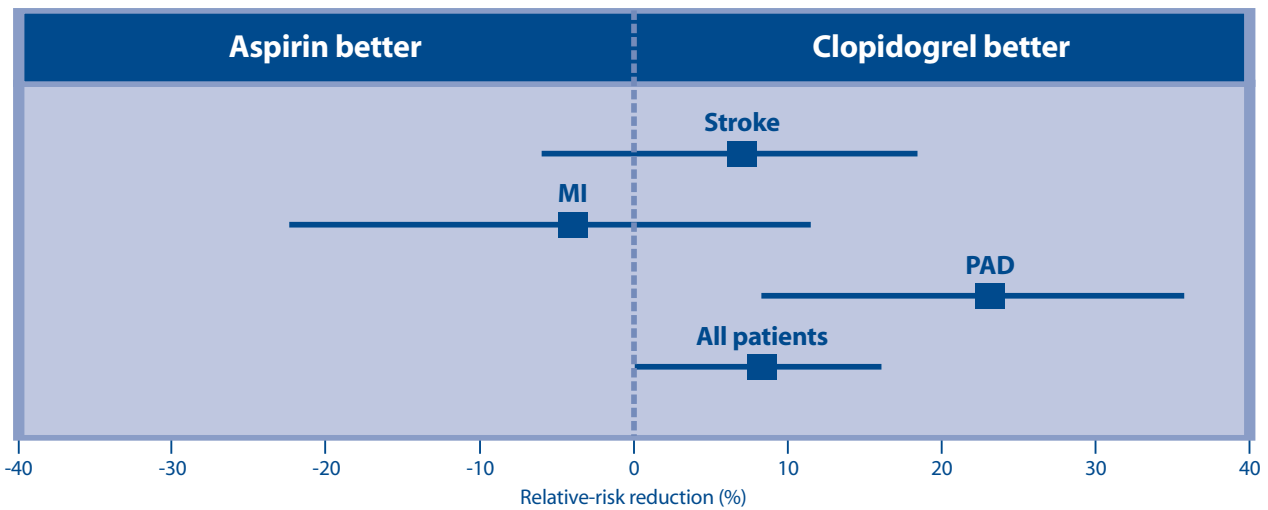
In patients with ischemic stroke or TIA within the prior 3 months, the evidence favors clopidogrel or aspirin-dipyridamole. Use aspirin for most patients with a more remote history of stroke.



Peripheral arterial disease (PAD)

The CAPRIE trial indicated that clopidogrel is more effective than aspirin for patients with severe PAD.⁸ However the CHARISMA trial assessed an aspirin-clopidogrel combination in these patients and found that it was no better than aspirin alone.⁷

Figure 4. Clopidogrel vs. aspirin for vascular events in the CAPRIE study.



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

An overview of these trials warrants using clopidogrel monotherapy in patients with PAD.

Primary prevention

Six large trials 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 meta-analysis of these trials are summarized below.¹⁵ While the use of aspirin is one of the most time-honored means of preventing MI, recent studies suggest that its use is not as simple a decision as it once seemed to be, especially for patients without existing heart disease and/or an increased risk of bleeding. Further, **all antiplatelet agents increase the risk of gastrointestinal and intracranial bleeding, even aspirin at low doses.**¹⁶



Table 2. Meta-analysis results of randomized trials evaluating aspirin for primary prevention.¹⁵

Outcome	Odds ratio (95% confidence interval) of outcome for aspirin vs. 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)

An odds ratio of 0.86 indicates that patients in the treated group would experience just 86% the risk of having the outcome studied, compared to controls; meaning a 14% reduction in risk.

In primary prevention, men derive benefit from aspirin mostly from a reduction in MI risk, whereas women derive a more modest benefit, attributable to a reduction in ischemic stroke. Aspirin does not reduce mortality in primary prevention for either men or women.

The modest benefit from the use of aspirin for primary prevention must be weighed against its risks. For many low-risk primary prevention patients, these risks may outweigh benefits¹⁷ The most recent (2009) United States Preventive Services Task Force (USPSTF) guidelines recommend considering a patient’s cardiovascular risk before recommending aspirin for primary prevention. Tools for assessing a patient’s 10-year risk of coronary heart disease and stroke can be found at www.med-decisions.com and <http://www.westernstroke.org/PersonalStrokeRisk1.xls>, respectively. Current USPSTF recommendations are provided in the following figure.

Figure 5. Risk/benefit of aspirin in primary prevention.

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	≥ 8%
Age 70-79 years	≥ 12%	Age 70-79 years	≥ 11%

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 above. 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.

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.



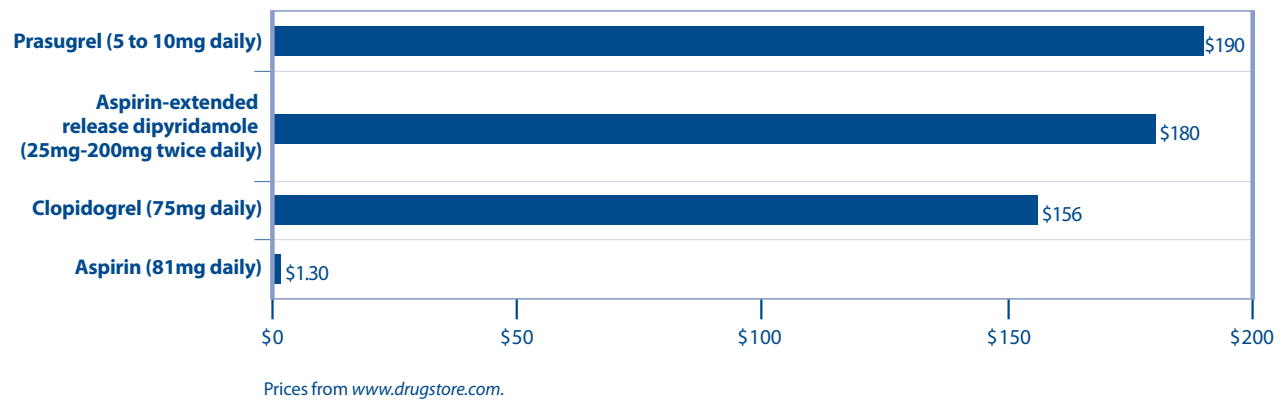
Because of the bleeding risk caused by antiplatelet therapy, aspirin should be prescribed for primary prevention in patients for whom the benefits of therapy outweigh its potential harm.

The economics are striking

The cost of clopidogrel (Plavix), dipyridamole-aspirin (Aggrenox) and prasugrel (Effient) are more than 100 times that of aspirin. Despite this, it can still be economically reasonable to prescribe these drugs in appropriately chosen patients. For example, one economic analysis found that clopidogrel (Plavix) used alone in patients with peripheral vascular disease appears to be highly cost-effective.⁹

Differences in cost may be particularly relevant when choosing between agents that are equally effective or equally safe. **This is especially important in patients for whom an unaffordable drug will result in non-compliance.**

Figure 6. Average monthly price for commonly used antiplatelet agents.



Summary of recommendations

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

Figure 7. Recommended treatments for cardiovascular conditions.

Condition	Recommended Treatment	Evidence
Acute coronary syndromes	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 are defined as: 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.

References: 1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* Aug 16 2001;345(7):494-502. 2. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* Nov 5 2005;366(9497):1607-1621. 3. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med.* Mar 24 2005;352(12):1179-1189. 4. Bowry AD, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. *Am J Cardiol.* Apr 1 2008;101(7):960-966. 5. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* Nov 15 2007;357(20):2001-2015. 6. Steinhubl SR, Berger PB, Mann JT, 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* Nov 20 2002;288(19):2411-2420. 7. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* Apr 20 2006;354(16):1706-1717. 8. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet.* Nov 16 1996;348(9038):1329-1339. 9. Schleinitz MD, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. *Am J Med.* Jun 15 2004;116(12):797-806. 10. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the CAPRIE and CURE studies. *Arch Intern Med.* Oct 25 2004;164(19):2106-2110. 11. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* Jul 24-30 2004;364(9431):331-337. 12. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* Nov 1996;143(1-2):1-13. 13. 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.* May 20 2006;367(9523):1665-1673. 14. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med.* Sep 18 2008;359(12):1238-1251. 15. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA.* Jan 18 2006;295(3):306-313. 16. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ.* Apr 1 1995;310(6983):827-830. 17. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* May 30 2009;373(9678):1849-1860.

Additional references documenting these recommendations are provided in the evidence document accompanying this material.

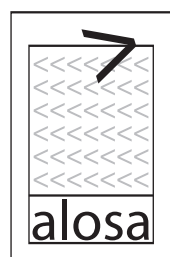
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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.



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