The Primary and Secondary Prevention of Coronary Artery Disease*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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The following chapter devoted to antithrombotic therapy for chronic coronary artery disease (CAD) is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do or do not outweigh risks, burden, and costs. Grade 2 suggests that individual patient values may lead to different choices (for a full understanding of the grading see the "Grades of Recommendation" chapter by Guyatt et al in this supplement, *CHEST* 2008; 133[suppl]: 123S–131S). Among the key recommendations in this chapter are the following: for patients with non–ST-segment elevation (NSTE)-acute coronary syndrome (ACS) we recommend daily oral aspirin (75–100 mg) [Grade 1A]. For patients with an aspirin allergy, we recommend clopidogrel, 75 mg/d (Grade 1A). For patients who have received clopidogrel and are scheduled for coronary bypass surgery, we suggest discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A). For patients after myocardial infarction, after ACS, and those with stable CAD and patients after percutaneous coronary intervention (PCI), we recommend daily aspirin (75–100 mg) as indefinite therapy (Grade 1A). We recommend clopidogrel in combination with aspirin for patients experiencing ST-segment elevation (STE) and NSTE-ACS (Grade 1A). For patients with contraindications to aspirin, we recommend clopidogrel as monotherapy (Grade 1A). For long-term treatment after PCI in patients who receive antithrombotic agents such as clopidogrel or warfarin, we recommend aspirin (75 to 100 mg/d) [Grade 1B]. For patients who undergo bare metal stent placement, we recommend the combination of aspirin and clopidogrel for at least 4 weeks (Grade 1A). We recommend that patients receiving drug-eluting stents (DES) receive aspirin (325 mg/d for 3 months followed by 75–100 mg/d) and clopidogrel 75 mg/d for a minimum of 12 months (Grade 2B). For primary prevention in patients with moderate risk for a coronary event, we recommend aspirin, 75–100 mg/d, over either no antithrombotic therapy or vitamin K antagonist (Grade 1A).
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Key words: atherosclerosis; primary prevention; secondary prevention; thrombosis

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; BMS = bare metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; DES = drug-eluting stent; IHD = ischemic heart disease; IMA = internal mammary artery; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; MIDCAB = minimally invasive direct coronary artery bypass; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; NSTE = non–ST-segment elevation; OPCAB = off-pump coronary artery bypass; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; QALY = quality of life year; RCT = randomized clinical trial; RR = relative risk; RRR = relative risk reduction; SC = subcutaneous; SK = streptokinase; STE = ST-segment elevation; TE = thromboembolism; TIA = transient ischemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

1.1.1. For patients with ACS with and without STE, we recommend aspirin initially at a dose of 75–162 mg and then indefinitely at a dose of 75–100 mg/d (Grade 1A).

1.1.2. For patients with STE ACS, with or without fibrinolytic therapy, we recommend clopidogrel as a 300-mg oral loading dose for patients ≤ 75 years of age and 75-mg starting dose for those > 75 years of age, and continued at a daily dose of 75 mg for 2–4 weeks (Grade 1A). **We suggest continuing clopidogrel for up to 12 months following hospital discharge** (Grade 2B).

1.1.3. For patients with NSTE ACS, we recommend combination therapy with aspirin (75–100 mg/d) and clopidogrel (75 mg/d) for 12 months (Grade 1A).

1.1.4. For patients in whom aspirin is contraindicated or not tolerated, we recommend clopidogrel monotherapy (75 mg/d) [Grade 1A].

1.1.5. For patients with symptomatic CAD, we suggest aspirin (75–100 mg/d) in combination with clopidogrel (75 mg/d) [Grade 2B].

Values and preferences: This recommendation places a high value on the probable small reduction in arterial vascular risk consequent on adding clopidogrel to aspirin and a low value on avoiding the additional bleeding and high cost associated with clopidogrel.

2.1. For most patients (all except the high-risk group described in Recommendation 2.2 below) in most health-care settings, following ACS, we recommend aspirin alone (75–100 mg daily) over oral vitamin K antagonists (VKAs) alone or in combination with aspirin (Grade 1B).

Values and preferences: This Recommendation places a

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relatively low value on prevention of thromboembolism, and a relatively high value on avoiding the inconvenience, expense, and bleeding risk associated with VKA therapy.

2.1.1. For most patients after MI, in health-care settings in which meticulous international normalized ratio (INR) monitoring and highly skilled VKA dose titration are expected and widely accessible, we suggest long-term (up to 4 years) high-intensity oral VKA (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral VKA (target INR, 2.5; range 2.0 to 3.0) with aspirin (≤ 100 mg/d) over aspirin alone (both Grade 2B).

2.2. For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on transthoracic echocardiography, those with atrial fibrillation and those with a history of a thromboembolic event, we suggest the combined use of moderate-intensity (INR, 2.0 to 3.0) oral VKA plus low-dose aspirin (≤ 100 mg/d) for at least 3 months after the MI (Grade 2A).

2.4. For long-term treatment of patients after percutaneous coronary intervention (PCI), we recommend aspirin at a dose of 75–100 mg/d (Grade 1A).

2.4.1. For patients undergoing PCI with bare metal stent (BMS) placement, we recommend aspirin (75–100 mg/d) plus clopidogrel over aspirin alone (Grade 1A).

2.4.1.1. For patients undergoing PCI with BMS placement following ACS, we recommend 12 months of aspirin (75–100 mg/d) plus clopidogrel (75 mg/d) over aspirin alone (Grade 1A).

2.4.1.2. For patients undergoing PCI with a DES, we recommend aspirin (75–100 mg/d) plus clopidogrel (75 mg/d for at least 12 months) [Grade 1A for 3 to 4 months; Grade 1B for 4 to 12 months]. **Beyond 1 year, we suggest continued treatment with aspirin plus clopidogrel indefinitely if no bleeding or other tolerability issues** (Grade 2C).

2.4.2. For patients undergoing stent placement with a strong concomitant indication for VKA, we suggest triple antithrombotic therapy (Grade 2C). **We suggest 4 weeks of clopidogrel following BMS and 1 year following DES** (Grade 2C).

Values and preferences: This recommendation places a high value on the prevention of thromboembolism, including stent thrombosis, and a lower value on minimizing bleeding risk.

For recommendations on the use of antiplatelet agents in other patient populations with atrial fibrillation, see the "Antithrombotic Therapy in Atrial Fibrillation" chapter.

2.5. For patients after stent placement, we suggest clopidogrel (Grade 1A) or ticlopidine (Grade 2B) over cilostazol. We recommend clopidogrel over ticlopidine (Grade 1A).

2.5.1. For aspirin-intolerant patients undergoing PCI, we recommend use of a thienopyridine derivative rather than dipyridamole (Grade 1B).

2.6. For patients who undergo PCI with no other indication for VKA, we recommend against VKA (Grade 1A).

3.1. In patients with congestive heart failure due to a nonischemic etiology, we recommend against routine use of aspirin or oral VKA (Grade 1B).

4.1.5. For all patients with CAD undergoing coronary artery bypass grafting (CABG), we recommend aspirin, 75 to 100 mg/d, indefinitely (Grade 1A). We suggest that the aspirin be started postoperatively (Grade 2A).

4.1.6. For patients undergoing CABG, we recommend against addition of dipyridamole to aspirin therapy (Grade 1A).

4.1.8. For patients with CAD undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/d po indefinitely (Grade 1B).

4.1.8.1. In patients who undergo CABG following NSTE-ACS, we suggest clopidogrel, 75 mg/d, for 9 to 12 months following the procedure in addition to treatment with aspirin (Grade 2B).

4.1.8.2. For patients who have received clopidogrel for ACS and are scheduled for CABG, we suggest discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A).

4.1.10. For patients undergoing CABG who have no other indication for VKA, we recommend clinicians not administer VKAs (Grade 1C).

4.1.10.1. For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKA in addition to aspirin (Grade 2C).

4.2.1. For all patients with CAD who undergo internal mammary artery (IMA) bypass grafting, we recommend aspirin, 75 to 162 mg/d, indefinitely (Grade 1A).

4.2.2. For all patients undergoing IMA bypass grafting who have no other indication for VKAs, we recommend against using VKAs (Grade 1C).

5.0. For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%), we recommend 75–100 mg/d of aspirin over either no antithrombotic therapy or VKA (Grade 2A).

5.1. For patients at particularly high risk of events in whom INR can be monitored without difficulty, we suggest low-dose VKA with a target INR of approximately 1.5 over aspirin therapy (Grade 2A).

5.3. For all patients we recommend against the routine addition of clopidogrel to aspirin therapy in primary prevention (Grade 1A). For patients with an aspirin allergy who are at moderate to high risk for a cardiovascular event, we recommend monotherapy with clopidogrel (Grade 1B).

5.4. For women < 65 years of age who are at risk for an ischemic stroke, and in whom the concomitant risk of major bleeding is low, we suggest aspirin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2A).

5.4.1. For women > 65 years of age at risk for ischemic stroke or MI, and in whom the concomitant risk of major bleeding is low, we suggest asprin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2B).

Values and preferences: The recommendation of aspirin over VKA places a relatively low value on a small absolute reduction in coronary events and deaths and a relatively high value on avoiding the inconvenience, cost, and minor bleeding risk associated with oral VKA. The low target INR value required in primary prevention typically mandates less frequent monitoring; on average every 2 to 3 months and is associated with lower risk of bleeding.

Patients, particularly those in the highest risk groups for whom systems permitting meticulous monitoring of anticoagulant therapy are available, who place a relatively high value on small absolute risk reductions in coronary events and are not influenced by an element of inconvenience and potential bleeding risk associated with VKA are likely to derive the greatest overall benefit from administration of VKA rather than aspirin.

Antithrombotic therapy is a mainstay in the management of patients with either acute or chronic coronary artery disease (CAD). The following chapter is devoted to the subject of chronic CAD and antithrombotic strategies designed for primary and secondary prevention of cardiovascular events.

The *ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non-ST Segment Elevation Myocardial Infarction* reflect a management-oriented nomenclature.[1] Patients with acute myocardial ischemia identified as having an acute coronary syndrome (ACS) are further differentiated into ACS with or without ST-segment ele-

vation (STE). The early treatment decisions are influenced by this distinction. This initial distinction has little influence on secondary prevention treatment strategy; therefore, the recommendations for long-term antithrombotic therapy following ACS are considered together.

This chapter considers the treatment of the following patient groups: (1) post-STE ACS; (2) post-non-STE (NSTE) ACS; (3) after percutaneous coronary intervention (PCI); (4) stable CAD; (5) congestive heart failure (CHF); (6) after coronary artery bypass grafting (CABG): and (7) coronary heart disease (CHD) risk factors. Table 1 describes both the question definition and eligibility criteria for studies considered in each section of the antithrombotic therapy recommendations that follow.

1.0 Post-STE and NSTS ACS Treatment

The following discussion and recommendations for post-STE and NSTE ACS management designate hospital discharge as an initiating point for the transition from short-term care to long-term care and the secondary prevention of cardiovascular events.

1.1 Antiplatelet Therapies
1.1.1 Short-term Antiplatelet Therapy Trials

ISIS-2[2] was a randomized, placebo-controlled, blinded trial of short-term therapy with IV streptokinase (SK), oral aspirin [160 mg/d for 1 month], both or neither among 17,187 patients with suspected myocardial infarction (MI). In addition to a 23% relative risk reduction (RRR) in 5-week vascular

Table 1—*Question Definition and Eligibility Criteria for Antithrombotic Agents in CAD (Section: Introduction)*

Section	Population	Intervention(s) or Exposure	Outcome	Methodology
1.1.1	STE and NSTE ACS	Aspirin	Mortality MI Stroke Bleeding	RCTs
1.1.2	NSTE ACS	Thienopyridines	Composite: death, MI, stroke Ischemia Bleeding	RCTs
1.2.1	NSTE ACS	UFH	Composite: death, MI Ischemia Bleeding	RCTs
1.2.2	NSTE ACS	LMWHs	Composite: death, MI Ischemia Bleeding	RCTs
1.2.3	NSTE ACS	Antithrombin therapy, indirect, selective factor Xa inhibitors	Composite: death, MI Ischemia Bleeding	RCTs and observational studies
2.1	After MI and after ACS (secondary prevention)	Oral VKA	Composite: death, MI, stroke Bleeding	RCTs
2.2	After MI and after ACS (secondary prevention)	Aspirin combined with oral VKA	Composite: death, MI, stroke Angiographic outcomes Bleeding	RCTs
2.3	After MI and after ACS (secondary prevention)	HMG-CoA reductase inhibitors	Composite: death, MI, stroke Angiographic outcomes Bleeding	RCTs
2.54	PCI	Oral antiplatelet therapies (aspirin and thienopyridines)	Mortality	RCTs
	After MI and after ACS (secondary prevention)		MI Stent thrombosis	Observational studies
3.1	CHF	Oral antiplatelet therapies with and without ACEIs and oral VKAs	Composite: death, MI, stroke Bleeding	RCTs and observational studies
4.1	CABG	Oral antiplatelet therapies and oral VKA	Graft patency	RCTs and observational studies
5.1	Primary prevention	Oral antiplatelet and anticoagulant therapy	Mortality MI Stroke Bleeding	RCTs

mortality among patients receiving SK, there was a 21% reduction among those receiving aspirin and a 40% reduction among those receiving a combination of SK and aspirin, which are all highly significant reductions. The early reduction in mortality with aspirin persisted when the patients were observed for a mean of 15 months. Aspirin reduced the risk of nonfatal reinfarction by 49% and nonfatal stroke by 46%. The increased rate of early nonfatal reinfarction noted when SK therapy was used alone is consistent with marked platelet activation after fibrinolytic therapy and was completely resolved when aspirin was added (3.8% vs 1.3%; p < 0.001).

Aspirin added to the benefit of SK therapy in all groups examined. In particular, among patients > 70 years of age, the combination markedly reduced mortality from 23.8 to 15.8% (p < 0.001) without increasing hemorrhage or stroke. Because of the overall poor prognosis among older individuals with acute MI, the absolute number of lives saved with aspirin and thrombolytic therapy increases with age (ie, 2.5 per 100 treated patients < 60 years of age and 7 to 8 per 100 treated patients ≥ 60 years of age).

ISIS-2 showed that short-term aspirin therapy for MI decreases mortality and reinfarction, has benefits in addition to those of fibrinolysis, and reduces reinfarction after fibrinolytic therapy. Consequently, aspirin therapy for patients with acute MI should accompany fibrinolytic therapy. Although associated with an increased rate of minor bleeding from 1.9 to 2.5%, aspirin therapy was not associated with an increased risk of major bleeding, including hemorrhagic stroke. The benefit of aspirin, in contrast to that of SK, was independent of the time of onset of treatment. However, early administration seems prudent.

The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28[3] and ClOpidogrel and Metoprolol in Myocardial Infarction (COMMIT)[4] trials evaluated the addition of clopidogrel to antithrombotic therapy with aspirin, heparin, and a fibrinolytic agent. In the CLARITY trial, the addition of a loading dose of 300 mg of clopidogrel followed by 75 mg/d in 3,491 patients aged < 75 years with acute STE MI was associated with a significant 36% reduction in the composite primary end point of death, MI, or an occluded infarct-related coronary artery (95% confidence interval [CI], 27–47%, p < 0.001) at the time of angiography. The greatest effect of clopidogrel was on coronary occlusion; this trial did not demonstrate benefits on reducing either death or MI. The benefit did not come at the expense of increased bleeding despite the concomitant use of a fibrinolytic agent, aspirin, unfractionated heparin (UFH), or

low-molecular-weight heparin (LMWH). In addition, the PCI-CLARITY subset of the trial demonstrated significantly better outcomes in the 1,863 patients who underwent angioplasty after clopidogrel therapy.

The Chinese COMMIT trial[4] of 45,852 patients with acute MI, half of whom received reperfusion therapy, demonstrated benefit from clopidogrel 75 mg/d compared with placebo; both groups received aspirin. The primary end point of death, MI or stroke was reduced by 9% (10.1% vs 9.3%, p = 0.002); mortality was reduced by 7% (8.1% vs 7.5%, p = 0.03). Overall, when all transfused, fatal, or cerebral bleeds were considered together, there was no significant excess risk associated with the use of clopidogrel (134 [0.58%] clopidogrel vs 125 [0.55%] placebo; p = 0.59). The average duration of treatment with clopidogrel for CLARITY and COMMIT was 16 days and 14 days, respectively.

1.1.2 Long-term Antiplatelet Therapy Trials

The Antiplatelet Trialists' Collaboration update[5] included 287 studies involving 135,640 high-risk (acute or previous vascular disease or another predisposing condition) patients in comparisons of antiplatelet therapy vs control and 77,000 similar patients in comparisons of different antiplatelet regimens. The analysis extended the direct evidence of benefit from antiplatelet therapy to a much wider range of patients at high risk of occlusive vascular disease.[5]

Overall, 7,705 (10.7%) serious vascular events occurred in 71,912 high-risk patients allocated antiplatelet vs an adjusted total of 9,502 (13.2%) such events among 72,139 control patients (22% odds reduction; p = 0.0001). Antiplatelet therapy was associated with a highly significant 15% relative reduction in vascular deaths (p = 0.0001) (similar across high- and low-risk groups), all-cause mortality (p < 0.0001), nonfatal MI (34% odds reduction; p < 0.001), nonfatal MI or death from coronary heart disease (26% odds reduction; p < 0.001) and stroke (25% odds reduction; p < 0.001). Overall, the relative odds of experiencing a major extracranial hemorrhage was increased 60% with antiplatelet therapy (odds ratio 1.6; p < 0.001). The increase in fatal hemorrhage was not significantly different from that for nonfatal hemorrhage, although only the excess of nonfatal hemorrhagic events achieved statistical significance.

1.1.3 Aspirin Dose

The optimal dose of aspirin for the prevention of cardiovascular events has not been definitively established by directly comparing two different dosages in

large clinical trials. The updated meta-analysis[6] does however provide useful information on the effects of different doses of aspirin. Overall, among 3,570 patients in three trials directly comparing aspirin doses ($\geq$ 75 mg vs < 75 mg/d), there were significant differences in vascular events (two trials compared 75–325 mg/d aspirin vs < 75 mg/d and one trial compared 500–1,500 mg of aspirin daily vs < 75 mg/d) favoring lower doses. Considering both direct and indirect comparisons of aspirin dose, vascular events were reduced 19% with 500–1,500 mg/d, 26% with 160–325 mg/d, and 32% with 75–150 mg/d. These data provide indirect support for administration of an aspirin dose of 75–100 mg/d for cardiovascular disease treatment.[6]

1.1.4 Aspirin and Clopidogrel for Secondary Prevention Among Patients With Established, Clinically Evident Atherothrombosis

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[7] was a prospective, randomized, blinded, placebo-controlled study that compared the efficacy and safety of clopidogrel plus aspirin with aspirin alone in patients deemed to be at high risk for a cardiovascular event. In the total population of 15,603 patients, the difference between the combined vs single antiplatelet therapy groups in the primary end point of MI, stroke, or death from cardiovascular disease was compatible with chance (6.8% vs 7.3%; relative risk [RR], 0.93; 95% CI, 0.83–1.05). In a subgroup of 12,153 patients with established cardiovascular disease, including either coronary artery disease, cerebrovascular disease or symptomatic peripheral vascular disease, the primary composite end point was marginally reduced with clopidogrel plus aspirin (compared with aspirin alone) [6.9% vs 7.9%; RR, 0.88; 95% CI, 0.77–0.998; p = 0.046]. Among all patients enrolled, the rates of GUSTO-defined severe bleeding were 1.7% and 1.3%, respectively, in the total population (p = 0.09). GUSTO-defined moderate bleeding was higher with combined therapy than aspirin alone (2.1% vs 1.3%, respectively; p < 0.001).[7]

A more narrowly defined subgroup[8] of 9,478 patients with documented prior MI, ischemic stroke, or symptomatic peripheral vascular disease underwent a median follow-up of 27.6 months. The rate of cardiovascular death, MI, or stroke was significantly lower in the clopidogrel plus aspirin arm than in the placebo plus aspirin arm (hazard ratio, 0.83; 95% CI, 0.72–0.96; p = 0.01). Moderate bleeding was significantly increased with combination therapy compared with aspirin alone: 2.0% vs 1.3% (hazard ratio, 1.60; 95% CI, 1.16–2.20; p = 0.004).

1.1.5 Comparative Safety Profiles of Aspirin and Clopidogrel in Primary and Secondary Prevention of Cardiovascular Events

McQuaid and Laine[9] undertook a systematic review to define the risk of patient-important adverse events with aspirin and clopidogrel. RRs were determined by meta-analysis of 22 trials for aspirin vs placebo and from single studies for aspirin vs clopidogrel, aspirin vs aspirin/clopidogrel, and clopidogrel vs aspirin/clopidogrel. Aspirin increased the risk of major bleeding (RR, 1.71; 95% CI, 1.41–2.08), major GI bleeding (RR, 2.07; 95% CI, 1.61–2.66), and intracranial bleeding (RR, 1.65; 95% CI, 1.06–5.99) vs placebo. No difference in major bleeding between 75–162.5 mg/d and > 162.5 and 325 mg/d aspirin vs placebo was observed. The absolute annual increases attributable to aspirin were: for major bleeding 0.13% (95% CI, 0.08–0.20); major GI bleeding, 0.12% (95% CI, 0.07–0.19); and intracranial bleeding, 0.03% (95% CI, 0.01–0.08).

We know of no studies comparing clopidogrel with placebo. In CAPRIE[10] the RRs of all GI bleeding and severe GI bleeding for aspirin (325 mg/d) vs clopidogrel were 1.34 (95% CI, 1.11–1.61) and 1.45 (95% CI, 1.00–2.10), respectively. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)[11,12] and MATCH[13] studies, aspirin alone and clopidogrel alone were associated with a reduced risk of any bleeding, any major bleeding, and major GI bleeding compared with combined therapy.

1.1.6 Economic Implications of Clopidogrel Therapy for Secondary Prevention

A number of economic analyses have examined the issue of adding clopidogrel therapy to aspirin for secondary prevention.[14–16] The impetus for these studies has been the combination of relatively modest incremental clinical benefits and relatively high drug costs, leading clinicians, policy makers, and others to be uncertain about the economic attractiveness of such therapy. Differences in the results of the published economic analyses can be traced back largely to two key issues: (1) differences in the clinical data used to inform the effectiveness portion of the analyses; and (2) differences in the assumed duration of therapy.

Although the cost of therapy raises the profile of the economic question, the absolute magnitude of effectiveness is the primary determinant of cost effectiveness (see the "Perioperative Management of Antithrombiotic Therapy" chapter). This derives from the fact that the cost of a 75 mg/d regimen of clopidogrel does not depend on disease severity or clinical risk, but the benefits do. In short, the same

up front investment in drug therapy can produce substantially different downstream benefit and cost-effectiveness pictures. The earliest analyses of clopidogrel for secondary prevention used models based, in part, on the CAPRIE Trial, which demonstrated an 8.7% relative reduction of the composite primary end point (ischemic stroke, MI, or vascular death) with clopidogrel vs aspirin given over a mean of 1.6 years and an approximate 5 per 1,000 absolute reduction in these events per year with no evidence of an effect on all-cause mortality.[10] With this level of benefit, modeling the use of lifetime clopidogrel therapy in addition to aspirin yielded a high (unattractive) cost-effectiveness ratio.[14]

In contrast, in the CURE Trial,[11] clopidogrel therapy for a mean of 9 months reduced the trial primary end point (cardiovascular death, MI, or stroke) by 20%, which translated into an absolute event reduction of 21 per 1,000. All-cause mortality was reduced by 4 per 1,000 with clopidogrel. Using the empirical CURE Trial data, Weintraub et al[16] calculated that treatment with clopidogrel increased life expectancy by approximately 0.07 life-years (about 26 days). Incremental costs of drug therapy given over a mean of 9 months were $766, but adverse events avoided in the clopidogrel arm reduced the incremental lifetime costs of that arm to between $340 to $440. The resulting cost-effectiveness ratio had a 90% to 95% chance of being below the US benchmark of $50,000 per life-year added.

A third analysis of clopidogrel therapy as secondary prevention used a Markov model and published data from CURE to generate estimates and provides useful insights into the major determinants of the cost-effectiveness of this therapy.[15] Assuming treatment duration with clopidogrel of 1 year, incremental survival was estimated as 0.1 additional quality-adjusted life year (QALY), while incremental lifetime costs were estimated to be $1,600. The resulting cost-effectiveness ratio was $15,400 per QALY. Varying the cost of clopidogrel between $2/d and $7/d from the base-case model had a relatively modest effect on the cost-effectiveness ratio ($8,900 per QALY to $26,000 per QALY). In contrast, continuing therapy beyond 2 years yielded progressively more and more unattractive cost-effectiveness ratios for the added years of therapy (eg, $730,000 QALY for the fifth year of therapy). The other major determinant of the cost-effectiveness of therapy was the annual risk of vascular events with aspirin alone, with rates < 6%/yr generally translating into cost-effectiveness ratios above $100,000 per QALY.

Although, to our knowledge, no economic analysis of CHARISMA[7] has yet been published, contrasting this trial with CURE can provide some reasonable insights about cost-effectiveness. First, the rates of vascular events in the placebo arm of CHARISMA with a median of 28 months of therapy were 7.3% overall, 5.5% in the subgroup with multiple risk factors, and 7.9% in the subgroup with clinically evident cardiovascular disease. Thus, this population was at significantly lower risk than the CURE population (event rate in placebo arm 11.4% with a mean of 9 months of therapy). Second, the RRR with clopidogrel in CHARISMA was smaller than in CURE: 7% overall (p = 0.22) and 12% in the subgroup with clinically evident cardiovascular disease (p = 0.046) vs 20% for CURE (p < 0.001). Thus, with a smaller relative benefit and a lower risk population, based on prior cost-effectiveness studies we can project that the incremental benefits of clopidogrel reflected in CHARISMA with costs of therapy for a median treatment period of 28 months would be unlikely to be economically attractive using conventional benchmarks.

What are the clinical implications of these economic insights? Although proprietary clopidogrel is relatively expensive among cardiovascular pharmaceuticals, use of a limited course of therapy as secondary prevention in addition to aspirin can provide good value for money provided that the target population is at sufficiently high risk, such as was reflected in CURE. Even in such populations, however, there are currently no persuasive data on the long-term clinical benefits of therapy and model-based projections suggest that continuing therapy past 2 years would be increasingly economically unattractive. In a lower-risk population, the smaller absolute incremental benefits of therapy do not appear to be sufficient to provide good value for money using conventional benchmarks. Finally, when generic clopidogrel becomes available and price competition lowers the cost of therapy, these economic analyses will need to be updated.

Recommendations

1.1.1. In patients with ACS with and without STE, we recommend aspirin initially at a dose of 75–162 mg and then indefinitely at a dose of 75–100 mg/d (Grade 1A).

1.1.2. For patients with STE ACS, with or without fibrinolytic therapy, we recommend clopidogrel as a 300-mg oral loading dose for patients ≤ 75 years of age and a 75-mg starting dose for those > 75 years of age and continued at a daily dose of 75 mg for 2–4 weeks (Grade 1A). **We suggest continuing clopidogrel for up to 12 months following hospital discharge** (Grade 2B).

1.1.3. For patients with NSTE ACS, we recommend combination therapy with aspirin (75–100

mg/d) and clopidogrel (75 mg/d) for 12 months (Grade 1A).

1.1.4. For patients in whom aspirin is contraindicated or not tolerated, we recommend clopidogrel monotherapy (75 mg/d) [Grade 1A].

1.1.5. For patients with symptomatic CAD, we suggest aspirin, 75–100 mg/d, in combination with clopidogrel, 75 mg/d (Grade 2B).

Values and preferences: This recommendation places a high value on the probable small reduction in arterial vascular risk consequent on adding clopidogrel to aspirin and a low value on avoiding the additional bleeding and high cost associated with clopidogrel.

1.2 Short-term Use of Anticoagulant Therapies

The "Antithrombotic Therapy for Non-ST-Segment Elevation" and "Acute ST Segment Elevation Myocardial Infarction" chapters by Harrington et al (NSTE ACS) and Goodman et al (STE MI) address the use of anticoagulant therapies in acute ACS.

2.0 LONG-TERM ANTICOAGULANT THERAPIES

2.1 Long-term Anticoagulant Trials

Anand and Yusuf[17] published a systematic overview of anticoagulation therapy in patients with CAD. Since it had long been suggested that the therapeutic window for oral anticoagulation is narrow, the investigators divided their analysis of anticoagulation control into those patients who had received high-intensity anticoagulation therapy (international normalized ratio [INR] between 2.8 and 4.8), moderate-intensity anticoagulation therapy

(INR, 2.0 to 3.0), and low-intensity anticoagulation therapy (INR, < 2.0). In comparisons of anticoagulation plus aspirin vs aspirin alone, patients were classified as moderate-to-high-intensity anticoagulation therapy (INR, ~ 2) and low-intensity anticoagulation therapy (INR, < 2.0).

The analysis included patients with coronary disease, including those who had experienced an acute MI. A majority of patients began therapy within 3 months of hospitalization. The major finding was that moderate-intensity and high-intensity anticoagulation therapy were effective in reducing the incidence of MI and stroke compared with control subjects; but at a cost of increased bleeding (Fig 1).

A series of randomized trials conducted prior to 1980 suggested that long-term oral anticoagulation therapy following acute MI might decrease the number of reinfarctions, pulmonary emboli, and cardiovascular deaths. Subsequently, the Sixty Plus Reinfarction Study[18] enrolled patients > 60 years of age who had been receiving oral anticoagulation therapy following transmural MI that had occurred at least 6 months earlier (mean, 6 years). This randomized, blinded trial compared continued treatment with oral anticoagulation therapy (INR, 2.7 to 4.5) to matching placebo. Mortality at 2 years was 13.4% in the placebo group and 7.6% in the group treated with anticoagulants (p = 0.017). Recurrent MI at 2 years was 15.9% in the placebo group and 5.7% in the anticoagulant treated group (p = 0.0001). Major and minor non-CNS bleeding occurred with greater frequency among anticoagulant-treated patients, but transfusion was rare and there were no fatal bleeding events.

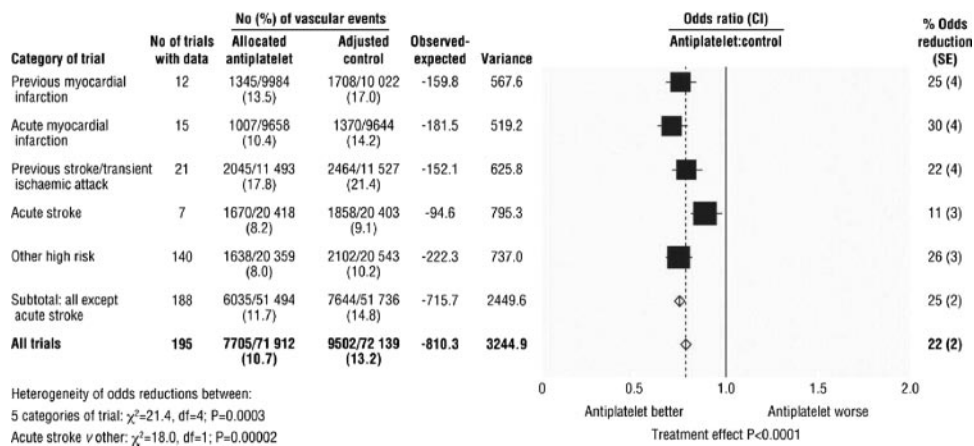The Warfarin Reinfarction Study (WARIS)[19] en-

FIGURE 1. Systematic overview of antiplatelet therapy in vascular disease.[5] Attention is directed to the subset of patients with AMI. df = degrees of freedom. Reprinted with permission from the BMJ Publishing Group. Antithrombotic Trialist's Collaboration. Collaborative Meta-Analyses of Randomized Trials of Antiplatelet Therapy for Prevention of Death, Myocardial Infarction, and Stroke in High Risk Patients. BMJ 2002; 324:71–86.

rolled patients who had sustained an acute MI, on average, 27 days previously. This randomized, blinded trial compared warfarin (INR, 2.8 to 4.8) to placebo in patients advised not to take aspirin. Significant reductions in all-cause mortality (24%), reinfarction (34%), and stroke (55%) were observed in those receiving warfarin. There were five intracranial hemorrhages with warfarin treatment, three of them fatal, and there were eight episodes of major extracranial hemorrhage with warfarin treatment, for a combined incidence of major bleeding of 0.6%/yr.

The Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) research group[20] enrolled patients who had sustained an acute MI within 6 weeks of hospital discharge. This randomized, blinded trial compared acenocoumarol (nicoumalone), phenprocoumon (INR, 2.8 to 4.8), or placebo. There was a favorable trend for the reduction of all-cause mortality, with statistically significant reductions in reinfarction and stroke with oral VKA therapy. The combined annual incidence of major bleeding was 1.4%/yr with oral VKA therapy and 0.4%/yr with placebo. Efficacy analyses revealed greater risk reductions with anticoagulation. An overview of these trials reinforces the observations of benefit.

Neri Serneri et al[21] evaluated heparin (12,500 U subcutaneous [SC] qd) among 6- to 18-month survivors of STE MI. There was a significant reduction in the rate of reinfarction, with favorable trends for the reduction of all-cause and cardiovascular mortality. Efficacy analyses provided stronger evidence for a benefit of heparin. There were no major hemorrhagic events and no evidence of osteoporosis assessed by serial density measurements.

2.2 Comparisons of Antiplatelet and Oral VKA Therapy and/or Combinations of Aspirin and VKA Trials

Several trials have compared oral anticoagulation with aspirin. The German-Austrian trial enrolled 942 patients within 30 to 42 days of acute MI and assigned them to aspirin, placebo, or phenprocoumon therapy.[22] Over a 2-year follow-up period, the aspirin-treated patients had statistically insignificant reductions of 26% for all-cause mortality and 46.3% for coronary mortality compared with phenprocoumon. Aspirin showed a favorable trend compared with placebo, but phenprocoumon did not.

In the Enquete de Prevention Secondaire de l'lnfarctus du Myocarde trial,[23] 1,303 patients were randomized a mean of 11.4 days following acute MI to aspirin or one of several anticoagulants. Over a mean follow-up period of 29 months, the all-cause

mortality rate was 10.3% with anticoagulation and 11.1% with aspirin. The study was stopped early when it became evident that statistically significant differences in outcome between treatment groups were unlikely.

The Aspirin/Anticoagulants Following Thrombolysis with Anistreplase (Eminase) and Recurrent Infarction (AFTER) study[24] enrolled 1,036 survivors of acute MI who had received anistreplase. Patients were randomized to treatment with anticoagulation (IV heparin followed by warfarin or other oral VKA) or aspirin (150 mg/d) and followed for the primary outcome of cardiac death or recurrent MI by 30 days. The rates of the primary outcome were 11.0% with anticoagulation and 11.2% with aspirin. The trial was stopped early because of a declining enrollment rate and lack of sufficient statistical power to demonstrate differences between the two therapies. The rate of severe bleeding or stroke was significantly higher with anticoagulation than with aspirin therapy (3.9% vs 1.7%, respectively; odds ratio [OR], 0.44; 95% CI, 0.20–0.97; p = 0.04).

The Coumadin Aspirin Reinfarction Study (CARS)[25] was a blinded study of 8,803 patients enrolled 3–21 days after an acute MI. Patients were randomized into one of three treatment arms: 160 mg of aspirin; 1 mg of warfarin plus 80 mg of aspirin; or 3 mg of warfarin plus 80 mg of aspirin. During a median follow-up of 14 months, the primary composite outcome of reinfarction, nonfatal ischemic stroke, or cardiovascular death occurred at a rate of 8.6% in the 160-mg aspirin group, 8.8% in the 1-mg warfarin plus 80-mg aspirin group, and 8.4% in the 3-mg warfarin plus 80-mg aspirin group. Major hemorrhage occurred in 0.74% of the aspirin group and 1.4% of the 3-mg warfarin/80-mg aspirin group. Among 3,382 patients assigned to 3-mg warfarin/ 80-mg aspirin, the INRs were 1.51 at week 1, 1.27 at week 4, and 1.19 at 6 months. The investigators concluded that low fixed-dose warfarin therapy (l or 3 mg) combined with low-dose aspirin therapy (80 mg) did not provide clinical benefit beyond that achievable with 160 mg of aspirin.

The CARS results are consistent with prior observations suggesting that warfarin is most effective at INR ranges between 2 and 3.5. Further, the secondary prevention data in both arterial and venous thrombotic disorders emphasize a requirement to surpass a lower anticoagulation threshold for benefit. In contrast, the results of the Thrombosis Prevention Trial (TPT)[26] suggest that warfarin therapy at a lower INR (approximately 1.5) may be beneficial in primary prevention (see subsequent section on primary prevention). The Combined Hemotherapy and Mortality Prevention study (CHAMP)[27] was an open-label Veterans Administration cooperative trial that sought

to demonstrate a 15% reduction in all-cause mortality in survivors of MI treated with combined therapy (ie, warfarin, INR 1.5 to 2.5, plus aspirin, 81 mg) compared with aspirin therapy (162 mg) alone. The study included 5,059 subjects, mostly men, with a mean age of 62 years. The mean INR was 1.9. Using an intention-to-treat analysis, there was no significant difference in the total mortality rate (17.3% vs 17.3%), cardiovascular mortality (4.7% vs 4.2%), nonfatal stroke (4.7% vs 4.2%), and nonfatal MI (13.1% vs 13.3%, respectively). Major bleeding, mostly GI, was more common in the combination therapy group than in the aspirin group (combination therapy group, 1.25 major episodes of bleeding per 100 patient-years; aspirin-alone group, 0.69 major episodes of bleeding per 100 patient-years). The investigators concluded that there was no survival advantage to adding warfarin to aspirin in survivors of MI.

The Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study[28] tested a higher INR range than CARS[25] and CHAMPS.[27] Moderate intensity warfarin anticoagulation (INR, 2.0–2.5; 3 mg/d) reduced coronary event rates compared with control patients with NSTE ACS. A majority of patients in both groups received aspirin. At 3 months, the rates of cardiovascular death, new MI, and refractory angina after hospital discharge were 5.1% in the warfarin group and 12.1% in the standard group, reflecting a 58% RRR for warfarin plus aspirin compared with aspirin alone (95% CI, 0.15–1.15; p = 0.08).

The randomized, open-label, multicenter Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT)-2 trial[29] enrolled 308 patients with acute MI who received unfractionated heparin, aspirin, and fibrinolytic therapy. Those who achieved Thrombolysis in Myocardial Infarction (TIMI)-3 flow in the infarct-related artery were then randomized to warfarin (heparin continued until INR 2.0–3.0) plus aspirin (80 mg/d) or aspirin (80 mg/d) alone (heparin discontinued).

Follow-up angiography at 3 months revealed reduced reocclusion rates (defined as TIMI < 2) in the warfarin plus aspirin group compared with those receiving aspirin alone (18% vs 30%, respectively; RR, 0.60; 95% CI, 0.39–0.93; p = 0.02), reflecting a 40% RRR in events. Most of this benefit centered on a significant reduction in the incidence of TIMI 0–1 (ie, anatomic reocclusions; 9% vs 25%, respectively). The results from APRICOT-2 support combination therapy in the post-MI setting for patients with STE MI.

The Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) trial provides further support for combined anticoagulant and antiplatelet therapy following ACS.[30] In this study, 999 patients were randomly assigned to high-intensity warfarin (INR, 3.0–4.0), moderate-intensity warfarin (INR, 2.0–2.5) plus aspirin (80 mg/d), or aspirin (80 mg/d) alone. At 12 months, the primary end point occurred in significantly fewer patients in the warfarin-only and warfarin plus aspirin groups than the aspirin-only group (5%, 5%, and 9%, respectively; p ≤ 0.05), and mortality was significantly lower in the two warfarin groups compared with the aspirin group (1.2%, 2.7%, and 4.5%, respectively; p = 0.01). The risk of major bleeding was higher with combination therapy than with warfarin alone.

The open-label, multicenter Warfarin-Aspirin Reinfarction Study (WARIS II)[31,32] was a long-term secondary prevention study in which 3,630 post-MI patients were randomized to receive either high-intensity warfarin (INR, 2.8–4.2), moderate-intensity warfarin (INR, 2.0–2.5) plus aspirin (75 mg/d), or low-dose aspirin (160 mg/d) alone. The primary end point was the rate of first occurrence of the composite end point of all-cause mortality, nonfatal reinfarction, and stroke. Patients in WARIS II were relatively young (~60 years), approximately three quarters were male, and roughly half were smokers.

About 6 out of 10 had experienced a recent STE MI, and slightly more than half had received fibrinolytic therapy. Patients were followed up for a mean of 4 years, with anticoagulation intensity managed on an outpatient basis. This study lasted longer than other trials of antithrombotic therapy in post-ACS patients.

At the 4-year follow-up, the primary end point was lower in the warfarin plus aspirin group than either the warfarin or aspirin-alone groups (15.0%, 16.7%, and 20.0%, respectively). Using a person-year model, these data gave an OR of 0.71 for the warfarin-plus-aspirin combination vs aspirin alone (95% CI, 0.60–0.83; p = 0.001), or a 29% relative odds reduction with combination therapy. The OR for warfarin vs aspirin was 0.81 (95% CI, 0.69–0.95; p = 0.03), reflecting the superiority of both warfarin arms over aspirin alone. However, the benefit of the warfarin plus aspirin group over the warfarin-only group did not reach statistical significance, with an OR of 0.87 (95% CI, 0.71–1.08; p = 0.20).

The cumulative hazard curves for the primary end point showed a significant divergence between the warfarin groups and the aspirin-only group at 4 years (p = 0.003), demonstrating the benefits of long-term anticoagulation. However, major nonfatal bleeding was three- to fourfold more frequent among the warfarin-only and combination groups than in the

aspirin-only group, although absolute percentages per year were relatively low (0.68%, 0.57%, and 0.17%, respectively).

The results from WARIS II and other studies suggest that combining aspirin with oral VKA therapy is superior to aspirin alone following ACS with or without STE. While these findings have relevant clinical implications, areas of uncertainty remain: (1) the intensity of anticoagulation was carefully controlled in WARIS II, and it is unclear whether this degree of success can be achieved in routine clinical practice; and (2) the benefit seen with anticoagulant therapy in the WARIS II cohort (*ie*, relatively young and low rates of revascularization) may not translate directly to other post-ACS populations, especially patients undergoing PCI and those of advanced age who are recognized to be at risk for hemorrhagic complications.

2.2.1 Economic Issues Related to Secondary Prevention With VKAs

As reviewed elsewhere in this chapter, there is evidence that moderate-intensity anticoagulation with warfarin or a similar VKA effectively reduces cardiovascular events after acute MI with or without concomitant aspirin therapy. Since warfarin is widely available in generic form, the cost of the drug itself is relatively low. The major economic issues regarding warfarin therapy relate to the induced costs of adverse events, principally severe or life-threatening hemorrhage, and the direct costs associated with monitoring the level of anticoagulation. Unfortunately, we have found no contemporary economic studies of this use of warfarin. Nonetheless, some general insights can be offered.

A proper accounting of the total long-term costs of a treatment strategy must include not only the cost of the therapy itself, which in this case is the cost of the warfarin and the cost of monitoring its use with serial INR testing, but also the costs (savings) that are attributable to the therapy. A recent metaanalysis calculated that warfarin plus aspirin given to patients following an ACS increased major bleeding by 1 per 100 relative to aspirin therapy alone.[33] Major bleeding is not only clinically undesirable, it is expensive. A recent study of warfarin anticoagulation estimated the hospitalization for bleeding costs approximately $16,000, with an average of 6 days in the hospital.[34] However, since there was only one incremental major bleed for every 100 post-ACS patients treated with warfarin and aspirin, the incremental costs associated with this complication average $160 per patient (*ie*, $16,000/100). Considering the potential benefit compared with aspirin alone, moderate-intensity warfarin therapy (INR, 2.0–3.0) significantly

reduces both the incidence of nonfatal thromboembolic stroke (by 9 per 1,000 patients) and the incidence of nonfatal MI (also by 9 per 1,000).[35] Since these complications are both associated with expenses of a similar magnitude to those of major bleeding, one may infer that the savings created by warfarin from reduced complications of CAD approximately cancel out the incremental costs from the adverse events due to therapy in the post-ACS population.

To our knowledge, the only published empirical economic data derived from a clinical trial of warfarin therapy following[20] acute MI comes from the ASPECT Trial performed in The Netherlands. In this study, oral anticoagulation was compared with placebo and therefore does not reflect contemporary management which includes aspirin. Including the costs of drug therapy, monitoring, and hospital-based complications, the warfarin strategy was less expensive overall than the placebo/usual care strategy. A more contemporary analysis of this issue needs to be performed.

The direct costs of INR monitoring are relatively modest, ranging between $216 and $340 per year in one recent study.[36] The more complex aspect of warfarin therapy economics relates to the interdependence between tight control of the INR, reduced risk of bleeding (due to avoidance of excessively high INRs), and preserved effectiveness in reduction of CAD-related adverse events (due to avoidance of excessively low INRs that are not protective). Interventions that improve INR control may therefore also reduce costs from bleeding and increase cost savings from reduced atherosclerotic events. Consistent with this concept, an economic analysis in high-risk atrial fibrillation patients on warfarin concluded that an anticoagulation management service both improved clinical outcomes and reduced net costs relative to usual INR management.[37]

Interesting innovations that will influence the future economic picture of secondary prevention with warfarin include the increased use of home anticoagulation monitoring, which may be less expensive than traditional monitoring[38] and cytochrome P450 2C9 genotyping to identify patients at higher risk of major bleeding with warfarin therapy.[39]

Recommendations

2.1. For most patients (all except the high-risk group described in Recommendation 2.2 below) in most health-care settings, following ACS, we recommend aspirin alone (75–100 mg/d) over oral VKAs alone or in combination with aspirin (Grade 1B).
Values and preferences: This recommendation places a relatively low value on prevention of thromboem-

bolism, and a relatively high value on avoiding the inconvenience, expense, and potential bleeding risk associated with VKA therapy.

2.1.1. For most patients after MI, in health-care settings in which meticulous INR monitoring and highly skilled VKA dose titration are expected and widely accessible, we suggest long-term (up to 4 years) high-intensity oral VKA (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral VKA (target INR, 2.5; range, 2.0 to 3.0) with aspirin (≤ 100 mg/d) over aspirin alone (both Grade 2B).

2.2. For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on transthoracic echocardiography, those with atrial fibrillation, and those with a history of a thromboembolic event, we suggest the combined use of moderate-intensity (INR, 2.0 to 3.0) oral VKA plus low-dose aspirin (≤ 100 mg/d) for at least 3 months after the MI (Grade 2A).

2.3 Patients Undergoing PCI

The "Antithrombotic Therapy for Non-ST-Segment Elevation ACS" chapter by Harrington et al addresses the periprocedural antithrombotic recommendations for patients undergoing PCI.

2.3.1 Dose of Aspirin When Given in Combination With Other Antithrombotic Drugs

Long-term aspirin therapy is recommended for patients with CAD who undergo any revascularization procedure, including PCI. When aspirin is given in combination with other antiplatelet agents or with anticoagulants, it is reasonable to use a daily dose of 75–100 mg, rather than 325 mg, to minimize hemorrhagic risk (see the "Antiplatelet Drugs" chapter by Patrono et al in this supplement). Although, to our knowledge, randomized trials comparing 75–100 mg with 325 mg of aspirin in this setting have not been conducted, a dose of 75–100 mg/d is supported by a post hoc analysis of data derived from the CURE Study.[40] Patients were classified into three aspirin-dose groups: < 100 mg, 101 to 199 mg, and ≥ 200 mg.[41] The combined incidence of cardiovascular death, MI, or stroke was reduced by clopidogrel regardless of aspirin dose, but the incidence of major bleeding increased with higher doses, both in patients randomized to aspirin plus placebo (1.9%, 2.8%, and 3.7%, respectively; p = 0.0001) and in those

Table 2—Effect of Antiplatelet Agents on Procedural Outcome After PCI

Study/yr	Clinical Status	Patients, No.	Type of Study	Treatment	Procedural Outcome, %			
					Death	MI	CABG or PTCA	Thrombus or Complications, No.
Schwartz et al[187]/1988	Elective	187	RCT	Aspirin, 330 mg tid and dipyridamole, 75 mg tid	Not reported	1.6†	2.1	
		189		Placebo	Not reported	6.9	2.1	
White et al[188]/1987	Elective	111	RCT	Aspirin, 325 mg bid and dipyridamole, 75 mg tid				5†
		112		Ticlopidine, 250 mg tid				2†
		110		Placebo				14
Barnathan et al[189]/1987	All patients	32	Observational study	Aspirin and dipyridamole				0*
		110		Aspirin alone				1.8†
		121		No aspirin				10.7
Mufson et al[190]/1988	Elective	253	RCT	Aspirin, 80 mg/d	0	3.6	3.6	
		242		Aspirin, 1,500 mg/d	0	3.9	3.7	
Lembo et al[77]/1990	Elective	117	RCT	Aspirin, 325 mg tid and dipyridamole, 75 mg tid	0.9	4.3	6.1	
		115		Aspirin, 325 mg tid	0	1.7	2.6	
Knudtson et al[78]/1990	Elective	134	RCT	Prostacyclin for 48 h	0	0.8	1.4	3.0†
		136		Placebo	0.7	2.0	0.7	10.3

*p < 0.05 compared with placebo.
†p < 0.01 compared with placebo.

given aspirin plus clopidogrel (3.0%, 3.4%, and 4.9%, respectively; p = 0.0009) [Table 2].

2.4 Long-term Thienopyridine Therapy After PCI

Extended treatment with the combination of aspirin and clopidogrel after PCI for an ACS[40] or after elective angioplasty[42] reduces the rate of ischemic events. The Clopidogrel for the Reduction of Events During Observation (CREDO) trial[42] was a randomized, blinded, placebo-controlled trial conducted in 2116 patients undergoing elective PCI. Patients were randomly assigned to receive a 300-mg clopidogrel loading dose or placebo 3 to 24 h before PCI. Thereafter, all patients received clopidogrel (75 mg/d) until day 28. From day 29 through 12 months, patients in the loading-dose group received clopidogrel (75 mg/d), while those in the control group received placebo. Both groups received aspirin throughout the study. The 12-month incidence of the composite of death, MI, or stroke in the intent-to-treat population was reduced by 26.9% in patients treated with long-term clopidogrel therapy (p = 0.02).

Drug-eluting stents (DES) were not yet available and therefore were not included in the study.

Compared with aspirin alone, there was an excess of minor and major bleeding with the combination of aspirin and clopidogrel in patients with NSTE MI in the CURE Trial[11,12] (Table 3), although the incidence of life-threatening bleeding was not different between the two groups.[42] Using the Thrombolysis in Myocardial Infarction (TIMI) criteria for major bleeding, the rate of major bleeding with the combination of aspirin plus clopidogrel was similar to that with aspirin alone (1.1% and 1.2%, respectively; p = 0.70). Major or life-threatening bleeding in the PCI-CURE study was similar in the two groups, even in patients who received a GPIIb–IIIa inhibitor. In the CREDO trial, major bleeding as defined by the TIMI criteria tended to be higher in the clopidogrel group than in those given placebo (8.8% and 6.7%, respectively; p = 0.07), although most of the major bleeding episodes were related to invasive procedure, such as CABG. Minor bleeding episodes were significantly more common with combination antiplatelet therapy in

Table 3—Benefits of Combined Use of Aspirin and Clopidogrel After PCI*

Variables	CURE[11] Aspirin Alone	Aspirin Plus Clopidogrel	RR	PCI-CURE[40] Aspirin Alone	Aspirin Plus Clopidogrel	RR	CREDO[42] Aspirin Alone	Aspirin Plus Clopidogrel	RRR
Patients, No.	6,303	6,259		1,345	1,313		1,063	1,053	
Events before PCI									
MI or refractory ischemia				15.3	12.1	0.76‡			
MI				5.1	3.6	0.68†			
Events to 30 d									
CV death, MI, urgent TVR				6.4	4.5	0.70†	8.3	6.8	0.82
CV death, MI				4.4	2.9	0.66†			
CV death				1.0	1.1	1.10	0.4	0	
MI				3.8	2.1	0.56	6.6	5.8	
Q-wave MI				2.4	0.8	0.35			
Urgent TVR				2.8	1.9	0.67	1.3	1.0	
9–12 mo Outcomes	**Cumulative**			**From PCI to 9 mo**			**Cumulative**		
CV death, MI, stroke	11.4	9.3	0.80§				11.5	8.5†	26.9
CV death, MI				8.0	6.0	0.75†	10.4	7.9	24.0
CV death	5.5	5.1	0.93	2.3	2.4	1.07	2.3	1.7	24.6
MI	6.7	5.2	0.77	3.4	4.5	0.71	8.4	6.7	20.8
Q-wave MI	3.1	1.9	0.60	3.5	1.5	0.43			
Non–Q-wave MI	3.8	3.5	0.89						
Stroke	1.4	1.2	0.86				0.9	0.9	10.0
CV death, MI, any revascularization				21.7	18.3	0.83†			
Refractory ischemia	9.3	8.7	0.93						
Any revascularization				17.1	14.2	0.82	21.0	21.3	− 1.1
Any TVR							13.6	13.1	4.0
Urgent TVR							2.2	2.0	8.1

*Data are presented as % unless otherwise indicated. CV = cardiovascular; TVR = target vessel revascularization. Patients undergoing stent placement received open-label thienopyridines for 28 days after PCI; strategies were assessed pretreatment with clopidogrel.
†p < 0.05.
‡p < 0.01.
§p < 0.001.

both the CURE and PCI-CURE studies. The CREDO trial did not find differences in minor bleeding between the two groups.

Multiple randomized trials have shown a marked reduction in angiographic restenosis and need for repeat revascularization with the use of DES compared with bare metal stents (BMS).[43,44] Because of the potential for delayed endothelialization of these devices, the combination of aspirin and a thienopyridine, most often clopidogrel, was given empirically for 2–6 months after the procedure.[45] The cumulative incidence of stent thrombosis in overview analyses of all randomized trials of DES was 1.2% with sirolimus stents (compared with 0.6% with BMS; 95% CI, 0.4 to 1.5) and 1.3% with paclitaxel stents (compared with 0.8% with BMS; 95% CI, 0.3–1.4).[46] Higher rates of late clinical events with DES, including death and MI, have been reported in the observational studies that indirectly compare outcomes with DES and BMS.[47–49]

2.4.1 Preventing Stent Thrombosis

Although uncommon, stent thrombosis represents a severe complication of stent implantation with a high rate of morbidity (mostly MI) and mortality.[50] Reports on the predictors of stent thrombosis following DES implantation have found that clinical (diabetes and renal failure), angiographic (bifurcation disease), and care (premature termination of antiplatelet therapy) characteristics are all associated with a higher risk of late stent thrombosis.[51] Impaired/delayed endothelialization, particularly with placement in the setting of an ACS and premature cessation of antiplatelet drug therapy are also associated with a higher risk of stent thrombosis, which can occur almost immediately (hours) after placement (acute stent thrombosis), soon (days) thereafter (subacute stent thrombosis), or later (beyond 30 days) [late stent thrombosis].[52]

BMS thrombosis, with the introduction of combined therapy with aspirin and clopidogrel, occurs in < 1% of patients, and is unusual after the first month.[53] In contrast, stent thrombosis following DES, although less frequent with dual antiplatelet therapy, can occur months-years after implantation. In the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) Registry,[54] 500 DES-treated MI patients discharged from the hospital on aspirin and thienopyridine therapy were followed for the next 11 months. A total of 68 patients (13.6%) discontinued thienopyridine drugs within 30 days of hospital discharge, and on follow-up were more likely to die during the next 11 months (7.5% vs 0.7%; adjusted hazard ratio 9.0; 95% CI, 0.2–60.5; p < 0.0001) and to be rehospitalized (23% vs 14%; adjusted hazard ratio, 1.5; 95% CI, 0.78 to 3.0; p = 0.08).

An observational study from the Duke Cardiovascular Database[55] including 3,165 patients receiving BMS and 1,501 patients with DES who were event free (death, MI, revascularization) at 6 months and 12 months, were followed up and self-reported clopidogrel use was used to classify patients into four groups: BMS with clopidogrel, BMS without clopidogrel, DES with clopidogrel, and DES without clopidogrel. Among patients with BMS, clopidogrel did not influence the incidence of death or MI at 24 months; however, in patients with DES, continued use of clopidogrel was associated with lower rates of death (0% vs 3.5%; 95% CI, 5.9–1.1%; p = 0.004) and death or MI (0.0% vs 4.5%; 95% CI, 7.1–1.9, p < 0.001) [Fig 2, *left* and *right panels*].

Information regarding the optimal duration of long-term aspirin and clopidogrel following DES
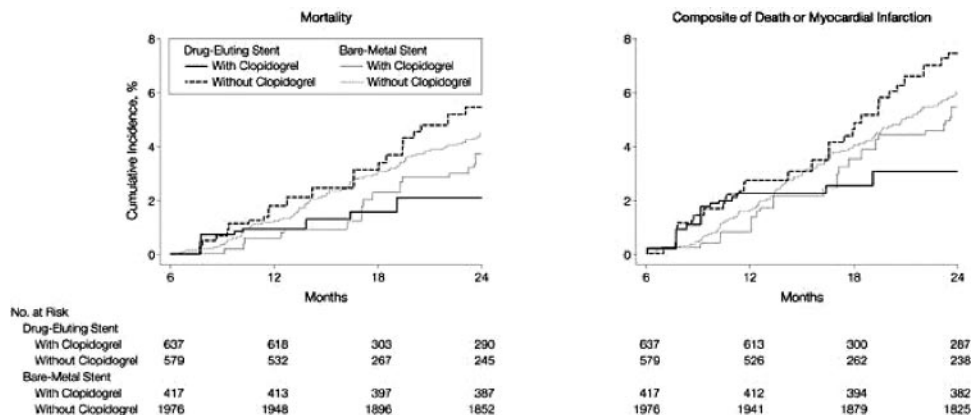

FIGURE 2. *Left panel*: Adjusted cumulative mortality rates using the 6-month landmark analysis; *right panel*: cumulative rates of composite of death or MI using the 6-month landmark analysis.[55]

continues to evolve.[56] A recent American Heart Association Science Advisory stresses the importance of 12 months of dual antiplatelet therapy and the education of patients and providers about the potential hazards associated with premature discontinuation of these drugs.[57]

2.4.2 Triple Antithrombotic Therapy

Treatment of patients with coronary stents becomes a challenge when they also require treatment with VKA because of associated atrial fibrillation, mechanical heart valve replacement, and other indications for long-term VKA therapy. Stent thrombosis is more likely when clopidogrel is withheld, whereas it is likely that stroke risk (in atrial fibrillation and mechanical valve patients) increases if VKA is withdrawn after stenting. However, bleeding risk increases when VKA is added to aspirin or clopidogrel or to both.

The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) Registry illustrates current practice patterns for combined antithrombotic therapy.[58] The study population comprised 103,742 patients enrolled between May 2003 and June 2006. A total of 7,201 patients (7% of the total population) were receiving VKA therapy at the time of hospital admission for ACS. From a population of 5,673 patients with complete outcomes and medication data, 1,357 (24%) were not discharged on a VKA. Patients in whom VKA therapy was discontinued more often experienced major bleeding and required a blood transfusion during their hospitalization and were more likely to have undergone PCI with stenting than those who continued VKA therapy. Overall, aspirin, clopidogrel, and VKA were used together in 59% of patients.

Multivariable regression analysis demonstrated the following factors independently associated with a decision not to continue VKA at the time of hospital discharge: discharge clopidogrel (OR, 3.11; 95% CI, 2.44–3.95), RBC transfusion (OR, 1.72; 95% CI, 1.18–2.52), nonwhite race (OR, 1.47; 95% CI, 1.15–1.89), prior stroke (OR, 1.22; 95% CI, 1.01–1.49) and PCI with or without stenting (OR, 1.04; 95% CI, 0.83–1.30). Stroke risk, as estimated by the CHADS$_2$ Score, was not associated with discharge VKA therapy. In contrast, when stratified by hemorrhagic risk that included age $\geq$ 65 years, prior stroke, history of bleeding, hematocrit $<$ 30%, diabetes mellitus, and a serum creatinine $>$ 1.5 mg/dL, patients with a higher risk score were less likely to receive VKA at the time of discharge. Thus, the CRUSADE Registry experience suggests that a perceived risk of hemor-

rhage may influence a clinician's decision to continue VKA to a greater degree than the perceived risk for thrombosis.

In the Global Registry of Acute Coronary Events (GRACE) Registry,[59] 800 patients with an ACS who underwent PCI and stenting (130 patients received a DES) were discharged on VKA and either dual (n = 580) or single (n = 220) antiplatelet therapy: data on the type of stent (BMS vs DES) were available on 482 patients. Approximately 22% of patients with a DES were discharged on a VKA and single antiplatelet agent. Use of single antiplatelet therapy was more common in Europe than in the United States (34% vs 17%, p $<$ 0.001). There were no differences in major bleeding during hospitalization or in the combined 6-month outcome of death or MI. At 6 months one fourth to one third of patients were not receiving antiplatelet therapy, only a VKA. Among patients treated initially with single antiplatelet therapy, the use of either aspirin or thienopyridine in combination with VKA was associated with similar outcomes. An analysis of 66 patients discharged from the Mayo Clinic after PCI with stenting who also had a concomitant indication for VKA therapy reported that six patients (9.2%) required medical attention after major hemorrhage.[60]

A population-based observational cohort study[61] included a total of 21,443 elderly survivors of acute MI. Hospitalizations for bleeding were observed in 1,428 patients (7%). Rates of bleeding, compared to aspirin alone, were higher, by approximately twofold, with combined antiplatelet, VKA-antiplatelet, and three-drug combination therapy; however, the overall risk when considered on a per patient-year basis was low.

A retrospective analysis using computerized PCI databases in six western Finnish hospitals[62] identified 239 patients with a long-term indication for VKA therapy. A similar number of patients undergoing PCI who did not have an indication for VKA served as the control group. Warfarin treatment was an independent predictor of death, MI, target vessel revascularization, and stent thrombosis (composite outcome measure) at 12-month follow-up (OR, 1.7; 95% CI, 1.0–3.0; p = 0.05), and its use was also associated with major hemorrhage (OR, 3.4; 95% CI, 1.2–9.3; p = 0.02). Triple therapy was employed in 48% of patients receiving stents. Stent thrombosis was highest in patients treated with VKA and aspirin. The incidence of stroke was highest (8.8%) among patients in whom VKA was substituted with double antiplatelet therapy. The case-control study suggests that stent thrombosis is more likely when clopidogrel is withheld, and stroke risk increases when VKA is

withdrawn after stenting. Bleeding can occur with either VKA plus aspirin or clopidogrel or triple therapy.

In the absence of randomized, controlled clinical trials, when VKA therapy is clearly indicated (as in a patient with atrial fibrillation with a history of prior stroke), frequent INR monitoring, if possible through an experienced Anticoagulation Clinic, should be undertaken, with consideration for targeting the lower end of the therapeutic range. Similarly, the lowest effective aspirin dose should be employed with combination therapies. Clinicians should consider proton pump inhibitors, particularly among patients with risk factor or a prior history of gastritis and/or peptic ulcer disease. The role of concomitant vitamin K supplementation to achieve greater INR stability and, in turn, reduce hemorrhagic risk requires further investigation.

Among patients undergoing PCI with strong consideration of concomitant stent placement, a BMS should be considered to minimize the duration of triple therapy—typically 4 weeks, followed by VKA plus aspirin.[63] While this is a shorter duration of aspirin and clopidogrel than is indicated typically based on all available data (12 months), 4 weeks represents the minimum length of dual antiplatelet therapy that seems associated with the period of risk from stent thrombosis. Whenever possible, clinicians should avoid quadruple antithrombotic therapy (LMWH, VKA, aspirin, thienopyridine) unless the patient is at very high risk for thrombosis (and at very low risk for bleeding).

2.4.3 Economics of Clopidogrel Use Following PCI With BMS

Several empirical economic analyses have examined the use of clopidogrel in the post-PCI setting. When the 1-year outcome differences were extended out to a lifetime time horizon with modeling, clopidogrel was associated with 0.15 to 0.19 extra life-years per patient.[64] The incremental 1-year costs of the clopidogrel therapy arm ranged between $560 and $660. The resulting cost-effectiveness ratio was less than $5,000 per life-year added with 98% of bootstrap samples yielding a cost-effectiveness ratio < $50,000.

The PCI-CURE Study was a prospectively defined substudy of the larger CURE Study.[40] Although an early invasive approach to ACS was discouraged in CURE, 2,658 patients subsequently underwent a PCI. Of these, 1,730 (65%) were done during the index hospitalization (median of 6 days following randomization) and 928 subsequently (median time to PCI, 49 days). Open label thienopyridine therapy was used for 2 to 4 weeks after PCI, following which

patients received their randomized therapy for 3 to 12 months (mean, 8 months). In the economic analysis of this trial, estimated life expectancy was increased by approximately 0.09 to 0.1 life-years with clopidogrel therapy.[65] Net incremental costs of clopidogrel therapy were lowered by the cost savings from fewer repeat revascularizations and averaged between $250 and $425. Resulting cost-effectiveness ratios were < $5,000 per life-year saved.

Economic analyses in Europe have generally reached similar conclusions. In a Swedish analysis using the CREDO clinical results and a Markov model, clopidogrel therapy for 12 months had a cost-effectiveness ratio of about Euro 3000 per life-year saved.[66] A second Swedish analysis using an empirical database of ACS patients together with the PCI-CURE results and a Markov model, calculated cost-effectiveness ratios less than Euro 10,000 per life-year saved.[67]

Thus, while CREDO and PCI-CURE differ in a number of details, both support the economic attractiveness of a limited course of clopidogrel therapy for up to 1 year following PCI with BMS. This result is obtained because the absolute reduction in adverse events (itself a product of the primary vascular event rate in the placebo group and the relative reduction in events due to therapy) is sufficiently large relative to the incremental costs of 1 year of clopidogrel therapy. In PCI-CURE, all patients had ACS usually with positive cardiac biomarkers or ST-segment changes to qualify for enrollment. In CREDO, two thirds of patients were referred for PCI due either to a recent MI or unstable angina. Thus, conclusions about clinical and economic attractiveness are most firm when considering therapy in ACS patients and uncertainty is greater regarding the use of 1 year of clopidogrel following PCI with BMS in lower-risk patients with stable CAD.

Recommendations

2.4. For long-term treatment after PCI, we recommend aspirin at a dose of 75–100 mg/d (Grade 1A).
2.4.1. For patients undergoing PCI with BMS placement, we recommend aspirin (75–100 mg/dy) plus clopidogrel over aspirin alone (Grade 1A).
2.4.1.1. For patients undergoing PCI with BMS placement following ACS, we recommend 12 months of aspirin (75–100 mg/d) plus clopidogrel (75 mg/d) over aspirin alone (Grade 1A).
2.4.1.2. For patients undergoing PCI with DES, we recommend aspirin (75–100 mg/d) plus clopidogrel (75 mg/d for at least 12 months) [Grade 1A for 3 to 4 months; Grade 1B for 4 to 12 months]**.
Beyond 1 year, we suggest continued treatment**

with aspirin plus clopidogrel indefinitely if no bleeding or other tolerability issues (Grade 2C).
2.4.2. For patients undergoing stent placement with a strong concomitant indication for VKA, we suggest triple antithrombotic therapy (Grade 2C). **We suggest 4 weeks of clopidogrel following BMS and 1 year following DES** (Grade 2C). *Values and preferences:* This recommendation places a high value on the prevention of thromboembolism, including stent thrombosis, and a lower value on minimizing bleeding risk.

For recommendations on the use of antiplatelet agents in other patient populations with atrial fibrillation, see the "Atrial Fibrillation" chapter.

2.5 Other Oral Antiplatelet Agents

Cilostazol, which selectively inhibits $3'5'$-cyclic nucleotide phosphodiesterase III, has antiplatelet and vasodilating effects. In addition, this agent also inhibits vascular smooth-muscle cell proliferation *in vitro*.[68] Early studies with cilostazol suggested that this agent could be used as an alternative to ticlopidine in patients undergoing stent implantation,[69] but cilostazol's effectiveness in preventing subacute thrombosis in patients with DES has been questioned.[70]

A number of studies have evaluated cilostazol for prevention of restenosis after coronary stenting.[68,71–75] These studies have yielded conflicting results. Although initial small studies suggested that cilostazol reduces restenosis, the largest study failed to demonstrate a benefit of cilostazol. One study randomized 409 patients undergoing elective stent placement to receive aspirin plus ticlopidine or aspirin plus cilostazol starting 2 days before stenting.[69] The angiographic restenosis rate was 27% in patients treated with aspirin and ticlopidine and 22.9% in those given aspirin and cilostazol (p = not significant [NS]). The Cilostazol for Restenosis Trial (CREST) trial[76] included 705 patients undergoing PCI with BMS placement randomized to cilostazol 100 mg bid, plus aspirin and clopidogrel or placebo plus aspirin and clopidogrel. At 6 months, patients receiving triple platelet-directed therapy had a larger in-stent minimal luminal diameter than those given aspirin and clopidogrel (p = 0.01).

The addition of dipyridamole to aspirin provides little incremental benefit over aspirin alone for the prevention of early complications after coronary angioplasty. In a study of 232 patients randomly assigned to aspirin alone (975 mg/d) or the combination of aspirin (975 mg/d) plus dipyridamole (225 mg/d) before coronary angioplasty, there were no differences in the frequency of Q-wave MI (1.7% vs 4.3%, respectively) or in the need for emergency CABG (2.6% vs 6.1%, respectively).[77] Other antiplatelet agents, such as prostacyclin, ketanserin, sarpogrelate, and sulotroban, have had little or no effect on the prevention of acute complications[78] or restenosis after PCI.[79–85]

Recommendations

2.5. For patients after stent placement, we suggest clopidogrel (Grade 1A) **or ticlopidine** (Grade 2B) **over cilostazol. We recommend clopidogrel over ticlopidine** (Grade 1A).
2.5.1. In aspirin-intolerant patients undergoing PCI, we recommend use of a thienopyridine derivative rather than dipyridamole (Grade 1B).

2.6 VKAs

Initially, antithrombotic regimens after stent placement included aspirin, dipyridamole, dextran, IV heparin, and warfarin for 30 days. These aggressive antithrombotic regimens were used in an attempt to prevent subacute stent thrombosis.[86,87] Randomized trials have since shown that warfarin provides little incremental benefit over aspirin alone on early outcomes in patients undergoing stent implantation. In the Stent Anticoagulation Restenosis Study (STARS) Trial,[88] the primary end point, a composite of death, revascularization of the target lesion, angiographically evident thrombosis, or MI within 30 days, occurred in 3.6% of patients assigned to receive aspirin alone, 2.7% of patients assigned to receive aspirin plus warfarin, and in only 0.5% assigned to receive aspirin plus ticlopidine (p = 0.001 for the comparison of all three groups). In a smaller series of 164 patients who were randomly assigned to aspirin (100 mg/d) or to aspirin plus warfarin after provisional coronary stenting, subacute closure occurred in 10.1% of those given aspirin alone and in 3.5% of those given aspirin plus warfarin (p = 0.09).[89]

Five trials have evaluated the effect of long-term warfarin on restenosis after PCI (Table 4).[90–94] A randomized trial of warfarin or placebo in 110 patients after angioplasty[91] showed no difference in restenosis in the two groups (29% and 37%, respectively). A second study of 248 patients randomly assigned to aspirin (325 mg/d) or warfarin also failed to identify an incremental benefit of warfarin over aspirin for the prevention of restenosis.[90] Another study randomized 191 patients undergoing uncomplicated percutaneous transluminal coronary angioplasty (PTCA) to aspirin (100 mg/d) or to aspirin plus warfarin for 6 months. Stents were implanted in 33% and 36% of patients in the two respective groups. Restenosis at 6 months occurred in 30% of patients assigned to aspirin and in 33% of those given aspirin

Table 4—Effect of Warfarin on Restenosis After PCI (Section 2.6)*

Study/yr	Study Design	Total Patients, No.	Angiographic Follow-up, No.	Stent Use, %	Treatment	Pretreatment Duration	Duration Therapy	Restenosis Rates, %
Urban et al[91]/1988	RCT	110	85	No	Warfarin (PT > 2.5 times normal)	None	5 mo	29
					Placebo			37
Kastrati et al[94]/1997	RCT	496	432	Yes	Warfarin (INR 3.5–4.5)	None	4 wk	28.9
					Ticlopidine 250 mg bid			26.8
Garachemani et al[92]/2002	RCT	191	176	36	Warfarin (INR 2.5–4.0)	None	6 mo	33
					Aspirin plus warfarin			30
Thornton et al[90]/1984	RCT	248	178	No	Aspirin, 325 mg qd	24 h	6 mo	27†
					Warfarin (to PT 2.5 times normal)			36
ten Berg et al[93]/2003	RCT	531	480	34	Coumarin (INR 2.1–4.8)	7 d	6 mo	38.9‡
					Placebo			39.1

*PT = prothrombin time. Restenosis is defined as > 50% follow-up diameter stenosis unless indicated otherwise.
†Restenosis defined a loss of 50% of initial gain.
‡Mean % stenosis at follow-up.

plus warfarin.[92] The Balloon Angioplasty and Anticoagulation Study (BAAS)[93] studied the effect of pretreatment with coumarins on 6-month angiographic outcomes in 531 patients. Subjects were randomized to aspirin alone or to aspirin plus a coumarin derivative started 1 week before the procedure. Mean luminal diameter at 6 months was similar in both groups.

Recommendation

2.6. In patients who undergo PCI with no other indication for VKA, we recommend against VKA (Grade 1A).

3.0 CHF With and Without CAD

3.1 Background

Five million Americans currently live with heart failure, and there are approximately 400,000 new cases each year; approximately 250,000 patients die and 75,000 have strokes attributable to heart failure annually. Because heart failure is marked by low cardiac output, relative stasis of blood in the intracardiac chambers and venous circulation, poor ventricular and atrial contractility, regional wall motion abnormalities, and a high prevalence of atrial fibrillation, patients with heart failure have high rates of systemic and pulmonary embolism (Table 5).[95–105] Early autopsy studies of patients with cardiomyopathy reported high rates of thromboembolism (TE). In 1958, Spodick and Littmann[106] reported a 50% incidence of TE in autopsy cases of CHF; nearly 30 years later, Roberts et al[107] found evidence of TE in 37% of 152 autopsied patients with dilated

cardiomyopathy. Four modern series of CHF patients and subsequent TE suggest a somewhat lower rate.[108–111]

In a widely cited longitudinal series of 104 patients with dilated cardiomyopathy, Fuster et al[95] reported systemic arterial embolism at a rate of 3.5/100 patient-years. Natterson et al[112] reported a 3.2/100 patient-year rate of TE in heart failure patients awaiting cardiac transplant. Sharma et al[113] reviewed 144 consecutive patients with severe left ventricular dysfunction and reported a 12.5% rate of TE > 27.6 months. Although the current rate of TE is lower than in early observations, thrombosis may still play an important contributing role in death and disability among this increasingly prevalent patient population. Recent studies have suggested that coronary thrombosis is common in heart failure patients dying of sudden death and even progressive pump failure.[114]

3.2 CHF: Interaction of Etiology and Outcomes

The underlying etiology of heart failure has important implications for prognosis and for treatment, including with antithrombotic therapies. Patients with an ischemic etiology constitute 70% of patients with systolic left ventricular dysfunction and heart failure while nonischemic etiologies make up 30%, with the leading causes being hypertension and idiopathic. This high prevalence of CAD in CHF patients represents a significant change in etiologies over the last 50 years: in the 1950s and 1960s, hypertension and valvular heart disease were the dominant causes of CHF and this may be reflected in part in the higher rates of TE found at autopsy during those decades.

Table 5—*Randomized Trials of ASA and VKA in Patients With Chronic Heart Failure: Clinical Description and Results (Section 3.1)*

Study/yr	Interventions	Patients Analyzed, No./Total (%)	Duration of Follow-up	Mortality, No./Total (%) (95% CI)	MI, No./Total (%) (95% CI)	Stroke, No./Total (%) (95% CI)	Hemorrhage, No./Total (%) (95% CI)	Comments
Aspirin vs placebo or no antithrombotic therapy								
Cleland et al[120]/2004	Control: no antithrombic therapy Aspirin, 300 mg/d	Control: 99/99 (100) Aspirin: 91/91 (100)	Mean, 27 ± 1 mo	Control: 21/99 (21) Aspirin: 27/91 (30) RR 1.40 (0.85–2.29)	Control: 7/99 (7) Aspirin: 8/91 (9) RR 1.24 (0.47–3.29)	Control: 2/99 (2) Aspirin: 2/91 (2) RR 1.09 (0.16–7.56)	Control: 0/99 (0) Aspirin: 1/91 (1) RR 3.26 (0.13–79.05)	
MacIntyre et al[191]/2005	Placebo Aspirin 75 mg/d	Overall 9/12; not reported per group	7 d	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)	All patients taking stable dose of ACEIs; all patients 25 mg captopril after 7 d
Clopidogrel vs aspirin								
Serebruany et al[105]/2002	Aspirin: 325 mg/d Clopidogrel and aspirin: clopidogrel 75 mg/d, and aspirin 325 mg/d	Aspirin: 25/25 (100) Clopidogrel and aspirin: 25/25 (100)	30 d	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)	All pretreated with aspirin, 325 mg/d
Warfarin vs no antithrombotic therapy								
Cleland et al[120]/2004	Control: no antithrombic therapy Warfarin target INR 2.5	Control: 99/99 (100) Warfarin: 89/89 (100)	Mean, 27 ± 1 mo	Control: 21/99 (21) Warfarin: 22/89 (25) RR 1.17 (0.69–1.97)	Control: 7/99 (7) Warfarin: 3/89 (3) RR 0.48 (0.13–1.79)	Control: 2/99 (2) Warfarin: 0/89 (0) RR 0.22 (0.01–4.57)	Control: 0/99 (0) Warfarin: 4/89 (4) RR 10.0 (0.55–183.2)	
Warfarin vs aspirin								
Cleland et al[120]/2004	Aspirin: 300 mg/d Warfarin target INR 2.5	Aspirin: 91/91 (100) Warfarin: 89/89 (100)	Mean, 27 ± 1 mo	Aspirin: 27/91 (30) Warfarin: 22/89 (25) RR 0.83 (0.51–1.35)	Aspirin: 8/91 (9) Warfarin: 3/89 (3%) RR 0.38 (0.11–1.40)	Aspirin: 2/91 (2) Warfarin: 0/89 (0) RR 0.20 (0.01–4.20)	Aspirin: 1/91 (1) Warfarin: 4/89 (4) RR 4.09 (0.47–35.88)	

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3.3 VKA and/or Aspirin

3.3.1 Metaanalysis

A pooled analysis of multiple randomized trials of oral anticoagulation in patients with heart failure revealed that patients receiving warfarin had less TE and lower mortality rates than those receiving no anticoagulation. Bleeding complications were more common in the warfarin group.[115] Because 75% of the information in the analysis came from 50-year-old evidence, the potential benefit of warfarin remains unclear.

3.3.2 Clinical Trials

Early studies investigating anticoagulation were predominantly conducted in patients with nonischemic cardiomyopathy and concomitant high prevalence of rheumatic heart disease and atrial fibrillation. In the 1950s, four small prospective controlled trials of warfarin vs placebo were conducted in hospitalized patients. Despite major methodologic limitations of these trials, warfarin proved beneficial in comparison to placebo.[106,116–119]

To our knowledge, the only modern randomized controlled trial of anticoagulation in patients with heart failure who were also in normal sinus rhythm, the Warfarin/Aspirin Study in Heart failure (WASH) study.[120] This pilot study had as its primary end point the feasibility of conducting a definitive study that would require 1,200 patients in the treatment arm. The principal secondary end point was a combination of all-cause mortality, nonfatal MI and nonfatal stroke. The study employed an open-label, but blinded end point adjudication design. Two hundred seventy-nine patients with clinical heart failure treated with diuretics and echocardiographic evidence of left ventricular dysfunction were randomized to receive oral anticoagulation with warfarin (target INR, 2.5), aspirin (300 mg/d), or no antithrombotic therapy and followed for 2.5 years. There was no significant difference in the composite end point of death, MI, or stroke in patients treated with warfarin vs aspirin vs no antithrombotic therapy (18% vs 22% vs 20%, respectively). Patients receiving warfarin spent fewer days in the hospital than those treated with aspirin or no antithrombotic therapy. There was an excess of all-cause hospitalizations due to exacerbations of heart failure in the aspirin group (p = 0.05). There were five major hemorrhages in the study, one on aspirin treatment and four on warfarin treatment. Serious adverse events among patients taking aspirin were 198 compared with 173 on warfarin and 178 on no antithrombotic therapy. The WASH study suggested that there is no advantage or disadvantage of anticoagulant therapy compared with antiplatelet therapy or placebo, emphasizing the need for large-scale investigations of antithrombin or antiplatelet therapy in patients with CHF.[120–122]

The HELAS trial[123] was a randomized, blinded, placebo-controlled study that compared aspirin and warfarin in patients in whom the heart failure was secondary to MI and compared placebo and warfarin if the cause was idiopathic. Patients with Class II–IV CHF, aged 20–80, with an ejection fraction ≤ 35% were randomized according to the etiology of their CHF. Although the trial did not achieve its recruitment target, preliminary results in 223 patients showed no difference in outcome in the two groups.

Four large-scale, nonrandomized cohort analyses of patients with heart failure and systolic dysfunction have been conducted. In the SOLVD study[124] of enalapril vs placebo in patients with left ventricular dysfunction (70% with an ischemic etiology), warfarin was associated with significantly lower risk of all-cause death and sudden death. The reduction of sudden death was independent of etiology. In the CONSENSUS trial[108] of enalapril vs placebo in class IV CHF, long-term anticoagulation with warfarin was associated with a 40% lower mortality, despite the fact that only 25% of the deaths were due to sudden death.

The vasodilator heart failure studies provide further observational evidence regarding the role of oral anticoagulation in preventing TE among CHF patients. In V-HeFT-I, there was no significant difference in the rates of TE between patients receiving long-term warfarin therapy and those who did not receive anticoagulation.[109] In V-HeFT-II,[97] there was an incidence of 2.1 events/100 patient-years among patients without antithrombotic therapy compared with 4.9 events/100 patient-years among patients who received warfarin. The incidence of thromboembolic events was higher in patients receiving warfarin (p = 0.01) This may reflect a difficulty in ascertaining whether the warfarin therapy was actually used in this higher-risk patient population. In addition these analyses were not adequately adjusted for other risk factors such as degree of heart failure, atrial fibrillation, age, gender, previous cerebrovascular disease, or left ventricular thrombus. In the SAVE trial[96] of post MI heart failure, all of ischemic etiology, warfarin was associated with an 81% reduction in stroke risk and aspirin was associated with a 56% reduction in stroke. No direct comparison of warfarin and aspirin was reported. In a retrospective analysis of the 324 patients in the PROMISE trial who were given warfarin, there was a significant reduction in stroke only among those with ejection fraction < 20% (0.6% vs 3.3%; p < 0.05).[111] The limitations of such analyses are important: it is not possible to completely adjust for differences in baseline characteristics

Treatment Drug/Daily Dose, mg	Onset, Postoperative d	Graft Patency, No. Patent of Grafts/ Treated (%)	Graft Patency, No. Patent of Grafts/ Control (%)	Study Duration, mo	p Value	Study/yr
Aspirin						
100	1	36/40 (90)	36/53 (68)	4	0.012	Lorenz et at al[129]/1984
100	− 7	122/128 (95)	132/145 (91)	6	NS	Hockings et al[130]/1993
150	1	639/745 (86)	615/750 (82)	1	0.058	Sanz et al[131]/1990
325	− 1	291/340 (87)	267/345 (77)	12	< 0.05	Goldman et al[132]/1989
325	− 1	347/371 (94)	327/384 (85)	< 2	< 0.01	Goldman et al[133]/1988†
325	− 1	62/365 (17)	74/376 (19.7)	36	0.404	Goldman et al[134]/1994†
324	0	112/119 (94)	88/100 (88)	12	0.01	Gavaghan et al[135]/1991
975	− 1	313/339 (92)	327/384 (85)	< 2	< 0.05	Goldman et al[133]/1988†
975	− 1	262/315 (83)	267/345 (77)	12	NS	Goldman et al[132]/1989†
1,200	3–4	65/81 (80)	54/74 (72)	24	NS	McEnany et al[136]/1982
975	3–5	87/111 (78)	76/95 (80)	12	NS	Sharma et al[137]/1983
975	3–5	100/114 (88)	116/147 (79)	12	NS	Brown et al[138]/1985
Aspirin plus dipyridamole						
150 + 225	1	646/742 (87)	615/750 (82)	1	0.017	Sanz et al[131]/1990
1,300 + 100	1	69/75 (92)	72/93 (77)	3–6	< 0.02	Mayer et al[139]/1981
990 + 225	− 1	87/95 (92)	88/118 (75)	6	< 0.01	Rajah et al[140]/1985
975 + 225	− 1, − 2	330/359 (92)	327/384 (85)	< 2	< 0.05	Goldman et al[133]/1988†
975 + 225	− 1, − 2	260/315 (83)	267/345 (77)	12	NS	Goldman et al[132]/1989†
975 + 225	0, − 2	425/478 (89)	364/486 (75)	12	< 0.05	Chesebro et al[141]/1984
975 + 225	3	27/33 (82)	50/61 (82)	6	NS	Pantely et al[142]/1979
975 + 225	3–5	119/138 (86)	116/147 (79)	12	NS	Brown et al[138]/1985
975 + 225	3–5	74/89 (83)	76/95 (80)	12	NS	Sharma et al[137]/1983
990 + 225	2–3	100/133 (75)	91/133 (68)	12	NS	Brooks et al[143]/1985
1,000 + 225	0	24/37 (65)	8/38 (21)	12	< 0.001	Pirk et al[144]/1986
Aspirin 325 or aspirin 975 or aspirin 975 plus dipyridamole 225	− 1, − 2	274/303 (90)‖	71/80 (89)	12	NS	Goldman et al[134]/1994
Dipyridamole						
400	− 2	316/413 (77)	305/421 (72)	12	NS	Ekeström et al[145]/1990
Ticlopidine						
500	2	185/220 (84)	153/207 (74)	12	0.01	Limet et al[146]/1987
500§	2	71/79 (90)	47/59 (80)	3	< 0.01	Chevigné et al[147]/1984
Sulfinpyrazone						
800	− 2	296/328 (90)	327/384 (85)	< 2	NS	Goldman et al[133]/1988†
800	− 2	248/303 (82)	267/345 (77)	12	NS	Goldman et al[133]/1988†
800	1	204/212 (96)	199/219 (91)	< 1	< 0.025	Baur et al[148]/1982
Oral anticoagulant						
	3–4	55/65 (85)	54/74 (72)	24	NS	McEnany et al[136]/1982
	3	29/37 (78)	50/61 (82)	6	NS	Pantely et al[142]/1979
	7	227/251 (90)	199/238 (85)	2	< 0.015	Gohlke et al[149]/1981

*Dipyridamole was started 2 days before operation; aspirin was started 12 h before operation.
†Dipyridamole was started 2 days before operation; aspirin was started on the day of operation.
‡All grafts were to left anterior descending coronary artery only in this subset analysis.
§Studied by scintigraphy or coronary angiography.

or for variations in compliance, adherence, and crossovers in an unspecified retrospective analysis.

The Veterans Administration performed the Warfarin Antiplatelet Trial And Chronic Heart failure (WATCH) trial.[125] Although originally planned to enroll 4,500 patients, the trial ended enrollment at 1,587 patients with New York Heart Association class II-IV with ejection fraction ≤ 40% who were randomized to warfarin or blinded antiplatelet therapy with aspirin or clopidogrel. The WARCEF study[126] is a two-arm, blinded, randomized multicenter trial with a target enrollment of 2,860 patients. The study is designed to test whether patients with low ejection fraction randomized to warfarin (target INR, 2.5–3) or aspirin (325 mg) have differences in the composite end point of death, recurrent stroke, or intracranial hemorrhage. Given the limited recruitment of the WATCH study and the slow recruitment of recruiting patients into the WARCEF study, a pooled analysis is planned to address whether mortality is reduced with warfarin compared with aspirin.

Results of a retrospective analysis of the SOLVD

study suggested that angiotensin-converting enzyme inhibitors (ACEI) are less effective in patients taking aspirin.[127] Four subsequent studies suggested a benefit of ACEI when combined with or without aspirin. The results of an analysis of four randomized trials of ACEI therapy with or without aspirin found no significant differences in the reduction of risk of major vascular events (p = 0.15) except MI (p = 0.01).[127]

Last, a community-based cohort study of 7,352 patients discharged after their first hospitalization for heart failure failed to identify an adverse relationship between aspirin use and either mortality rates or heart failure readmission rates on ACE inhibition-derived benefit.[128]

Recommendation

3.1. In patients with CHF due to a nonischemic etiology, we recommend against routine use of aspirin or oral VKA (Grade 1B).

4.0 ANTITHROMBOTIC THERAPY IN PATIENTS WITH SAPHENOUS VEIN AND INTERNAL MAMMARY BYPASS GRAFTS

This section begins with a brief discussion of surgical techniques, anastomotic devices, and antifibrinolytic agents and includes a discussion of the prevention of saphenous vein graft occlusion following CABG. Table 6 lists details of studies comparing the effects of antithrombotic therapy with placebo on graft patency in randomized controlled trials in CABG with vein grafts. The second section describes the prevention of internal mammary artery (IMA) bypass graft occlusion following CABG.[129–149]

4.1 Prevention of Saphenous Vein Graft Occlusion Following CABG

4.1.1 Surgical Techniques and Anastomotic Devices

Approaches to coronary arterial surgery have changed dramatically over the past decade, with marked advances in minimally invasive direct coronary artery bypass (MIDCAB), off-pump coronary artery bypass (OPCAB), and totally endoscopic, robot-assisted coronary artery bypass grafting (TECAB). Advances in surgical techniques[150] demanded equally advanced accessory technologies to include visualization systems, stabilizers, and anastomotic devices[151] to permit requisite surgical precision on a beating heart.

4.1.2 Graft Patency Rates for MIDCAB and OPCAB Procedures

The promise of minimally invasive surgical revascularization and off-pump procedures has focused on shortened recovery time, hospital length of stay, and transfusion requirements.[152] One area of interest is graft patency. A meta-analysis of 5 randomized trials comparing off-pump vs on-pump coronary bypass surgery, for a total of 842 and 998 grafts, respectively, identified a reduction in graft patency with OPCAB procedures (OR 1.51; 95% CI, 1.15–1.99; p = 0.003).[152]

The experience to date with MIDCAB and OPCAB procedures with direct, endoscopic and telesurgical approaches to harvesting the internal thoracic artery has been reasonable though limited by the size of the studies,[153,154] and further investigation is warranted.

4.1.3 Graft Patency With Anastomic Devices

The placement of a foreign material or device within a coronary artery provokes an inflammatory and thrombotic response. Accordingly, criteria for anastomotic devices have been developed to limit the "blood-nonintimal surface area" to 1.3 mm^2. Several anastomotic devices, including the St. Jude Symmetry Aortic Connector and Distal Anastomic Device (St. Jude Medical; St. Paul, MN), were removed from the market when saphenous graft occlusion rates approached 30% at 30 days of follow-up. Other devices, such as the Corlink automated aortic anastomotic system (Bypass Ltd; Herzelia, Israel), have caused either occlusion or stenosis in 20% and 11% of grafts, respectively. The experience with Magnetic Vascular Positioner (Ventrica Inc; Fremont, CA) and C-Port devices (Cardica, Inc; Redwood City, CA) has been more favorable.[151] The safety of both proximal and distal anastomotic devices in off-pump coronary artery bypass will require further investigation.

4.1.4 Aprotinin in Coronary Bypass Surgery

Strategies to reduce surgical bleeding risk and associated morbidity and mortality have an important place in clinical practice. Aprotinin, an antifibrinolytic agent approved in 1993, has been shown to foster hemostasis in high-risk cardiovascular surgery. The drug's overall safety has been questioned recently following publication of a large observational study[155] involving 4,374 patients who underwent surgical revascularization. Aprotinin use was associated with a high incidence of postoperative renal failure requiring dialysis. In addition, patients receiving aprotinin had a 55% increase in either MI or CHF, and a near twofold increase in the overall incidence of ischemic stroke or encephalopathy. A 5-year follow-up study performed by the same investigators[156] identified a higher rate (20.8% 5-year mortality compared to 12.7% for control; covariate

adjusted hazard ratio, 1.48; 95% CI, 1.19–1.85). Neither aminocaproic acid nor tranexamic acid use was associated with an increased mortality.

4.1.5 Treatment With Antiplatelet Agents: Aspirin

A systematic review[157] conducted by the Antiplatelet Trialists' Collaboration showed that treatment with antiplatelet agents, especially when initiated early, was associated with improved graft patency for an average of 1 year after surgery. The data suggest that similar improvements in bypass graft patency could result from starting antiplatelet agents before operation or within 24 h thereafter. In addition, higher and hence more gastrotoxic doses of aspirin were no more effective than 75 to 325 mg/d (see the "Antiplatelet Drugs" chapter by Patrono et al in this supplement). The pooled odds reduction for graft closure was 44% in the five trials that compared low-dose aspirin (75 to 325 mg/d), and 50% in the nine trials that compared high-dose aspirin (500 to 1,500 mg/d) with placebo or control therapy, but this difference was not statistically significant.

Table 6 shows results of trials comparing aspirin with placebo. A 3-year follow-up study of 455 patients by Goldman et al[134] published in 1994 showed that use of aspirin, 325 mg/d, for 2 additional years after an initial year of therapy showed no long-term benefit on saphenous vein bypass graft patency compared to placebo (62/365 = 17% vs 74/376 = 19.7%; p = 0.40). Among patients with patent saphenous vein bypass grafts 7 to 10 days after operation, the 3-year patency was more related to operative technique and underlying disease than to therapy with aspirin after the first year.

Timing of Aspirin Administration: Indirect comparison of studies that started aspirin before vs after surgery administration of aspirin did not reveal differences in patency rates. One randomized clinical trial (RCT) published in 1991 compared the effects of preoperative aspirin, 325 mg/d (started the day before surgery), with aspirin begun 6 h after surgery.[158] Early aspirin was not more effective than aspirin after operation (started on the day of surgery) at improving early (7- to 10-day) graft patency, but it was associated with increased bleeding complications.

Recommendation

4.1.5. For all patients with CAD undergoing CABG, we recommend aspirin, 75 to 100 mg/d, indefinitely (Grade 1A)**. We suggest that the aspirin be started postoperatively** (Grade 2A)**.**

4.1.6 Treatment With Antiplatelet Agents: Aspirin in Combination With Dipyridamole

The Antiplatelet Trialists' Collaboration overview[157] found no benefit of the combination of aspirin and dipyridamole over aspirin alone on graft patency. Individual trials performed since 1990 have failed to show a convincing benefit attributable to the addition of dipyridamole to a background of aspirin therapy following CABG.[129–133,135–143,159–162]

Recommendation

4.1.6 For patients undergoing CABG, we recommend against addition of dipyridamole to aspirin therapy (Grade 1A)**.**

4.1.7 Indobufen

Indobufen is a reversible platelet cyclooxygenase inhibitor that allows platelet function to recover promptly after discontinuation. In three randomized trials, graft patency after indobufen was compared to aspirin combined with dipyridamole. Efficacy was similar,[163–165] although indobufen was associated with fewer adverse events or better tolerance.[164] In one of the investigations,[163] both the indobufen arm of the study and the aspirin-plus-dipyridamole arm showed low patency rates. Indirect comparison to aspirin alone suggests similar patency rates for indobufen. Since there is a lack of direct comparison with aspirin and because indobufen has no proven effects on long-term patency, we do not make a recommendation for the use of indobufen.

4.1.8 Clopidogrel

Investigators compared clopidogrel to aspirin in a subgroup analysis of the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events trial.[10] In subgroup analyses, these investigators[166] sought to determine whether antiplatelet therapy with clopidogrel would be more effective than aspirin in patients who underwent coronary artery bypass surgery. They determined the event rates for all-cause mortality, vascular death, MI, stroke, and rehospitalization for the 1,480 patients with a history of cardiac surgery randomized to either clopidogrel or aspirin. The annual event rates were 22.3% in the 705 patients randomized to aspirin and 15.9% in the 775 patients randomized to clopidogrel (p = 0.001). They observed a RRR in each of the individual end points examined, including a 42.8% RRR in vascular death in patients receiving clopidogrel vs aspirin (p = 0.030).

The CURE trial[10] randomized 12,562 patients with NSTE ACS to receive clopidogrel (300 mg immediately followed by 75 mg qd) or placebo in

addition to aspirin, 75 to 325 mg/d, for 3 to 12 months. The first primary outcome was a composite of death from cardiovascular causes, nonfatal MI, or stroke, and the second primary outcome was death from cardiovascular causes, nonfatal MI, stroke, or refractory ischemia. The benefits of clopidogrel were consistent across a broad range of patient subsets including those with revascularization procedures following randomization (n = 4,577). Moreover, the benefit of clopidogrel tended to be higher in patients who had undergone a revascularization procedure prior to enrollment in the study (RR of the first primary outcome, 0.56; 95% CI, 0.43 to 0.72). The study did not report results of the primary end point separately for the 2,072 patients (16.5%) who underwent CABG after randomization or the 2,568 patients (21.2%) who underwent PTCA. There was no difference in overall bleeding risk between patients with CABG receiving clopidogrel or placebo (1.3% vs 1.1%; RR, 1.26; 95% CI, 0.93–1.71). However, in most patients scheduled for CABG surgery, investigators discontinued the study medication before the procedure (median time before the procedure, 5 days). In the 910 patients in whom the study medication was discontinued > 5 days before the procedure (5 days being the duration of the effect of clopidogrel), there was no apparent excess of major bleeding within 7 days after surgery (4.4% of the patients in the clopidogrel group vs 5.3% of those in the placebo group). In the 912 patients who stopped taking the medications within 5 days before CABG surgery, the rate of major bleeding was 9.6% in the clopidogrel group and 6.3% in the placebo group (RR, 1.53; p = 0.06). Overall, the risk of minor bleeding was significantly higher in clopidogrel-treated patients (5.1% vs 2.4%; p = 0.001).

Recommendations

4.1.8. For patients with CAD undergoing CABG who are allergic to aspirin, we recommend clopidogrel, 300 mg, as a loading dose 6 h after operation followed by 75 mg/d po indefinitely (Grade 1B)**.**
4.1.8.1. In patients who undergo CABG following NSTE ACS, we suggest clopidogrel, 75 mg/d, for 9 to 12 months following the procedure in addition to treatment with aspirin (Grade 2B)**.**
4.1.8.2. For patients who have received clopidogrel for ACS and are scheduled for coronary bypass surgery, we suggest discontinuing clopidogrel for 5 days prior to the scheduled surgery (Grade 2A)**.**

4.1.9 Ticlopidine

Ticlopidine, 500 mg/d, starting 2 days after operation was effective in maintaining graft patency in two RCTs.[146,147] However, ticlopidine is associated with serious adverse effects including fatal thrombocytopenic purpura or neutropenia.[167,168] Because of the uncertain balance of benefits and risks and because other antiplatelet agents are available, we do not make a recommendation regarding ticlopidine. Overall, the use should be restricted to clinical settings wherein thienopyridine is required (eg, after PCI placement) when clopidogrel is not available.

4.1.10 Treatment With Oral Anticoagulants: VKAs

Three randomized trials[136,142,149] compared oral anticoagulants with placebo for long-term graft patency; in each case, anticoagulants were started 3 to 7 days after operation. One study[136] investigated long-term patency of vein grafts after follow-up of up to 24 to 48 months. From an initial group of 216 patients, vein graft patency was determined in only 111 patients (220 grafts) during the follow-up period, and discontinuation of therapy was high (55 patients were not reevaluated). There was a trend toward better cumulative graft patency in patients receiving warfarin, but the results did not achieve statistical significance.

A small study[149] reported increased graft patency with VKAs. This study enrolled 89 patients with 251 saphenous vein grafts who were treated with phenprocoumon (prothrombin time 1.5 to 2.0 times the control) beginning on the seventh postoperative day. The control group was similar in terms of clinical characteristics with 84 patients receiving 238 grafts. Eight weeks following surgery, graft patency (90.4% vs 84.6%) and numbers of patients with all grafts patent (81% vs 67%) were significantly greater in the anticoagulation group. Patients with a graft flow of < 90 mL/min at the time of surgery benefited from anticoagulation. No graft with a flow > 90 mL/min was occluded.

Pantely et al[142] randomly assigned 50 patients to one of four groups to determine the effects of antiplatelet or anticoagulant therapy on graft patency: 24 patients served as controls; 13 patients received aspirin, 325 mg tid, and dipyridamole, 75 mg tid; and 13 patients received closely regulated warfarin therapy begun on the third postoperative day. Six months after surgery, all patients underwent coronary angiography to assess graft patency. There were no statistically significant differences between groups in various clinical, hemodynamic, and angiographic findings. Vein graft patency was 50 of 61 grafts (82%) in control patients and 29 of 37 grafts (78%) with warfarin (p < 0.5). All patients had at

least one patent graft. There was no benefit from treatment with either aspirin plus dipyridamole or VKAs.

In other studies, VKAs begun from 14 days prior to operation to 2 days after operation (sometimes with heparin) yielded a graft patency comparable to low-dose aspirin (50 mg or 100 mg) or low-dose aspirin in combination with dipyridamole.[159,169–172] Fewer bleeding complications occurred with aspirin plus dipyridamole than with oral anticoagulants.[169] Warfarin has also been compared to dipyridamole alone (both started 2 or 3 days after surgery).[171] Graft patency after 1 year or 2 years was comparable for the two regimens (96% for dipyridamole and 89% for warfarin).

Recommendations

4.1.10. For patients undergoing CABG who have no other indication for VKA, we recommend clinicians not administer VKAs (Grade 1C)**.**
4.1.10.1. For patients undergoing CABG in whom oral anticoagulants are indicated, such as those with heart valve replacement, we suggest clinicians administer VKA in addition to aspirin (Grade 2C)**.**

4.1.11 Bleeding Complications of Antithrombotic Therapy in CABG

Evidence regarding bleeding complications during CABG with vein grafts is limited because only few selected trials[129,130,133,135,136] report these data. Therefore, there is a high risk of reporting bias for blood loss associated with antithrombotic therapy. For example, Lorenz et al[129] reported that there was no blood loss in aspirin-treated (100 mg started 1 day postoperatively, n = 29) and placebo-treated (n = 32) patients. Hockings et al[130] described blood loss of 1,193 mL in aspirin-treated patients (100 mg started 7 days preoperatively), compared to 989 mL in the placebo group (n = 52, p > 0.05). In the RCT by Gavaghan et al[135] blood loss in the aspirin group (325 mg started on the day of CABG, n = 127) was similar compared to the placebo group (n = 708; 732 mL vs 708 mL, p > 0.05). Goldman et al[133] reported higher blood loss in the aspirin-treated group (started one day preoperatively) compared to the placebo group. In that RCT, 154 patients receiving 325 mg of aspirin had 965 mL of blood loss, and 155 patients receiving 975 mg had 1,175 mL of blood loss, compared to 805 mL in the 153 patients randomized to placebo (p < 0.02 for both comparisons). VKA-treated patients were more likely to cause major and minor bleeding in 68 patients receiving a VKA started on days 3 or 4 postoperatively (4.4% major bleeding and 10.3% minor bleeding), compared to no reported bleeding in the placebo group (p < 0.01).[136]

4.2 Prevention of Internal Mammary Bypass Graft Occlusion Following CABG

No study included only patients with IMA bypass grafts. The data for prevention of IMA bypass graft occlusion following CABG are limited to subgroup analysis of relatively small studies investigating bypass grafting with both venous and arterial grafts. Although the results are inconclusive, aspirin is indicated because of its overall efficacy in patients with CAD.

4.2.1. Aspirin With and Without Dipyridamole

The VA Cooperative study[173] evaluated the efficacy of aspirin in long-term patency of internal mammary grafts. After receiving 325 mg/d of aspirin for 3 years, IMA graft occlusion rate was 10.3% (8 of 78 patients) vs 7.9% for those treated with placebo (7 of 89 patients, p = 0.60). There was also no effect on IMA graft patency when investigators compared aspirin initiated 12 h before with aspirin administered 6 h after surgery.

An RCT[139] evaluated the effect of high-dose aspirin, 1,300 mg/d, plus dipyridamole, 100 mg/d, starting on the first postoperative day, on IMA patency rates at 3 to 6 months in 18 patients with IMA grafts to the left anterior descending artery. At follow-up, overall patency was 98% (44 of 45 IMA grafts remained patent) with no differences between placebo and treatment groups.

van der Meer et al[174] compared the efficacy and safety of aspirin, aspirin plus dipyridamole, and oral anticoagulant agents on IMA graft occlusion. The investigators assessed graft patency at 1 year in 494 patients who received both IMA and vein grafts. These patients were a subgroup of a prospective, randomized vein graft patency study in 948 patients assigned to treatment with aspirin, aspirin plus dipyridamole, or VKAs. The design was blinded for both aspirin groups, but open-label for VKA treatment. Patients received dipyridamole (5 mg/kg body weight per 24 h IV, followed by 200 mg bid) or VKA (target INR, 2.8 to 4.8) before operation, or low-dose aspirin (50 mg/d) after operation. The combined clinical outcomes were MI, thrombosis, major bleeding, or death. Occlusion rates of distal anastomoses were 4.6% in the aspirin-plus-dipyridamole group and 6.8% in the oral anticoagulant group, vs 5.3% in the aspirin group (p > 0.05). Rates of the combined outcomes were 23.3% and 13.3% in the aspirin-plus-dipyridamole group and the aspirin group, respec-

Table 7—Analysis of Trials Using Acetylsalicylic Acid for Primary Prevention (Section 5.1)*

Study/yr†	Absolute Risk in Control Group, %/yr	Absolute Benefit From Aspirin, %/yr	OR	95% CI
Cardiovascular events				
US[177]/1989	0.67	0.11	0.82	0.71 to 0.96
UK[178]/1989	1.34	− 0.04	1.02	0.82 to 1.27
TPT[180]/2003	1.71	0.41	0.74	0.57 to 0.97
HOT[181]/1998	1.05	0.16	0.85	0.73 to 0.99
Weighted mean	0.92	0.13	0.85	0.78 to 0.94
MI				
US[177]/1989	0.44	0.18	0.56	0.48 to 0.71
UK[178]/1989	0.93	0.03	0.96	0.73 to 1.25
TPT[180]/2003	1.33	0.31	0.76	0.57 to 1.03
HOT[181]/1998	0.36	0.13	0.65	0.49 to 0.85
Weighted mean	0.52	0.15	0.70	0.62 to 0.79
Strokes				
US[177]/1989	0.18	− 0.04	1.22	0.93 to 1.59
UK[178]/1989	0.41	− 0.07	1.16	0.80 to 1.68
TPT[180]/2003	0.32	0.10	0.69	0.38 to 1.26
HOT[181]/1998	0.42	0.01	0.98	0.78 to 1.24
Weighted mean	0.29	− 0.02	1.06	0.91 to 1.24
All-cause mortality				
US[177]/1989	0.41	0.02	0.96	0.79 to 1.15
UK[178]/1989	1.59	0.16	0.88	0.71 to 1.09
TPT[180]/2003	1.31	− 0.05	1.03	0.78 to 1.36
HOT[181]/1998	0.86	0.06	0.93	0.79 to 1.09
Weighted mean	0.73	0.05	0.94	0.85 to 1.04

*Reprinted with permission from the BMJ Publishing Group. Sanmuganathan PS, Ghahramani P, Jackson PR, et al. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomized trials. Heart 2001; 85:265–271. See Table 6 for expansion of abbreviations.
†These references refer to this document.

tively, and 17.1% in the VKA group. Thus, IMA graft patency at 1 year was not improved with oral anticoagulant agents over aspirin plus dipyridamole or low-dose aspirin alone.

Mayer et al[139] performed an RCT in patients with left IMA to the left anterior descending coronary artery. Saphenous vein grafts were used for the left anterior descending coronary artery if the IMA was inadequate and for all other vessels. Patients (n = 174) received either 1,300 mg of aspirin and 100 mg of dipyridamole (po each day) or no drug. Patients returned 3 to 6 months after operation for repeat angiography. Of the 45 IMA grafts in both groups, only 1 IMA graft was occluded and there was no significant difference between the two groups.

Recommendations

4.2.1 For all patients with CAD who undergo IMA bypass grafting, we recommend aspirin, 75 to 162 mg/d, indefinitely (Grade 1A).
4.2.2 For all patients undergoing IMA bypass grafting who have no other indication for VKAs, we recommend against using VKAs (Grade 1C).

5.0 PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS

5.1 Aspirin, VKA or Both

Five large trials have investigated aspirin in men free of a history of previous major vascular events (MI or stroke) and one trial was devoted to answering the question among women.[175] A metaanalysis[176] using published results included data from the US and UK physicians, TPT, and HOT trials (Tables 7 and 8). The doses of aspirin in the four trials were 162.5 mg/d (ie, 325 mg on alternate days), 500 mg/d, 75 mg/, and 75 mg/d, respectively. Major noncerebral bleeding complications included episodes that caused death, transfusion or operation, for which there were data from two of the trials and episodes

Table 8—Systematic Overview of Trials With Aspirin With Primary Prevention (Section 5.1)*

Variables	United States	United Kingdom	TPT	PPP	WHS	HOT
Patients, No.	22,071	5,139	2,540	4,495	39,876	18,790
Aspirin	11,037	3,429	1,268	2,226	19,934	9,399
Placebo	11,034	1,710	1,272	2,269	19,942	9,391
Aspirin dose, mg/d	162.5	500	75	100	50	75
Trial duration, yr	5.0	6.0	6.8	3.6	10.1	3.8
Male gender, %	100	100	100	42.5	Not available	53
Mean age, yr	Not available	Not available	57.5	64.4	55	61.5
Age < 60 yr, %	75	47	Not available	28	90	Not available
Smokers, %	11	13	41	15	13	16
Hypertension, %	9	10	26	69	26	100
Diabetes mellitus, %	2	2	Not available	16	Not available	8

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from the other two trials not classed as minor. The analysis indicated that aspirin was associated with a RRR in all cardiovascular events of 15% (95% CI, 6–22%) and a RRR in MI of 30% (21–38%) and a nonsignificant RRR of 6% in all-cause mortality. Aspirin increased the relative risk of stroke by 6% (not significant), but increased the relative risk of bleeding complications significantly by 69% (38–107%).

In contrast to secondary prevention wherein aspirin use reduces both fatal and nonfatal coronary events, aspirin in the setting of primary prevention appears to reduce only nonfatal events. According to the meta-analysis,[176] the risk of major bleeding balanced the reduction in cardiovascular events when the risk of the latter was 0.2% per annum. The upper 95% CI for this estimate suggested that harm from aspirin is unlikely to outweigh benefit if the risk of a cardiovascular event is at least 0.8% per annum, equivalent to a risk of a major coronary event of 0.6% per annum. Considering the number needed to treat, the analysis suggests that aspirin for primary prevention is safe and worthwhile at a risk of a major coronary episode of 1.5% per annum, safe but of limited value at a coronary event risk of 1.0% per annum, and unsafe at a risk of 0.5%. Only the men in TPT were at greater risk than 1.5% per annum, their risk for all cardiovascular events being 1.71% per annum and for MI 1.33% per annum; consequently the absolute benefit of aspirin was greater than in the other trials. Advice on aspirin for primary prevention requires accurate estimation of the absolute coronary event risk and should be encouraged among both the primary care and cardiology communities to maximize the benefit and minimize the risk of treatment. When aspirin is used, the available data support a dose of no more than 100 mg/d.

5.2 Individual Trials

The Physicians' Health Study[177] was a blinded, placebo-controlled, randomized trial of 22,071 participants designed to test two primary prevention hypotheses in a population free of MI, stroke, transient ischemic attack (TIA), cancer and current liver or renal disease, peptic ulcer, or gout. It was postulated that aspirin would decrease mortality from cardiovascular disease and that beta-carotene would decrease cancer incidence. The participants, aged 40 to 80 years, were randomly allocated to treatment with low-dose aspirin (eg, Bufferin; Bristol-Myers Squibb; New York, NY), 325 mg qod, or placebo and to beta-carotene, 50 mg qod, or placebo according to a 2 × 2 factorial design. The aspirin component was

terminated in 1998 at the recommendation of the Data and Safety Monitoring Board because of a clear reduction of MIs, a low likelihood of detecting a benefit of aspirin on cardiovascular mortality before the year 2000, and the high prevalence of aspirin use among participants following the occurrence of a nonfatal vascular event.

The principal outcome of cardiovascular death occurred at a rate of only 15% of that expected for a general population of similar white men over a similar period and was not different between aspirin (0.23%/yr) and placebo (0.24%/yr).[177] The total death rate also was not different (aspirin 0.4%/yr; placebo 0.42%/yr). There was a reduction in the rates of MI with aspirin (0.26%/yr) vs placebo (0.44%/yr; RRR, 44%; p < 0.00001). The overall stroke rate was higher with aspirin (0.22%/yr) vs placebo (0.18%/yr; p = 0.15) as was the rate of hemorrhagic stroke (0.04%/yr) vs placebo (0.02%/yr; p = 0.06). The combined outcome of "important vascular events" (nonfatal MI, nonfatal stroke, and death from a cardiovascular cause) was significantly reduced in the aspirin group (0.56%/yr) vs the placebo group (0.68%/yr; RRR, 18%; p = 0.01). The inclusion of sudden deaths, if one considers the possibility that most are secondary to cardiovascular events, would raise the possibility that aspirin reduces both fatal and nonfatal MIs.

The British Doctors' Study[178] was an open-label, randomly allocated trial of aspirin, 500 mg/d, vs aspirin avoidance (2:1 ratio of aspirin vs avoidance) among 5,139 participants with no history of stroke, definite MI, or peptic ulcer. Participants were observed for up to 6 years. Vascular death rates, including that of sudden death from unknown cause, and those of peptic ulcer and gastric hemorrhage were lower with aspirin (0.79%/yr) vs no-aspirin (0.84%/yr; RRR, 6%; p = NS). Total mortality was not reduced significantly with aspirin (1.44%/yr vs 1.6%/yr; p = NS), and there were not fewer confirmed MIs (aspirin 0.9%/yr; no-aspirin 0.93%/yr; p = NS). Although there *were* significantly fewer confirmed TIAs in the aspirin group (0.16%/yr vs 0.28%/yr; p < 0.05), there were also more confirmed strokes (aspirin 0.32%/yr vs 0.29%/yr; p = NS) and a greater number of disabling strokes in the aspirin group (aspirin 0.19%/yr vs 0.07%/yr; risk ratio, 2.58; p < 0.05).

The Thrombosis Prevention Trial (TPT)[26] differed from the two previous trials not only in recruiting men who had not experienced major, clinically manifest episodes of ischemic heart disease (IHD) but who were also at increased risk. TPT recruited 5,499 men aged 45–69 at entry through 108 general practices in the United Kingdom. Eligible participants fell in the top 20% of a risk score distribution based on smoking, family history, body mass index,

BP, serum cholesterol level, plasma fibrinogen level, and factor VII activity, each weighted according to its association with IHD in the first Northwick Park Heart Study.[179] Of eligible patients, 52% entered the trial. The two regimens evaluated consisted of low-intensity oral anticoagulation to an INR of about 1.5 with warfarin and a controlled-release 75-mg formulation of aspirin. The design was factorial with the following four treatment groups: active warfarin/active aspirin (WA); active warfarin/placebo aspirin (W); placebo warfarin/active aspirin; and placebo warfarin/placebo aspirin.

The mean warfarin dose required was 4.1 mg daily (range, 0.5–12.5 mg). There were 410 events of IHD (fatal 142, nonfatal 268). The main effect of warfarin (comparing WA and W vs the other two groups; $p = 0.02$) was a 21% reduction in all events, chiefly due to a 39% reduction in fatal events ($p = 0.003$), so that warfarin reduced the death rate from all causes by 17% ($p = 0.04$). The main effect of aspirin (WA and A vs W and placebo) was a reduction in all IHD events of 20%, which was almost entirely due to a 32% reduction ($p = 0.004$) in nonfatal events. Recent analyses have suggested a strong interaction between recruitment systolic BP and the treatment effect of aspirin; patients with BP levels ≤ 130 mm Hg derived considerably more benefit than those with higher pressures, while patients with BPs ≥ 145 mm Hg had neither a beneficial nor a harmful effect. In addition, there may have been a significant excess of fatal coronary events in men aged ≥ 65 at entry. This could account for the 12% higher overall mortality rate from coronary events. In the individual treatment groups, the absolute reductions in all IHD events compared with placebo were the following: warfarin, 2.6 events per 1,000 person-years; aspirin, 2.3 events per 1,000 person-years; warfarin/aspirin, 4 events per 1,000 person-years. Neither W nor A aspirin alone affected the incidence of all strokes, although WA increased hemorrhagic strokes ($p = 0.009$). Of the 10 hemorrhagic strokes that occurred, 7 were in the WA group, and the mean systolic BP of these men at trial entry was 158 mm Hg, compared with 146 mm Hg in those experiencing other strokes and 135 mm Hg in those who did not have strokes. Major noncerebral bleeding episodes were about twice as frequent in the active treatment groups as in the placebo-warfarin-plus-placebo-aspirin group, but the differences were nonsignificant and there was no significant difference in frequency among the three active treatment groups (WA, W, and A). Less serious bleeding occurred most frequently in the WA group. Full compliance with a lowered risk of fatal CHD by nearly 50% and ex-W users had a retained risk reduction of 23% for fatal events (0.66; 95% CI, 0.41–1.04).[180]

5.3 Platelet-directed Therapy

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial[7] randomized 15,603 patients with clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75 to 162 mg/d) or placebo plus low-dose aspirin and followed them for 28 months. The primary efficacy end point was a composite of MI, stroke, or death from cardiovascular causes. The rate of the primary efficacy end point was 6.8% and 7.3%, respectively (RR, 0.93; 95% CI, 0.83–1.05; $p = 0.22$). Among patients with multiple risk factors, the rate of MI, stroke or cardiovascular death was higher in those who received combination therapy (RR, 1.2; 95% CI, 0.91–1.59; $p = 0.20$), and the rate of death from cardiovascular causes was increased significantly (3.9% vs 2.2%; $p = 0.01$). In the subgroup of patients with clinically evident atherothrombosis, the primary end point rate was 6.9% with combined treatment and 7.9% with aspirin alone (RR, 0.88; 95% CI, 0.77–0.998; $p = 0.046$).

The Hypertension Optimal Treatment (HOT) trial was principally concerned with the management of hypertension, specifically to assess optimum target diastolic BP.[181] It also randomized participants to treatment with aspirin or placebo. A total of 19,193 subjects from 26 countries between 50 and 80 years (mean, 61.5 years) with diastolic BP between 100 and 115 mm Hg (average, 105 mm Hg) were randomly assigned a target BP and randomly assigned to daily treatment with 75 mg of aspirin or placebo. The average follow-up time was 3.8 years (range 3.3–4.9 years), giving a total of 71,051 patient-years.

The random assignment to diastolic BP target groups was among ≤ 90 mm Hg, ≤ 85 mm Hg, or ≤ 80 mm Hg. Antihypertensive therapy with felodipine, 5 mg qd, was administered to all participants. Additional therapy and dose increments were with ACEI or β-blockers with the possibility of adding a diuretic agent.

Major cardiovascular events were defined as all MIs (fatal and nonfatal), all strokes (fatal and nonfatal), and all cardiovascular deaths. Silent MI was documented by ECGs at randomization and at the final visit.

In summary, the BP-lowering (and main) component of the trial showed reductions in diastolic BP of 20.3 mm Hg, 22.3 mm Hg, and 24.3 mm Hg, respectively, in the target groups of ≤ 90 mm Hg, ≤85 mm Hg, and ≤ 80 mm Hg. The lowest incidence of major cardiovascular events occurred at an achieved mean diastolic BP of 82.6 mm Hg, and the lowest risk of cardiovascular mortality occurred at 86.5 mm Hg. Further reduction below these BPs was safe.

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-9	[-9]
35-39	-4	[-4]
40-44	0	[0]
45-49	3	[3]
50-54	6	[6]
55-59	7	[7]
60-64	8	[8]
65-69	8	[8]
70-74	8	[8]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-2
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	2
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-2]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[1]
≥280	≥7.25	[1]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	2	[2]
35-44	0.91-1.16	2	[2]
45-49	1.17-1.29	1	[1]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-2	[-3]

Step 4

Blood Pressure				
Systolic (mm Hg)	Diastolic (mm Hg)			
	<80	80-84	85-89	90-99	≥100
<120	-3 [-3] pts			
120-129	0 [0] pts			
130-139		0 [0] pts		
140-159			2 [2] pts	
≥160				

+ Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes		

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

Step 8 (determine CHD risk from point total)

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
≤-2	1%	[≤-2]	[1%]
-1	2%	[-1]	[2%]
0	2%	[0]	[2%]
1	2%	[1]	[2%]
2	3%	[2]	[3%]
3	3%	[3]	[3%]
4	4%	[4]	[4%]
5	5%	[5]	[4%]
6	6%	[6]	[5%]
7	7%	[7]	[6%]
8	8%	[8]	[7%]
9	9%	[9]	[8%]
10	11%	[10]	[10%]
11	13%	[11]	[11%]
12	15%	[12]	[13%]
13	17%	[13]	[15%]
14	20%	[14]	[18%]
15	24%	[15]	[20%]
16	27%	[16]	[24%]
≥17	≥32%	[≥17]	[≥27%]

Step 9 (compare to average person your age)

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	<1%	<1%	<1%
35-39	<1%	<1%	1%
40-44	2%	1%	2%
45-49	5%	2%	3%
50-54	8%	3%	5%
55-59	12%	7%	7%
60-64	12%	8%	8%
65-69	13%	8%	8%
70-74	14%	11%	8%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dL, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-1	[-1]
35-39	0	[0]
40-44	1	[1]
45-49	2	[2]
50-54	3	[3]
55-59	4	[4]
60-64	5	[5]
65-69	6	[6]
70-74	7	[7]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	1
≥190	≥4.92	1

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-3]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[2]
≥280		[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	2	[2]
35-44	0.91-1.16	1	[1]
45-49	1.17-1.29	0	[0]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-1	[-2]

Step 4

Blood Pressure				
Systolic (mm Hg)	Diastolic (mm Hg)			
	<80	80-84	85-89	90-99	≥100
<120	0 [0] pts			
120-129	0 [0] pts			
130-139		1 [1] pts		
140-159			2 [2] pts	
≥160				

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

Step 8 (determine CHD risk from point total)

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
<-3	1%		
-2	2%		
-1	2%	[<-1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥14	≥56%	[≥14]	[≥53%]

Step 9 (compare to average person your age)

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	3%	1%	2%
35-39	5%	4%	3%
40-44	7%	4%	4%
45-49	11%	8%	4%
50-54	14%	10%	6%
55-59	16%	13%	7%
60-64	21%	20%	9%
65-69	25%	22%	11%
70-74	30%	25%	14%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dL, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

There were 209 episodes of MI, 82 in those assigned to aspirin and 127 to placebo, representing a reduction of 36% (p = 0.002) and the prevention of 1.5 episodes per 1,000 person-years. The addition of silent MI to the analysis attenuated the overall beneficial effect attributable to aspirin. There were 315 major cardiovascular events in patients receiving aspirin compared with 368 in the placebo group, a reduction that was borderline in significance. There were no clear differences in cardiovascular mortality or total mortality. The number of strokes, including cerebral hemorrhages, was almost identical in the two groups. Nonfatal major bleeding and minor bleeding occurred more frequently in those receiving aspirin. The results of the HOT trial suggest that the main beneficial effect of aspirin is a reduction in the number of nonfatal MIs.

Participants in the HOT trial were at intermediate risk because of their BP levels at entry, and all received BP-lowering regimens. The rate of all MIs was reduced by aspirin therapy from 3.6 to 2.1 events per 1,000 patient-years (relative reduction 36%; absolute reduction 1.5 events per 1,000 patient-years). There was no difference between the aspirin-treated and placebo groups in terms of the number of fatal hemorrhagic events, but there were 129 nonfatal major bleeding events in the aspirin-treated group compared with 70 in the placebo group, the excess mainly attributable to GI, nasal, and "other" episodes. There were 12 nonfatal cerebral bleeding events in each group. There were 156 minor bleeding episodes in the aspirin-treated group compared with 87 in the placebo group, the main contribution to this excess being nasal bleeding.

The Primary Prevention Project[182] was an open-label, factorial trial to evaluate long-term treatment with aspirin (and vitamin E) in the prevention of major fatal and nonfatal cardiovascular events. Participants were men and women aged 50 years or more with at least one major recognized cardiovascular risk factor (age ≥ 65 years, systolic Bp ≥ 160 mm Hg or diastolic pressure ≥ 95 mm Hg on at least three occasions, total cholesterol ≥ 6.4 mmol/L on at least two occasions, diabetes mellitus, body mass index ≥ 30 kg/m^2, family history of MI under the age of 55 years in a parent or sibling). Criteria for exclusion were treatment with platelet active agents, long-term use of anti-inflammatory agents or anticoagulants, contraindications to aspirin, other diseases with a poor prognosis, and those not likely to be able to comply with the trial requirements.

Eligible patients were randomly allocated to 100 mg enteric-coated aspirin daily or to no aspirin (and to vitamin E or no vitamin E). The principal end point was the cumulative rate of cardiovascular death, nonfatal MI, and nonfatal stroke. Assuming a rate of 1.5% per annum for this end point, an estimated 7,500 participants would need to be followed for 5 years to detect a 25% reduction at the 5% level of significance and with 90% power. At the second planned interim analysis of results in July 1998, the external safety and efficacy monitoring committee advised discontinuing the trial because of evidence from other trials of the value of aspirin (and because it was unlikely that there would be any demonstrable effect of vitamin E). Accordingly, randomization ended in December 1998.

Between 1994 and 1998, 4,495 participants were recruited, some 95% by general practitioners and 5% by hospital hypertension units. Mean age was 64.4 years, and 2,583 (57.7%) of those recruited were women. In all, 4,150 (92.3%) of the participants were followed-up clinically. For 314 (7.0%) participants, information on vital status was obtained through census offices. Mean follow-up was 3.6 years, giving a total of 16,390 person-years. By the end of the trial, 19.3% of participants randomized to aspirin had stopped taking treatment, the most common reason (7.9%) being side effects. Some 7.2% not randomized to aspirin were taking it at the end of the trial.

The RR for the main combined end point was 0.71 (95% CI, 0.48–1.04), for total cardiovascular events 0.77 (0.62–0.95; p < 0.05), cardiovascular deaths 0.56 (0.31–0.99; p < 0.05), noncardiovascular deaths 2%, all deaths 19%, all MI 0.69 (0.38–1.23), nonfatal MI 0.69 (0.36–1.33), all strokes 0.67 (0.36–1.27;

FIGURE 3. *Top panel*: CHD score sheet for men using total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) categories. Uses age, total cholesterol (or low-density lipoprotein cholesterol), high-density lipoprotein cholesterol (HDL-C), BP, diabetes, and smoking; estimates risk for CHD over a period of 10 years based on Framingham[187] experience in men 30–74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal BP, total cholesterol 160 to 199 mg/dL (or low-density lipoprotein cholesterol 100–129 mg/dL), HDL-C of 45 mg/dL in men, no diabetes, and no smoking. Use of the low-density lipoprotein cholesterol categories is appropriate when fasting low-density lipoprotein cholesterol measurements are available. *Bottom panel*: CHD score sheet for women using total cholesterol or low-density lipoprotein cholesterol categories. Uses age, total cholesterol, high-density lipoprotein cholesterol, BP, diabetes, and smoking. Estimates risk for CHD over a period of 10 years based on Framingham[187] experience in women 30–74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal BP, total cholesterol 160 to 199 mg/dL (or low-density lipoprotein cholesterol 100–129 mg/dL), high-density lipoprotein cholesterol of 55 mg/dL in women, no diabetes, and no smoking. Use of the low-density lipoprotein cholesterol categories is appropriate when fasting low-density lipoprotein cholesterol measurements are available. Pts = points; Chol = cholesterol.

NS), lower extremity arterial disease 0.60 (0.33–1.08) and revascularization procedures 0.70 (0.40–1.24; NS). Of the 19 MIs in those taking aspirin, 15 were nonfatal and in those not on aspirin the respective numbers were 28 and 22. For stroke, 15 of the 16 events in those on aspirin were nonfatal and 18 out of 24 in the no-aspirin group.

For any cardiovascular event including cardiovascular deaths, nonfatal MI and nonfatal stroke, TIAs, angina pectoris, lower extremity arterial disease, and revascularization procedures, the RRR was 0.77 (p = 0.014). The direction and size of effects closely overlapped in men and women.

Of 16 strokes in the aspirin group, two were hemorrhagic and three were considered disabling while of the 24 cases in the no aspirin group three were hemorrhagic and four disabling. There were 24 other bleeding episodes in those on aspirin, 17 of which were GI, compared with 6 in those not receiving aspirin and of which 5 were GI.

Aspirin therapy reduced ischemic cardiac events in four of the five trials, the effect being most marked for nonfatal MI and among patients with a cardiac profile placing them at a > 10% risk of an event in a 10-year period. Although there were trends to increased total stroke and hemorrhagic stroke with aspirin in the United States Physicians' Trial and the UK Doctors Trial,[183] there were trends toward a lower number of total strokes with aspirin in TPT and virtually no difference in the fourth (HOT). A main distinguishing characteristic between the first two trials and the other three was the considerably lower dose of aspirin, 75 mg daily, in TPT and HOT and 100 mg in PPP. There is a consistent failure in all five trials to show a reduction in all-cause mortality by aspirin although this is not surprising as none of the single trials were sufficiently large enough to demonstrate or exclude an effect on all cause mortality. In the United States Physicians' Trial,[178] the risk of MI among men aged 40 to 49 was only 0.1%/yr (1 MI per year per 1,000 men), whereas among men aged 60 to 69, the rate of MI was 0.82%/yr (8.2 MIs per year per 1,000 men). Among the older men, the absolute risk reduction with aspirin was about 4.4 infarcts per year per 1,000 men treated. Similarly, the absolute benefits were greater among men with diabetes mellitus, with systolic or diastolic hypertension, who smoked cigarettes and who had a lack of exercise.

In other settings of vascular disease, there are trials that indicate that women benefit from aspirin therapy when the underlying condition is an ACS. However, the lower incidence of cardiac events for women compared with men means that there are smaller absolute benefits among women at a given age. If there is no difference between men and

women in bleeding episodes, this can create a different benefit to risk equation in women.

The trials used different characteristics for defining those at risk of coronary events. The UK and US physicians trials recruited doctors not ineligible on account of previous cardiovascular events or taking aspirin for other reasons but otherwise specified no risk factors for selection into the trial (though these were recorded at entry for comparison between the actively- and placebo-treated groups and, in the case of the US trial, for subgroup analyses according to various risk factors). UK and US physicians may have been at somewhat higher risk than participants in the other trials on account of inclusion of large proportions of older men. The higher risk of cardiovascular and coronary events in TPT was due to the inclusion of a larger number of risk factors for defining eligibility than for the other trials. In TPT, there was a highly significant interaction between systolic BP at entry and the effectiveness of aspirin, those with the lowest pressures experiencing greatest benefit, while aspirin treatment neither increased nor decreased risk significantly in those with higher BPs. A similar though nonsignificant trend was observed in the US Physicians' Trial. However, since both aspirin and elevated BP contribute to a risk of cerebral hemorrhage, several groups have rightly advised that raised BP should be optimized before aspirin therapy is instituted.

5.4 Effects in Women

The effect of antithrombotic therapy among women is an area of considerable interest with accumulating evidence. In HOT, it appeared that while men benefited from aspirin therapy, women did not. In PPP both men and women appeared to benefit about equally. A prospective cohort study of 28,678 US registered female nurses, aged 34 to 65 years, without known CAD, stroke, or cancer also evaluated the effect of aspirin use on cardiovascular outcomes.[184] Among women taking one to six aspirins per week, the age-adjusted RR of a first MI was 0.68 (p = 0.005). This benefit was confined to women ≥ 50 years (RR, 0.61; p = 0.002). There were trends toward fewer deaths from cardiovascular events (RR, 0.89; p = 0.56) and fewer important vascular events (RR, 0.85; p = 0.12), but there was no difference for the incidence of stroke (RR, 0.99).

The Women's Health Study (WHS)[175] was a 2×2 factorial trial of low-dose aspirin, ie, 100 mg alternate days, and vitamin E. Between September 1992 and May 1995, > 1.7 million female health professionals were invited to consider the trial. Just > 450,000 completed questionnaires, and just > 65,000 were willing and eligible to join the trial. Women were to

be aged $\geq$ 45 years with no history of vascular disease, cancer, or other major chronic illness. They should also have had no side effects to any of the study medications and should not be taking nonsteroidal anti-inflammatory drugs (NSAIDs) more than once a week. They were not eligible if they were taking anticoagulants, steroids, or vitamin supplements. There was a 3-month run-in period of placebo tablets to identify those likely to be compliant with long-term treatment. The trial was designed to have a power of 85% to detect a 25% reduction in the primary end point, which was a combination of major cardiovascular events including nonfatal MI, nonfatal stroke, and death from cardiovascular causes. Follow-up rates for morbidity and mortality were 97.2% and 99.4%, respectively. The aspirin and placebo groups were similar in baseline characteristics.

During the 10-year follow-up period, there were 477 major cardiovascular events in the aspirin group and 522 in the placebo group, a nonsignificant reduction of 9% (RR, 0.91; 95% CI, 0.80–1.03; p = 0.13). Aspirin had no significant effect on fatal or nonfatal MI (RR, 1.02; 95% CI, 0.84–1.25; p = 0.83). There was also no significant decrease in cardiovascular causes (RR, 0.95; 95% CI, 0.74–1.22; p = 0.68). Lack of an effect of aspirin on the risk of MI overall was not explained by concomitant use of NSAIDs. There was a 17% reduction in the risk stroke in the aspirin group as compared with the placebo group (RR, 0.83; 95% CI, 0.69–0.99; p = 0.04). This reduction was mainly due to the 24% reduction in ischemic stroke (RR, 0.76; 95% CI, 0.63–0.93; p = 0.009) balanced by an increase in the risk of hemorrhagic stroke (RR, 1.24; 95% CI, 0.82–1.87; p = 0.31). There were 127 episodes of GI bleeding requiring transfusion in the aspirin group compared with 91 in the placebo group (RR, 1.40; 95% CI, 1.07–1.83; p = 0.02).

In subgroup analyses, there were significant reductions in major cardiovascular events, ischemic stroke, and MI among women who were 65 years or over, in whom the risk of the primary end point was reduced by 26% due to aspirin. There was a greater benefit of aspirin among former smokers and those who had never smoked than in current smokers.

Data from the Women's Health Study[175] allowed age-specific estimates of the 10-year number needed to treat (NNT) [CV events avoided] and number needed to harm (NNH) for low-dose aspirin compared with placebo. Among women $\geq$ 65 years old, the NNT was 47 and the NNH was 128. In contrast, for women aged 55 to 64 years, the NNT was 2,001 and the NNH was 196. Thus, women aged 45 to 54 years do not benefit from routine aspirin administration for primary prevention.

A sex-specific metaanalysis[185] of RCTs including a total of 51,342 women and 44,114 men reported that aspirin therapy was associated with a significant 12% reduction in cardiovascular events (OR, 0.88; 95% CI, 0.79–0.99; p = 0.03) and a 17% reduction in stroke (OR, 0.83; 95% CI, 0.70–0.97; p = 0.02), reflecting a significant reduction in ischemic stroke (OR, 0.76; 95% CI, 0.63–0.93; p = 0.008) among women. In men, aspirin therapy was associated with a significant 14% reduction in cardiovascular events (OR, 0.86; 95% CI, 0.78–0.94; p = 0.01) and a 32% reduction in MI. Aspirin did not, however, exert a significant effect on stroke or cardiovascular mortality. Aspirin treatment was found to increase the risk of bleeding among both women and men.

5.4.1 Effect of VKA on Fatal vs Nonfatal Events

Warfarin appears to have similar efficacy to aspirin for the prevention of all IHD outcomes, but it is particularly effective in reducing fatal events, resulting in a statistically significant reduction in all-cause mortality (RRR, 17%; p = 0.04).[113] More recently and using a method that corrects for noncompliance while purportedly preserving the benefits of randomization, TPT suggests that full compliance with warfarin (to a target INR of 1.5) may lower the risk of fatal coronary events by 50% rather than the 39% originally reported.[180] This possible reduction in the most serious manifestation of CHD contrasts with the generally more modest effect of aspirin on fatal events.

5.5 Determining Patient Risk

The Framingham Heart Study[186] provides well-defined patient cohorts, long-term follow-up, and documentation of clinical events. Accordingly, the data set has been used to predict patient risk for cardiovascular events based on age, sex, total cholesterol, smoking status, and systolic BP (Fig 3, *top* and *bottom panels*). By definition, patients at low, moderate, and high risk for future cardiovascular events have Framingham risk scores of < 5 points, 5–10 points, and > 10 points, respectively. In general, patients at moderate to high risk have a 20% likelihood of experiencing a cardiovascular event over a 10-year period (from the time of initial assessment).

Recommendations

5.0. For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%), we recommend 75–100 mg aspirin daily over either no antithrombotic

therapy or VKA (Grade 2A).

5.1. For patients at particularly high risk of events in whom INR can be monitored without difficulty, we suggest low-dose VKA with a target INR of approximately 1.5 over aspirin therapy (Grade 2A).

5.3. For all patients, we recommend against the routine addition of clopidogrel to aspirin therapy in primary prevention (Grade 1A). **For patients with an aspirin allergy who are at moderate to high risk for a cardiovascular event, we recommend monotherapy with clopidogrel** (Grade 1B).

5.4. For women < 65 years of age who are at risk for an ischemic stroke, and in whom the concomitant risk of major bleeding is low, we suggest aspirin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2A).

5.4.1. For women > 65 years of age at risk for ischemic stroke or MI, and in whom the concomitant risk of major bleeding is low, we suggest aspirin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2B).

Values and preferences: The recommendation of aspirin over VKA places a relatively low value on a small absolute reduction in coronary events and deaths and a relatively high value on avoiding the inconvenience, cost, and minor bleeding risk associated with oral VKA. The low target INR value required in primary prevention typically mandates less frequent monitoring; on average every 2 to 3 months and is associated with lower risk of bleeding.

Patients, particularly those in the highest risk groups for whom systems permitting meticulous monitoring of anticoagulant therapy are available, who place a relatively high value on small absolute risk reductions in coronary events and are not influenced by an element of inconvenience and potential bleeding risk associated with VKA are likely to derive the greatest overall benefit from administration of VKA rather than aspirin.

Conflict of Interest Disclosures

Dr. Becker reveals no real or potential conflicts of interest or commitment.

Dr. Berger discloses that he has spoken at Council of Medical Education-approved scientific symposia supported by Bristol-Myers Squibb, Sanofi-Aventis, the Medicines Company, Astra-Zeneca, Medtronic, Schering-Plough, Lilly, and Daiichi Sankyo. He has served as a consultant for PlaCor, Lilly, Daiichi Sankyo, Molecular Insight Pharmaceuticals, and CV Therapeutics. Dr.

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Dr. Meade discloses that he has received grant monies from the Medical Research Council and the British Heart Foundation. He also has investments that are managed by a stockbroker that may or may not have elements connected with the pharmaceutical industry.

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