Update on Aspirin in the Treatment and Prevention of Cardiovascular Disease

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Abstract

Antiplatelet therapy, most notably aspirin, has been well documented to reduce risks of subsequent cardiovascular disease (CVD) in secondary prevention, acute myocardial infarction (MI), acute occlusive stroke, as well as in primary prevention. In secondary prevention, the most recent Antithrombotic Trialists' Collaboration reviewed 194 published randomized trials of antiplatelet therapy, mostly aspirin, involving more than 212 000 patients (ie, 135 000 using antiplatelet therapy or control and 77 000 using different antiplatelet regimens). In a very wide range of patients who have survived a prior occlusive vascular event—including MI, transient ischemic attacks, occlusive stroke, unstable and stable angina, percutaneous coronary interventions, and coronary artery bypass graft—aspirin prevents about 25% of serious vascular events. Among patients suffering acute MI or acute occlusive stroke, aspirin begun promptly and continued long-term reduces risks of subsequent MI, stroke, and vascular death. In acute coronary syndromes, clopidogrel added to aspirin further reduces the risk of important vascular events, but not mortality, and causes more side effects, especially bleeding. For patients undergoing percutaneous coronary interventions, the addition of a short-term infusion of a glycoprotein IIb/IIIa receptor antagonist to aspirin prevents additional vascular events during the early in-hospital period but also increases the risk of major bleeding. Ongoing research is investigating other combinations of different antiplatelet drugs. In all these high-risk patients, there is a small excess of major bleeding among those assigned at random to aspirin, which is far outweighed by the magnitude of benefits on CVD. During an acute MI, after a loading dose of 160 mg to 325 mg aspirin, daily doses ranging from 75 to 150 mg daily are as effective as higher doses. For long-term treatment, the effects of doses <75 mg daily are less certain. Although side effects are dose-related, especially in doses > 325 mg daily, no antiplatelet regimen is more effective than aspirin for long-term use. In primary prevention, 5 randomized trials have been published involving more than 60 000 apparently healthy men and women. Persons randomized to receive aspirin in these trials had significant reductions in risk of a first MI (32%) and important vascular events (15%). Since the numbers of strokes and vascular deaths were insufficient to distinguish between the benefits found in secondary prevention and no effect, use of aspirin in primary prevention should be weighed in light of the cardiovascular risk profile, the side effects of the drug, and its clear benefit in reducing risk of a first MI. Aspirin should be an adjunct, not an alternative, to managing other cardiovascular risk factors. Recently, the US Preventive Services Task Force and the American Heart Association recommended aspirin use for all men and women whose 10-year risks are > 6% and ≥10%, respectively. In all these patient categories, including secondary prevention, acute MI and acute occlusive stroke, as well as primary prevention, increased and appropriate use of aspirin will prevent large numbers of premature deaths and MIs.

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Cardiovascular disease (CVD), which includes coronary heart disease (CHD) and stroke, is the leading clinical and public health problem in the United States and increasingly so throughout the world. Despite significant declines in mortality from both CHD and stroke, CVD remains the leading cause of death in the United States.[1] The World Health Organization estimates that CVD will be the leading cause of death worldwide by the year 2020.[2] Thus, effective therapies to treat and prevent CVD are of importance clinically as well as from a public health perspective, in the United States and worldwide.

Whereas the primary underlying cause of most CVD events is atherosclerosis, the proximate cause is thrombosis. Antiplatelet agents inhibit thrombosis. The wide range of available antiplatelet agents includes aspirin, ticlopidine, and dipyridamole, as well as newer agents, such as clopidogrel and glycoprotein IIb/IIIa receptor antagonists. The various antiplatelet agents target different phases in platelet activation, with varied mechanisms of action and adverse event profiles.

Aspirin is by far the antiplatelet drug most widely tested in randomized trials of treatment and prevention of CVD. Despite being one of the most widely used over-the-counter drugs of the 20th century, the benefits of aspirin in the treatment and prevention of CVD have only relatively recently been recognized. In spite of clear evidence of CVD benefits of aspirin in secondary and primary prevention, as well as during acute coronary syndromes, especially myocardial infarction (MI), there remains underutilization and mismedication.[3]

Epidemiology of Cardiovascular Disease

According to the 2002 Heart and Stroke Statistical Update, CVD affects nearly 62 million Americans.[4] CHD becomes the leading cause of death in men by 45 years of age, and in women by age 65 years. Although the majority of women in the United States perceive breast cancer to be their leading cause of death, in 1999 approximately 43 000 women died from breast cancer[5] but nearly 513 000 women died from CVD.[4]

As regards morbidity, 1 in 5 men and women has some form of CVD.[4] In 1999, CVD ranked highest among all disease categories in numbers of hospital discharges. Currently, 6.2 million men and 6.4 million women have a history of MI and/or angina pectoris. Adults who have survived MI or another hypertension-related disease remain at risk for congestive heart failure and for other life-threatening CVD events. The rate of sudden cardiac death among post-MI patients is 4 to 6 times higher than among those who have not had a cardiovascular event; after suffering a first MI, an estimated 25% of men and 38% of women will die within 1 year.[4] In 2002, CHD has become the leading cause of premature and permanent disability in the US labor force; the healthcare costs of CVD morbidity and mortality are estimated at $329.2 billion.[4]

Benefits of Aspirin in Cardiovascular Disease

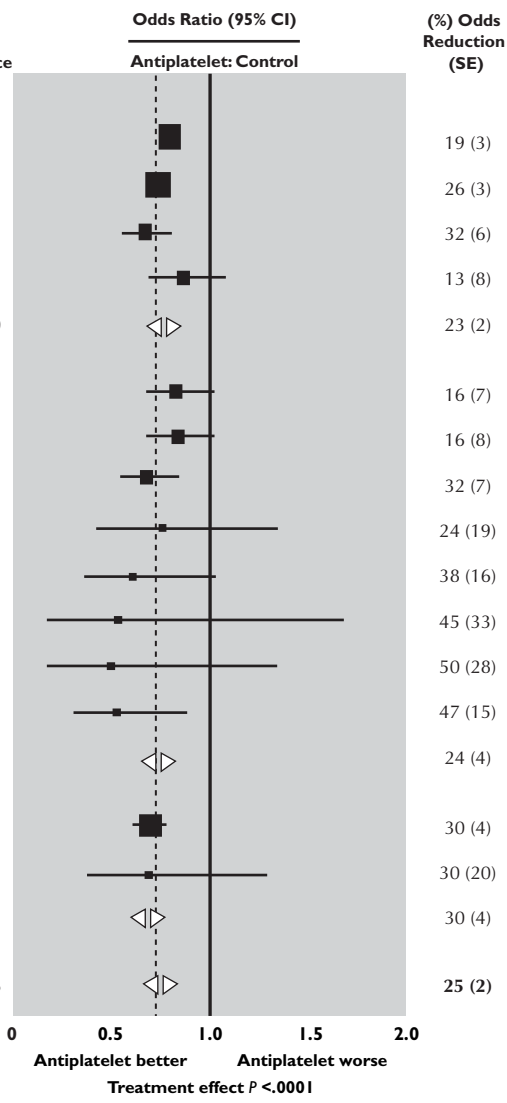
Mechanism of action. About 30 years ago, it was first demonstrated that aspirin irreversibly acetylates platelet-dependent cyclooxygenase, which prevents the formation of thromboxane A_2, a powerful promoter of aggregation, for the life duration of the platelet—approximately 7 to 10 days.[6]

Secondary Prevention: Randomized Trials. In 1988, the Antiplatelet Trialists' Collaboration (ATC) published their first meta-analysis of 25 randomized trials of about 25 000 survivors of MI, stroke, or transient ischemic attacks (TIA) involving prolonged (ie, >1 month) antiplatelet therapy in the reduction of important vascular events (ie, nonfatal MI, nonfatal stroke, and vascular death).[7] By 1994, the second ATC analyzed 145 randomized trials involving approximately 70 000 high-risk and 30 000 low-risk patients, as well as 29 trials comparing different antiplatelet regimens involving another 10 000 high-risk patients.[8] The third ATC included 287 trials: 197 involving 135 000 patients randomized to antiplatelet therapy or control and 90 trials that compared different antiplatelet regimens among 77 000 patients (**Figure 1**).[9] The vast majority of these trials tested aspirin as the antiplatelet regimen.

Antiplatelet therapy, primarily with aspirin, clearly and consistently afforded significant protection against CVD in these trials in all high-risk groups (eg, among patients with prior MI, stroke, TIAs, or other vascular disease that would increase their risk of occlusive vascular events; **Figure 2**).[9] Patients given aspirin had a 25% reduction in serious vascular events, as a result of 34% reduction in nonfatal MI,

Figure 1. Indirect Comparisons of Proportional Effects of Different Antiplatelet Regimens on Vascular Events in High-Risk Patients

Category of Trial	No. of Trials With Data	No. (%) of Vascular Events: Allocated Antiplatelet	No. (%) of Vascular Events: Adjusted Control	Observed-Expected	Variance	(%) Odds Reduction (SE)
Aspirin alone (mg daily):						
500-1500	34	1621/11 215 (14.5)	1930/11 236 (17.2)	−147.1	707.8	19 (3)
160-325	19	1526/13 240 (11.5)	1963/13 273 (14.8)	−219.9	742.6	26 (3)
75-150	12	366/3370 (10.9)	517/3406 (15.2)	−72.0	183.8	32 (6)
<75	3	316/1827 (17.3)	354/1828 (19.4)	−18.9	136.5	13 (8)
Any aspirin*	65	3829/29 652 (12.9)	4764/29 743 (16.0)	−452.3	1717.0	23 (2)
Other antiplatelet drugs:						
Dipyridamole	15	392/2696 (14.5)	458/2734 (16.8)	−30.9	173.0	16 (7)
Sulfinpyrazone	19	315/2411 (13.1)	361/2416 (14.9)	−23.8	140.7	16 (8)
Ticlopidine	42	278/3435 (8.1)	385/3475 (11.1)	−50.5	132.3	32 (7)
Suloctidil	6	47/364 (12.9)	59/367 (16.1)	−5.6	20.5	24 (19)
Picotamide	4	41/1583 (2.6)	66/1602 (4.1)	−12.2	25.8	38 (16)
Sulotroban	4	8/406 (2.0)	14/409 (3.4)	−3.2	5.3	45 (33)
Triflusal	2	10/314 (3.2)	19/309 (6.1)	−4.7	6.7	50 (28)
Other†	9	41/647 (6.3)	73/641 (11.4)	−16.1	25.6	47 (15)
Any other single agent	101	1132/856 (9.5)	1435/11 953 (12.0)	−147.0	529.9	24 (4)
Aspirin + another antiplatelet drug:						
Aspirin + dipyridamole	46	1036/9703 (10.7)	1393/9738 (14.3)	−172.6	488.7	30 (4)
Aspirin + sulfinpyrazone	2	32/283 (13.4)	50/278 (18.0)	−6.5	18.5	30 (20)
Any combination	48	1074/9986 (10.8)	1443/10 016 (14.4)	−179.1	507.2	30 (4)
All trials	**188**	**6035/51 494 (11.7)**	**7644/51 736 (14.8)**	**−715.7**	**2449.6**	**25 (2)**



Only meta-analyses involving 500 or more high-risk patients are shown. We excluded high-risk patients with acute stroke. Stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials (black squares) along with its 99% confidence interval (horizontal lines). Meta-analysis of results for each main comparison and for all trials (and 95% confidence interval) is represented by open diamonds. Adjusted control totals have been calculated after converting any unevenly randomized trials to even ones by counting control groups more than once, but statistical calculations are based on actual numbers from individual trials.

Heterogeneity of odds reductions between:

Different aspirin doses: $\chi^2 = 7.7$, $df = 3$; $P = .05$.

Other antiplatelet vs any aspirin: $\chi^2 = 10.8$, $df = 8$; $P > .1$.

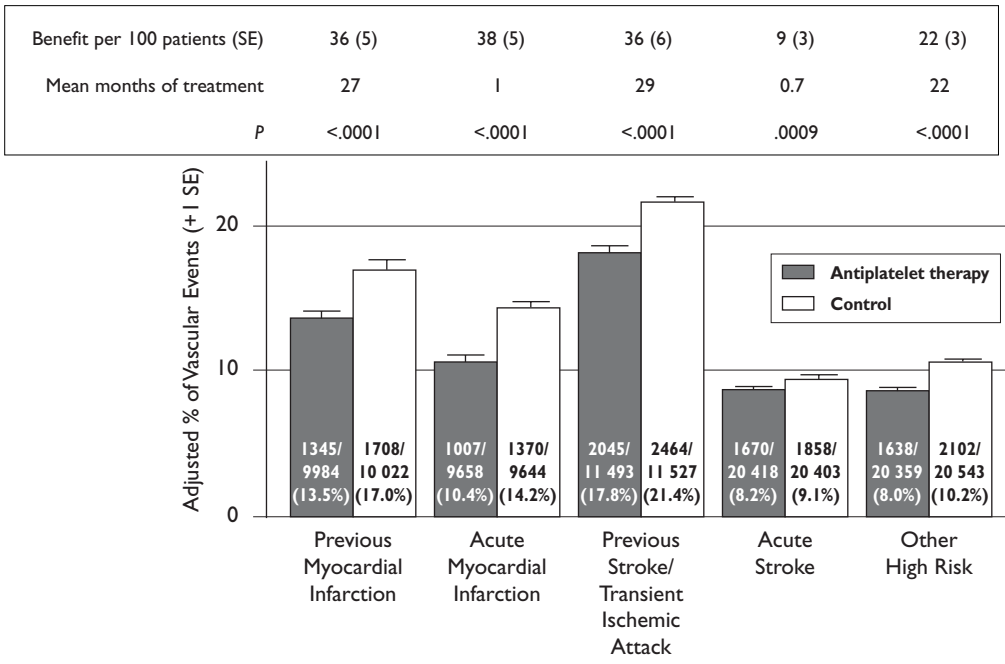
CI indicates confidence interval; SE, standard error.

*Some trials contributed to more than one comparison.

†Includes ibuprofen, flurbiprofen, GR32191B, dazoxiben, and trapidil.

Adapted with permission from Antithrombotic Trialists' Collaboration.[9]

Figure 2. Absolute Effects of Antiplatelet Therapy on Vascular Events (Myocardial Infarction, Stroke, or Vascular Death)



Adjusted control totals have been calculated after converting any unevenly randomized trials to even ones by counting control groups more than once.
SE indicates standard error.
Adapted with permission from Antithrombotic Trialists' Collaboration.[9]

The benefits of aspirin were similar for doses ≥75 mg, but uncertainty remains about the benefit of daily aspirin doses of < 75 mg.

25% reduction in nonfatal stroke, and 17% reduction in vascular death.[9] In addition, there was no increased risk of nonvascular death. Aspirin use results in a significant, 15% decrease in CVD mortality among patients who have survived a wide range of prior occlusive events, and a significant, 25% reduction in important vascular events.[9]

In these trials, the dose of aspirin ranged from 30 mg to > 1500 mg daily. The benefits of aspirin were similar for doses ≥75 mg, but uncertainty remains about the benefit of daily aspirin doses of < 75 mg.[9]

The gastrointestinal (GI) side effects and bleeding did not increase significantly between 75 and 325 mg daily doses but did increase with doses > 325 mg/day; therefore, the dosing range of aspirin recommended for secondary prevention was between 75 and 325 mg/day.

The United Kingdom trial of Transient Ischemic Attack (UK-TIA) provides perhaps the best data concerning GI side effects and bleeding with doses of aspirin ranging from 300 to 1200 mg daily.[10] More than 2400 patients were randomized to receive placebo, aspirin 300 mg/day, or aspirin 600 mg twice daily. The rates of GI side effects were 25% for placebo, 29% for aspirin 300 mg daily, and 39% for aspirin 1200 mg daily. GI

bleeding rates were 1.6%, 2.6%, and 4.9%, respectively.[10]

In the 1980s, the US Food and Drug Administration (FDA) approved aspirin for the treatment of patients with prior MI and unstable angina, as well as men with prior TIAs (**Table 1**).[11-13] In 1998, the FDA expanded the indications for aspirin to include women with prior TIAs, patients with prior occlusive stroke or chronic stable angina, and those who have undergone revascularization procedures.[12,13]

Acute Coronary Syndromes: Randomized Trials. The Second International Study of Infarct Survival (ISIS-2) examined the effects of aspirin administered during acute MI. ISIS-2 randomized 17 187 men and women from 417 participating hospitals within 24 hours of onset of symptoms of MI to 1 of 4 treatment regimens: (1) aspirin (160 mg/day) for 30 days; (2) 1-hour intravenous infusion of 1.5 million units (MU) of streptokinase; (3) 1.5 MU streptokinase plus aspirin (160 mg/day) for 30 days; or (4) placebo.[14] At 35 days, patients randomized to aspirin or to streptokinase had significant reductions in vascular mortality (23% [2*P* <.00001] and 25% [2*P* <.00001], respectively). Patients receiving aspirin also had significant reductions in nonfatal reinfarction (2*P* <.00001) and nonfatal stroke (2*P* <.01), with no increased incidence of hemorrhagic stroke or GI bleeding and a small increase in minor bleeding. The combination of aspirin plus streptokinase had additive benefits, affording patients a 42% reduction in vascular mortality.[14] The benefits of aspirin were similar regardless of time to initiation of therapy following onset of symptoms. The benefits of streptokinase were greater when administered early. During acute MI, uncoated aspirin is preferable. Patients using enteric-coated aspirin are instructed to crush or chew the tablets to achieve a rapid clinical antithrombotic effect. In 1997, the FDA approved the use of aspirin, in doses ranging from 160 to 325 mg/day, for the treatment of acute MI.[12]

Table 1. FDA-Approved New/Expanded Indications for Aspirin

Year of Change	New/Amended Indications
1980	Men with prior TIA
1985	Patients with prior MI and unstable angina, without reference to gender
1997	Management of acute MI (aspirin 162.5 to 325 mg at onset of suspected MI)
1998	Secondary prevention of CVD, including: Women and men with prior TIA Patients with prior occlusive stroke or chronic stable angina Patients with unstable angina Patients who have undergone revascularization procedures

TIA indicates transient ischemic attack; MI, myocardial infarction; CVD, cardiovascular disease.
Sources: References 11,12,13.

Table 2. Benefit-to-Risk Ratio of Aspirin and Thrombolytic Therapy

Type of Therapy	Use in Acute MI (%) 1987	Use in Acute MI (%) 1989	% Potentially Eligible to Receive Therapy	Effect of Treatment of 1000 Patients with Acute MI: Premature Deaths Avoided	Effect of Treatment of 1000 Patients with Acute MI: Cerebral Hemorrhages Caused
Aspirin therapy	39	72	99.9	23	0
Thrombolytic therapy	27	40	67	25	2-3

MI indicates myocardial infarction.
Adapted with permission from Hennekens et al.[11]

Table 3. Main Clinical Events in Hospital

Event	Number (%) of Those with Discharge Forms in Allocated Group		Absolute Benefit with Aspirin per 1000 (SD)*	2*P*
	Aspirin (n = 10 335)	Placebo (n = 10 320)		
Deaths				
All deaths	343 (3.3)	398 (3.9)	5.4 (2.6)	.04
Due to initial stroke	144 (1.4)	175 (1.7)	3.0 (1.7)	.08
Due to recurrent stroke (any type)	99 (1.0)	108 (1.2)	0.9 (1.4)	>.1
Due to other (or unknown) causes	100 (1.0)	115 (1.1)	1.5 (1.4)	>.1
Recurrent stroke (fatal or not)				
All	335 (3.2)	351 (3.4)	1.6 (2.5)	>.1
Ischemic	167 (1.6)	215 (2.1)	4.7 (1.9)	.01
Hemorrhagic†	115 (1.1)	93 (0.9)	−2.1 (1.4)	>.1
Unknown	53 (0.5)	43 (0.4)	−1.0 (0.9)	>.1
Death or nonfatal stroke	545 (5.3)	614 (5.9)	6.8 (3.2)	.03
Pulmonary embolism				
All	12 (0.1)	20 (0.2)	0.8 (0.6)	>.1
Fatal	5 (0.1)	10 (0.1)	0.5 (0.4)	>.1
Nonfatal	7 (0.1)	10 (0.1)	0.3 (0.4)	>.1
Transfused (or fatal) extracranial bleeding				
All	86 (0.8)	58 (0.6)	−2.7 (1.2)	.02
Fatal	39 (0.4)	31 (0.3)	−0.8 (0.8)	>.1
Nonfatal	47 (0.5)	27 (0.3)	−1.9 (0.8)	.02

SD indicates standard deviation.
*Negative numbers indicate more events occurred in aspirin than in placebo group.
†Includes cerebral hemorrhage or hemorrhage transformation of original infarct.
Adapted with permission from CAST (Chinese Acute Stroke Trial) Collaborative Group.[15]

A benefit-to-risk analysis suggests that for every 1000 patients who have an acute MI, aspirin initiated within 24 hours of onset of symptoms would prevent 23 premature deaths, with no increase in cerebral hemorrhage.[11] In comparison, thrombolytic therapy given within 12 hours would result in the prevention of 30 premature deaths but would also cause 2 to 3 cases of nonfatal cerebral bleeding, with a net benefit of 10 premature deaths prevented for every nonfatal cerebral bleeding (**Table 2**).[11] It is currently estimated that wide use of aspirin in patients having an acute MI would prevent 5000 to 10 000 premature deaths annually in the United States.[1]

The Chinese Acute Stroke Trial (CAST) examined the effects of aspirin in 21 106 patients with suspected acute ischemic stroke.[15] Patients who presented within 48 hours of suspected stroke were randomized to receive either aspirin 160 mg/day or placebo for up to 4 weeks. The results of the trial demonstrated a significant, 14% (2*P* = .04) reduction in mortality during the treatment period and a 12% reduction in risk of death or nonfatal stroke at 4 weeks, compared with placebo. In addition, patients in the aspirin group had significantly (2*P* = .01) fewer recurrent ischemic strokes than did those in the placebo group. Aspirin was also associated with 2:1000 rate of hemorrhagic strokes in patients with suspected ischemic stroke (**Table 3**).[15] Pooled analysis of the data from CAST and from the International Stroke Trial revealed that doses of 160 mg

to 325 mg of aspirin, when administered early to patients with suspected ischemic stroke, had a modest but definite net reduction in early deaths or nonfatal strokes within the first few weeks after initiation of aspirin therapy, compared with placebo (**Figure 3**).[15,16] CAST investigators estimated that 10 000 premature deaths and new-onset nonfatal stroke or MI could be prevented annually through the early administration of aspirin to 1 million patients with ischemic stroke, and continued therapy after hospital discharge would further reduce morbidity and mortality.[15]

Primary Prevention of CVD: Randomized Trials. To date, 5 major primary prevention trials of aspirin have been conducted involving more than 55 000 apparently healthy men and women. The US Physicians' Health Study (PHS) of 22 071 healthy male US physicians[17] and the British Doctors Trial (BDT) of 5139 male physicians[18] were completed during the late 1980s. The Thrombosis Prevention Trial (TPT) of 5085 men[19] and the Hypertension Optimal Treatment (HOT) study of 18 790 (47% women) patients[20] were completed during the late 1990s, and the Primary Prevention Project (PPP) trial of 4495 (55% women) patients[21] was completed in 2000. In all these trials patients were randomized to aspirin and had follow-up durations ranging from 4 to 6 years. The PHS and BDT used aspirin regimens of 325 mg every other day and 500 mg/day, respectively, whereas the TPT and HOT used 75 mg/day of aspirin and the PPP used 100 mg/day of enteric-coated aspirin.[17-21]

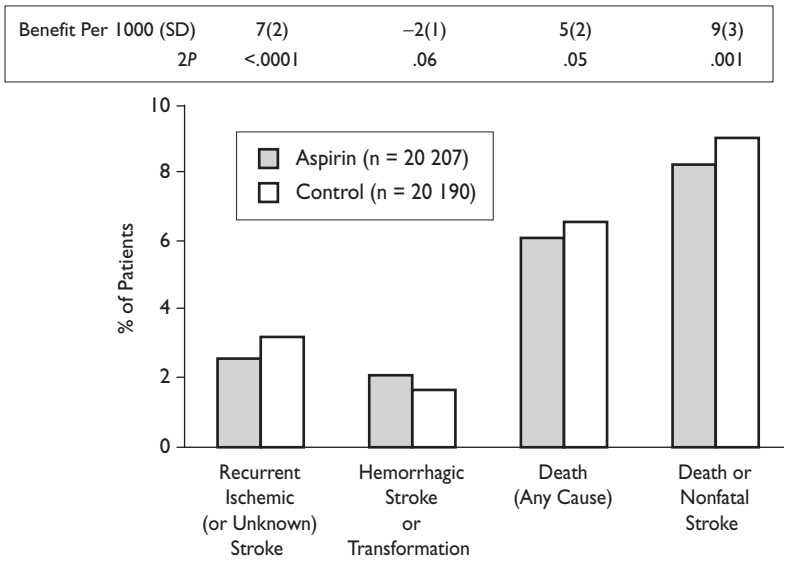
The PHS was the first study to demonstrate that aspirin reduced the risk of a first MI among apparently healthy men.[17,22] This trial was terminated early based on the unanimous recommendations of the Data and Safety Monitoring Board primarily because of the extreme, statistically significant (P <.00001), 44% reduction in risk of first MI; however, as a consequence there were insufficient strokes and deaths to distinguish between the most plausible benefits in secondary prevention trials and no effect.[17,22]

The smaller BDT used an open design and its results showed no significant cardioprotective benefits of aspirin. Because of its small sample size, this trial could not have detected even a 44% reduction in risk for first MI, as was shown in the PHS. However, when results of these 2 trials were combined, aspirin was found to significantly reduce the risk of nonfatal MI by 33% (P <.00001).[22]

The use of aspirin and/or warfarin in the primary prevention of ischemic heart dis-

The USPSTF acknowledged that the optimal dose of aspirin for the primary prevention of CVD is, as yet, unknown but noted that dosages of approximately 75 mg/day appear to be as effective as higher doses.

Figure 3. Overview of Absolute Effects of Early Aspirin Treatment in Acute Ischemic Stroke on Clinical Events



SD indicates standard deviation.
Adapted with permission from CAST (Chinese Acute Stroke Trial) Collaborative Group.[15]

Table 4. Third US Preventive Services Task Force Conclusions About Aspirin and CVD

- Good evidence: Aspirin decreases the incidence of CHD in high-risk adults
- Good evidence: Aspirin increases the incidence GI bleeding
- Fair evidence: Aspirin increases the incidence of hemorrhagic strokes
- Aspirin is beneficial in patients who have a 5-year CVD risk ≥3% (10-year CVD risk >6%)
- Optimal dosage: At least 75 mg/day has shown efficacy comparable to that of higher-dose regimens

CVD indicates cardiovascular disease; CHD, coronary heart disease; GI, gastrointestinal.
Source: US Preventive Services Task Force.[24]

ease (IHD) was examined in the TPT.[19] Men ages 45 to 69 years with no history of peptic ulceration, MI, or stroke were randomized to 1 of 4 treatment groups: active warfarin vs active aspirin; active warfarin vs placebo aspirin; placebo warfarin vs active aspirin; placebo warfarin vs placebo aspirin. Warfarin use resulted in a 21% reduction in all (ie, fatal and nonfatal) IHD and a 17% reduction in all-cause mortality. Warfarin had no benefit on the incidence of stroke. Aspirin use reduced all IHD by 20%, predominantly because of a 32% reduction in nonfatal events. However, aspirin had no significant effect on fatal events and little or no benefit on stroke. The combination of warfarin and aspirin led to a 34% reduction of all IHD but increased hemorrhagic and fatal strokes. Overall, the combination of aspirin and warfarin prevented approximately 12 times as many IHD events as it caused strokes; however, the strokes that occurred were more likely to be hemorrhagic and fatal. These results indicate that either warfarin or aspirin alone would prevent approximately 3 episodes of IHD per 1000 men treated for 1 year; the combination of aspirin and warfarin would prevent 5 events of IHD per 1000 men treated.[19]

The AHA recommended the use of low-dose aspirin, 75 to 160 mg/day, in men and women with a 10-year risk of CHD ≥10%.

The randomized HOT trial examined the role of low-dose aspirin therapy in the prevention of CVD in patients with hypertension.[20] In this trial, men and women with hypertension and a diastolic blood pressure (BP) between 100 and 115 mm Hg were randomized to a target diastolic BP of < 90, < 85, or < 80 mm Hg. The antihypertensive agent felodipine was given to all patients. Angiotensin-converting enzyme inhibitors, beta blockers, or diuretics were added as needed to reach target BP. HOT was unique in investigating the benefits of aspirin in hypertensive patients, because hypertension has been considered by some to be a contraindication to aspirin therapy. The combination therapy used in HOT resulted in substantial reductions in BP. The use of aspirin significantly (P <.03) reduced the incidence of major cardiovascular events.[20] Aspirin conferred the greatest cardioprotective effect against fatal and nonfatal MI (32%) but had no significant effect on the incidence of stroke.[20]

The PPP trial assessed aspirin and vitamin E therapy in primary prevention of cardiovascular events in people with 1 or more major cardiovascular risk factors.[21] In this trial, men and women were randomized to receive aspirin 100 mg/day, vitamin E (300 IU/day), or 1 of 2 placebo groups. Aspirin therapy reduced the frequency of all end points, with significant reductions in cardiovascular death (P = .049) and any cardiovascular events (P = .014), compared with placebo.[21] Findings for vitamin E were null. The trial was terminated early based on the evidence of aspirin's benefits documented in earlier trials.[23]

The third US Preventive Services Task Force (USPSTF) reviewed the trials of aspirin in the primary prevention of

CVD.[24] The USPSTF concluded that there is "good evidence that aspirin decreases the incidence of coronary heart disease in adults at high risk for heart disease, good evidence that aspirin increases the incidence of GI bleeding, and fair evidence that aspirin increases the incidence of hemorrhagic strokes" (**Table 4**).[24] The USPSTF determined that aspirin is most beneficial in primary cardioprevention among patients with a 5-year risk ≥ 3% or 10-year risk > 6%. The USPSTF acknowledged that the optimal dose of aspirin for the primary prevention of CVD is, as yet, unknown but noted that dosages of approximately 75 mg/day appear to be as effective as higher doses.[24]

In July 2002, the American Heart Association (AHA) released an updated Guidelines for Primary Prevention of Cardiovascular Disease and Stroke, integrating earlier guidelines and consensus statements developed since the initial guidelines' approval in 1997. The AHA recommended the use of low-dose aspirin, 75 to 160 mg/day, in men and women with a 10-year risk of CHD ≥10%.[25]

In summary, the primary prevention trials indicate that aspirin therapy conclusively reduces the risk of first MI, but the results are less conclusive with regard to stroke and vascular death.[13] Secondary prevention trials demonstrate that aspirin confers a significant reduction in ischemic stroke with a small, nonsignificant increase in hemorrhagic stroke as well as in cardiovascular death. Primary prevention trials have not yet consistently demonstrated a significant decrease in ischemic stroke but have shown a small increase in hemorrhagic stroke and no significant effect on cardiovascular death. The confidence intervals around these point estimates, however, include the point estimates of benefits seen in the recent overview of the secondary prevention trials.[9]

Conclusions

The totality of evidence overwhelmingly supports the routine administration of aspirin for the secondary prevention of cardiovascular events in patients who have had MI, occlusive stroke, or TIA; in those who have unstable or stable angina; in persons who have undergone percutaneous coronary interventions; as well as during acute MI. In the acute setting, a loading dose of 160 mg to 325 mg aspirin should be used, followed by doses of 75 mg to 325 mg daily for long-term treatment. In primary prevention, the USPSTF and the AHA guidelines recommend aspirin therapy for all apparently healthy men and women whose 10-year risk for a first CHD event is > 6% and ≥ 10%, respectively. In all these patient categories in secondary and primary prevention, increased and appropriate use of aspirin will prevent many premature deaths and first MIs.

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