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REVIEW

Aspirin to Prevent Heart Attack and Stroke: What's the Right Dose?

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ABSTRACT

Despite hundreds of clinical trials, the appropriate dose of aspirin to prevent myocardial infarction (MI) and stroke is uncertain. In the US, the doses most frequently recommended are 80, 160, or 325 mg per day. Because aspirin can cause major bleeding, the appropriate dose is the lowest dose that is effective in preventing both MI and stroke because these two diseases frequently co-exist. Five randomized clinical trials have compared aspirin with placebo or no therapy for the prevention of stroke and MI. These trials varied with regard to the dose of aspirin, the duration of treatment, and, most important, the populations selected for study varied in their baseline risk of stroke and MI. In men, 160 mg/day consistently lowered the risk of MI. In women, doses of 50 mg, 75, and 100 mg/day did not significantly decrease the risk of MI; therefore, the appropriate dose in women must exceed 100 mg/day. The appropriate dose for the primary prevention of stroke in men and women has not been established. Doses of 75 and 100 mg/day have been ineffective in men and women. The appropriate dose must be at least 160 mg/day. The lowest dose to prevent recurrent MI or death in patients with stable coronary artery disease (CAD) is 75 mg/day. In acute MI the lowest dose is 160 mg/day. In patients with a history of stroke or transient ischemic attack (TIA), 50 mg/day has been shown to be effective in men and women. In acute stroke, 160 mg/day is effective in preventing recurrent stroke or death. The risk of major bleeding with 160 mg/day is the same as with 80 mg/day: 1 to 2 cases per 1000 patient years of treatment, and the risk of fatal bleeding is the same with 80 and 160 mg/day. These studies indicate that the most appropriate dose for the primary and secondary prevention of stroke and MI is 160 mg/day. © 2006 Elsevier Inc. All rights reserved.

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In 1950, Lawrence Craven, a general practitioner in Glendale, Calif, was the first to report that aspirin may prevent myocardial infarction (MI), and in 1956 he was the first to report that aspirin may also prevent strokes.¹ Now, more than 50 years later, after hundreds of clinical trials, it has been well established that Craven was correct; aspirin can prevent MI and stroke.^{2,3} However, the appropriate dose of aspirin remains uncertain. The dose in clinical trials has ranged from 50 to 1200 mg per day. Craven recommended a dose of 325 mg per day, although he noted that 325 mg 5 times a week may be sufficient.¹

The appropriate dose of aspirin should be sufficient to prevent MI, as well as stroke, because these 2 diseases have the same risk factors and frequently co-exist. Ideally, the appropriate dose would be effective for primary and secondary prevention, in women as well as in men.

THE SEARCH FOR THE LOWEST EFFECTIVE DOSE

Because aspirin has significant side effects; principally bleeding, especially gastrointestinal (GI) bleeding, many clinical trials have sought to determine the lowest effective dose of aspirin to prevent MI and stroke.

The Antithrombotic Trialists' Collaboration reviewed 287 studies involving 135 000 patients that compared antiplatelet therapy to controls.³ They concluded that doses of 75 to 325 mg of aspirin are effective and that there is no additional benefit to doses higher than 325 mg per day. They also noted

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that 75 to 150 mg/day seems to be as effective as 325 mg and that the effects of doses less than 75 mg were less certain.³

It is now widely accepted that the optimal dose is 325 mg/day or less.² However, there is no agreement whether the optimal dose is 80, 160, or 325 mg/day. Because the cost of aspirin is nominal, if there were no side effects of aspirin, the appropriate dose to ensure efficacy would be 325 mg per day. However, in order to minimize gastrointestinal toxicity and bleeding, the appropriate dose of aspirin is the lowest dose that is consistently effective in preventing MI and stroke.

PRIMARY PREVENTION TRIALS

Five major randomized clinical trials have compared aspirin with placebo or control in the primary prevention of MI and stroke⁴⁻⁸ as shown in Table 1. These trials utilized doses of aspirin ranging from 50 mg/day (100 mg every other day [QOD])⁴ to 500 mg/day.⁸ The duration of treatment ranged from 3.6 years to 10 years. All the participants in these trials were aged 40 years or older, but the mean age of the participants in these trials varied. Two of the studies included only men,^{7,8} one included only women,⁴ and the other two included men and women.^{5,6} Some studies selected participants with risk factors for cardiovascular disease or who had hypertension.⁵

Given the heterogeneity of these trials, the risk of MI and stroke in the participants in these 5 trials varied significantly. Therefore, it is not surprising that the results were quite variable.

Table 1 Primary Prevention Trials: Prevention of MI and Stroke

Trial	Ref	ASA dose/day	MI	P	Stroke	P
WHS	4	50 mg*	+2%	ns	-17%	.04
HOT	5	75 mg Men	-42%	.001	-1%†	ns
		75 mg Women	-19%	ns		
PPP	6	100	-31%	ns	-33%	ns
PHS	7	160†	-44%	<.001	+22%	ns
UK	8	500 mg/D	-3%	ns	+17%	ns

ASA = aspirin; WHS = Women's Health Study; HOT = Hypertension Optimal Treatment study; PPP = Primary Prevention Project; PHS = Physician's Health Study; UK = British physician study.

*50 mg/day = 100 mg QOD.

†160 mg/day = 325 mg QOD.

‡Stroke data for men and women combined.

CLINICAL SIGNIFICANCE

- There is general agreement that the appropriate dose to prevent myocardial infarction and stroke is 325 mg/day or less. The most frequently recommended doses are 81 mg, 160 mg, or 325 mg/day.
- In randomized clinical trials, doses of less than 160 mg/day were ineffective in the primary prevention of stroke or myocardial infarction.
- In randomized clinical trials, the risk of major bleeding was the same for those taking 81 or 160 mg/day, 1 to 2 cases per 1000 years of treatment.
- These studies indicate that the most appropriate dose of aspirin to prevent myocardial infarction and stroke is 160 mg/day.

Peto et al⁸ randomized 5139 presumably healthy British male doctors (median age 60 years) to 500 mg of aspirin per day or no aspirin. After 6 years of follow-up, there was no significant difference in the incidence of MI or stroke in those taking or not taking aspirin. It should be noted that many of these physicians discontinued aspirin during the trial due to GI symptoms. Halfway through the study, only 70% of those assigned to aspirin were still taking aspirin.

The U.S. Physicians' Health Study (PHS) randomized 22071 U.S. male physicians aged 40 years and older to placebo, or to 325 mg of aspirin every other day.⁷ After an average follow-up of 60.2 months, there was a significant 44% reduction in MI in those aged 50 and older. There was an insignificant increase in strokes.⁷

The Primary Prevention Project (PPP) studied the effect of 100 mg aspirin in 4495 people (2583 women) aged 50 or older with one or more major cardiovascular risk factors.⁶ After an average of 3.6 years of follow-up, there was a significant reduction in cardiovascular deaths and total cardiovascular events in women as well as men. However, the decrease in MI and the decrease in stroke were not statistically significant.⁶

In the Hypertension Optimal Treatment (HOT) study, 18790 patients (8831 women) aged 50 or older with hypertension were randomized to receive 75 mg aspirin or placebo.⁵ After an average follow-up of 3.8 years, there was a nonsignificant decrease in the incidence of stroke in those receiving aspirin.⁵ The incidence of MI was significantly reduced by 42% in men, whereas there was an insignificant reduction in MI of 19% in women.⁹

In the WHS, 39876 healthy women aged 45 years or older were randomized to a very low dose of aspirin: 100 mg every other day or placebo.⁴ After 10 years of follow-up, there was a significant 17% reduction in stroke in those treated with aspirin. However, the reduction in stroke in women aged 65 and older was not significant. The incidence of MI was not decreased in the total patient population. However, there was a significant 34% decrease in MI in women aged 65 or older.

LOWEST DOSE FOR PRIMARY PREVENTION OF MI

As shown in Table 1, the lowest reported dose to prevent myocardial infarction in women, 50 mg/day (100 mg QOD), was reported by the WHS, but it was limited to women aged 65 years or older.⁴ In the total group of women aged 45 and

older, there was an insignificant 2% increase in myocardial infarction. These findings in the WHS were not consistent with the results in women in other trials. In the HOT trial, a daily dose of 75 mg in women age 50+ with hypertension resulted in an insignificant decrease in MI of 19%.⁵ In the Primary Prevention Project,⁶ 100 mg per day resulted in an insignificant decrease in MI of 31% in men and women aged 50 years and older who had at least one major cardiovascular risk factor.

The combined results of these studies indicate that the lowest effective dose of aspirin to prevent MI in women aged 50 or older is more than 100 mg per day.

In men, the lowest effective dose to prevent MI was reported in the HOT trial.⁹ Men aged 50 or older with hypertension had a significant 42% reduction in MI with a daily dose of 75 mg. However, in the PPP trial 100 mg of aspirin resulted in a statistically insignificant 31% reduction in MI.⁶ In the U.S. physicians study,⁷ 325 mg of aspirin QOD led to a significant 44% reduction in MI in men aged 50 or older. Given these data, the lowest effective dose for the primary prevention of MI in men age 50 and older is 160 mg/day.

LOWEST DOSE FOR PRIMARY PREVENTION OF STROKE

As shown in Table 1, the lowest reported effective dose for the primary prevention of stroke, 50 mg/day, was reported by the WHS.⁴ This dose resulted in a statistically significant reduction in stroke of 17%.⁴ However, in women aged 65 or older, a reduction in stroke of 22% was not statistically significant. As with the case of MI, these findings from the WHS are inconsistent with the other primary prevention trials. In the HOT Trial, 75 mg per day in men and women led to a statistically insignificant decrease in stroke of 1%.⁵ In the PPP trial, 100 mg per day led to an insignificant 33% reduction in stroke.⁶ These studies indicate that the appropriate dose of aspirin for the primary prevention of stroke in women aged 50 or older is more than 100 mg per day.

In men, 75 mg per day,⁵ 100 mg per day,⁶ 160 mg/day (325 mg QOD),⁷ and 500 mg/day⁸ either increased or failed to significantly decrease the incidence of stroke. The appropriate dose of aspirin for the primary prevention of stroke in men has not been established.

Three randomized trials have compared aspirin in doses of 50 mg,¹⁰ 75 mg,¹¹ and 325 mg¹² per day to placebo in preventing strokes in patients with atrial fibrillation (AF). The incidence of stroke was reduced in each trial, but the decrease was statistically significant in only one, the Stroke Prevention in Atrial Fibrillation trial (SPAF I).¹² In the SPAF I trial, 325 mg of aspirin per day resulted in a significant 42% reduction in stroke as compared with placebo. It should be noted that a trial comparing 150 to 160 mg of aspirin/day with placebo in patients with AF has not been reported.

These data indicate that the lowest effective dose of aspirin to prevent stroke in patients with AF is 325 mg/day.

SECONDARY PREVENTION OF MI

The Swedish Angina Pectoris Aspirin Trial (SAPAT) randomized 2035 patients (977 women) with stable angina pectoris to aspirin 75 mg/day versus placebo.¹³ None of the patients had a history of prior MI. All patients also received sotalol. After a median follow-up of 50 months the incidence of MI and sudden death was a significant 34% lower in those treated with aspirin plus sotalol, compared with those receiving sotalol plus placebo. In addition, there was a 25% reduction in stroke that was not statistically significant in those taking aspirin.¹³

In a Veterans Administration (VA) study of 1266 men with unstable angina, 325 mg of aspirin daily significantly decreased the risk of MI or sudden death by 51% in those taking aspirin.¹⁴ In the Relationship between Insulin Sensitivity and Cardiovascular disease risk (RISC) study of 796 men with unstable angina, there was a significant 31% reduction in MI or sudden death after a daily dose of 75 mg aspirin for 30 days.¹⁵

In the Second International Study of Infarct Survival (ISIS-2) study,¹⁶ 17 187 patients with acute MI were randomized to 165 mg per day of aspirin for 1 month versus placebo. Recurrent MI was significantly reduced by 45%, and vascular death was significantly decreased by 23%.

These studies indicate that the lowest effective dose to prevent MI or sudden death in patients with stable coronary artery disease (CAD) or unstable angina is 75 mg/day. In patients with acute myocardial infarction (AMI), the lowest effective dose to prevent recurrent MI or death is 160 mg per day.

SECONDARY PREVENTION OF STROKE

The European Stroke Prevention Study (ESPS) randomized 6602 patients with a history of stroke or TIA to 1 of 4 regimens: aspirin 50 mg/day, dipyridamole 400 mg/day, dipyridamole plus aspirin, or placebo.¹⁷ After 2 years of treatment, the incidence of stroke in those taking aspirin was significantly reduced by 18%.

In the Chinese Acute Stroke Trial (CAST), 21 106 with acute ischemic stroke were randomized to aspirin, 160 mg/day or placebo.¹⁸ After 4 weeks, the incidence of recurrent stroke or death in those receiving aspirin was a significant 10% lower than those receiving placebo.

These 2 studies indicate that aspirin, 50 mg/day, can significantly reduce the rate of recurrent stroke in patients with a history of stroke or TIA. In patients with acute ischemic stroke, 160 mg/day of aspirin can significantly reduce the rate of recurrent stroke or death.

Table 2 summarizes the lowest effective dose to significantly reduce MI and stroke in varying patient populations. The dose varies from 50 to 160 mg/day (with the exception of primary stroke prevention in men, and the prevention of stroke in patients with AF). These findings are consistent with the report of the Antithrombotic Trialists that 75 to 150 mg of aspirin is as effective as higher doses.³

Table 2 Lowest Effective Dose (mg/day)

Primary prevention	
MI in men age 50+	160
MI in women age 50+	>100
Stroke in men 50+	Unknown
Stroke in women 50+	>100
Stroke in men/women with AF	325
Secondary prevention	
MI in men/women with CAD	75
MI/death in men/women with AMI	160
Stroke in men/women with HX stroke/TIA	50
Stroke/death in men/women with acute stroke	160

MI = myocardial infarction; AF = atrial fibrillation; CAD = coronary artery disease; AMI = acute myocardial infarction; HX = history of; TIA = transient ischemic attack.

BLEEDING COMPLICATIONS OF ASPIRIN

The incidence of peptic ulcer is increased during aspirin therapy. In the WHS,⁴ the incidence in those treated with aspirin was 2.7%, compared with 2.1% in controls. In the PHS study,⁷ the incidence in those taking aspirin (1.4%) was not significantly greater than placebo (1.2%). In the British Physician study,⁸ the incidence in those taking aspirin was 2.5% versus 1.6% in the controls. There was no consistent relationship between the dose of aspirin and the incidence of peptic ulcer in these studies. The aspirin dose in the PHS was 3 times greater than in the WHS, yet the incidence of peptic ulcer was lower in the PHS and was not significantly greater than those taking a placebo.⁷

The risk of major bleeding, in most cases GI bleeding, is clearly increased with aspirin therapy, as shown in Table 3. However, the excess risk of major bleeding with aspirin in these studies was modest, ranging from 0.19 to 1.6 cases per 1000 patient-years. This is consistent with the rate of 2 per 1000 patient-years reported by the Antithrombotic Trialists.³ The excess rate of major bleeding was not related to the dose of aspirin in these 5 trials. The rate was higher in the HOT study,⁵ which prescribed 75 mg/day, than in the UK study,⁸ where the dose was 500 mg/day.

Table 4 indicates the number of patients with fatal bleeding during aspirin therapy compared with placebo in 5

Table 3 Major Bleeding During Aspirin Therapy

Study	ASA Dose/Day	Major bleeds			Excess/1000 Pt/y
		ASA	Placebo	P	
WHS ⁴	50 mg	127	91	.02	0.19
HOT ⁵	75 mg	129	70	<.001	1.6
PPP ⁶	100 mg	17	5	.008	1.5
PHS ⁷	160 mg	48	28	.02	0.36
UK ⁸	500 mg	11	7	ns	0.32

ASA = aspirin; WHS = Women's Health Study; HOT = Hypertension Optimal Treatment study; PPP = Primary Prevention Project; PHS = Physician's Health Study; UK = British physician study

Table 4 Fatal Bleeding During Aspirin RX

Study	Dose/Day	Fatal Bleeds		
		ASA	Placebo	Pt./years
WHS ⁴	50 mg	2	3	199 380
HOT ⁵	75 mg	7	8	17 850
PPP ⁶	100 mg	1	3	80 928
PHS ⁷	160 mg	1	0	55 175
UK ⁸	500 mg	3	3	15 417
	Total	14	17	368 750

WHS = Women's Health Study; HOT = Hypertension Optimal Treatment study; PPP = Primary Prevention Project; PHS = Physician's Health Study; UK = British physician study.

randomized controlled studies during 368 750 patient years of therapy. There were actually more fatal bleeds in the placebo patients than in those taking doses of aspirin ranging from 100 mg QOD to 500 mg per day. The absence of an increase in fatal bleeding in these 5 randomized clinical trials is in stark contrast to predictions of excess deaths due to major GI hemorrhage predicted from epidemiological modeling.¹⁹

ARE BLEEDING COMPLICATIONS RELATED TO THE DOSE OF ASPIRIN?

As noted in Tables 3 and 4, there seems to be no relationship between aspirin dose and the incidence of major bleeding or fatal bleeding in the 5 primary prevention trials.

The Antithrombotic Trialists Collaboration³ reported meta-analyses of 287 studies of antiplatelet therapy versus control in 135 000 patients. The risk of a major extracranial bleed with daily aspirin doses ranging from <75 mg to 325 mg is shown in Table 5. There was no significant difference in the relative risk of a major extracranial bleed in those receiving <75 mg versus those receiving 160 to 325 mg per day.

Serebruany et al²⁰ reported a similar meta-analysis of the bleeding complications in 50 randomized controlled trials of antiplatelet agents involving 338 191 patients. They classified major bleeding as intracranial bleeding, overt bleeding with a decrease in hemoglobin >5 g/dL, or a decreased hematocrit >15%.

Their findings, as shown in Table 6, are consistent with those of the Antithrombotic Trialists.³ There was no significant difference in the incidence of major bleeding between

Table 5 Relative Risk of Major Bleeding During Aspirin Therapy³

Daily Dose (mg)	Relative Risk	95% Confidence Interval
<75	1.7	0.8 to 3.3
75-150	1.5	1.0 to 2.3
160-325	1.4	1.0 to 2.0

Table 6 Incidence of Major Bleeding During Aspirin Therapy²⁰

Dose (mg/day)	No. patients	Rate	95% CI
<100	13 337	1.7%	1.4-1.9%
100-325	43 489	1.7%	1.5-1.8%
>325	1409	2.5%	1.7-3.3%

those taking <100 mg versus those taking 100 to 325 mg of aspirin per day. It should be noted that the incidence of minor bleeding was clearly related to aspirin dose. The incidence of minor bleeding was 1.8% when the dose was less than 100 mg and 6.5% with doses of 100 to 325 mg.

CONCLUSIONS

In the U.S., the 3 doses of aspirin most frequently recommended for the prevention of stroke and MI are 80, 160, and 325 mg/day. In Europe and other countries, 75, 150, and 300 mg/day are commonly recommended. Randomized clinical trials have shown that the lowest dose, 75 or 80 mg/day, is inadequate for primary prevention of stroke and MI in men and women and has not been shown to be adequate in patients with acute stroke or acute MI, as shown in Table 2. Of note, a recent report suggests that a daily dose of 100 mg or less of aspirin may be associated with a higher incidence of aspirin resistance in patients with coronary artery disease.²¹

These studies indicate that a daily dose of 160 mg of aspirin (or 325 mg QOD) is adequate to prevent MI and stroke in men and women, with 3 exceptions. The dose adequate for primary prevention of MI in women and the dose adequate for the primary prevention of stroke in men and women are unknown, but in both cases the dose must exceed 100 mg/day. A dose of 325 mg/day is required for the prevention of stroke in patients with AF who are not candidates for long-term warfarin therapy.

The primary risk of taking 160 mg of aspirin/day is the same as taking 80 mg/day: an increased risk of major bleeding of 1 to 2 cases per 1000 patient years of treatment.

There is no evidence that the risk of major bleeding or fatal bleeding with a daily dose of 160 mg/day is greater than with a dose of 80 mg or less. The principal disadvantage of 160 mg as compared with a daily dose of 80 mg or less is an increase in minor bleeding.

The data from these randomized clinical trials indicate that the optimal dose of aspirin to prevent MI and stroke, ie, the dose that maximizes efficacy while minimizing toxicity, is 160 mg/day. Of note, this dose is not much different from that suggested by Craven more than 50 years ago; 325 mg 5 times a week!¹

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