

Aspirin in Primary Prevention of Cardiovascular Events

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Aspirin has demonstrated a clear benefit in secondary prevention of coronary syndrome, while aspirin's effect in primary prevention is unclear. This report will explore the role of aspirin as primary prevention for various vascular events. It strives to provide a clear guide for clinicians on whether or not to prescribe aspirin for their patients for primary prevention. Current guidelines and recent trials failed to show clear benefit against primary prevention, with risks outweighing benefits in moderate to high risk patients. A thoughtful discussion between patients and their doctors should be conducted before beginning aspirin use. More studies are needed to gain a better understanding of aspirin use in primary prevention.

Keywords: Aspirin; Cardiovascular events; Prevention

Ebers papyrus described over 700 remedies utilized by ancient Egyptians several thousand years ago.¹ One of these remedies was the bark of the willow tree. It was prescribed to relieve aches and pains, as well as for inflammation. Other civilizations used willow bark for similar purposes. For example, the ancient Greeks used willow bark to decrease pain during labor and delivery. In 1828, Bucher refined willow bark and called it salicin. To decrease its irritant effect on the stomach, acetyl salicylic acid was developed by a German dye manufacturer known as the Bayer company.² They called the drug aspirin, and it continues to be known by that name, having been regarded by some as the wonder drug.

As early as the 1700s, active research was conducted that proved this compound to be effective in treating diseases associated with fever, chills, and sweating such as malaria.³ It was not until 1975, however, that a series of laboratory studies showed that aspirin exerts its effect, in part, on human platelets. The mechanism of that effect is related to action on the prostaglandins.⁴ With current knowledge about the role of

platelets in patients with acute coronary syndrome, aspirin emerged as an accepted drug in the management of such conditions and has an integral role in the secondary prevention of cardiovascular events.⁵

Aspirin has demonstrated a clear benefit in secondary prevention of coronary syndrome. The ISIS-2 (Second International Study of Infarct Survival) study included 17,187 patients divided into four categories: (1) intravenous streptokinase infusion within 1 hour after acute myocardial infarction (MI); (2) aspirin, 160 mg for one month; (3) both active treatments; and (4) neither treatment.⁶ The conclusion of this study was that aspirin alone and thrombolysis alone each demonstrated a reduction in 5-week vascular related deaths, while the combination of both aspirin and thrombolysis had significantly greater benefits than either medication alone, such as fewer re-infarctions, strokes, and deaths. However, streptokinase was associated with cerebral hemorrhages and excessive bleeding that required blood transfusion. This led to the exploration of the benefit of aspirin in primary prevention.

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This report will explore the role of aspirin as primary prevention for various vascular events. It strives to provide a clear guide for clinicians on whether or not to prescribe aspirin for their patients.

Non-Randomized Trials

In the latter half of the 20th century, low dose aspirin was reported to prevent coronary artery disease and stroke. The main effects of aspirin are expressed in non-nucleated cells, like platelets. Thromboxane A₂, produced by activated platelets, has prothrombotic properties. Aspirin inhibits thromboxane A₂ production by irreversibly inhibiting COX1, thereby lowering platelet aggregation and COX2 at higher doses, leads to analgesic and antipyretic effect. Van Wormer et al⁷ performed a cross-sectional study carried out in the Marshfield Epidemiologic Study Area (MESA) looking at aspirin overutilization for primary prevention of coronary artery disease. This study included 23,701 individuals aged between 30–79 years without prior cardiovascular disease and diabetes. United States Preventive Service Task Force (USPSTF)⁸ guidelines (2009) for aspirin usage are for men aged 45–79 years with moderate or greater 10-year cardiovascular risk and for women aged 55–79 years with moderate or greater 10-year stroke risk. Age, sex, systolic blood pressure, body mass index (BMI), smoking, high density lipoprotein cholesterol, and total cholesterol were considered for risk calculation. According to this study, one in every five individuals regularly on aspirin are not indicated for primary prevention of cardiovascular disease. This study also found that male patients, older individuals seen often by a provider, and obese patients were prescribed aspirin for primary prevention of cardiovascular diseases irrespective of the risk score. Surprisingly, individuals with higher BMI, even with low risk, were inappropriately placed on aspirin for primary prevention considering obesity itself is a risk factor for developing cardiovascular disease. More research is needed to obtain a better understanding of aspirin use in obese patients. The combined findings observed that aspirin was over utilized in the low risk group and underutilized in the high risk groups.

A study by Lippi et al⁹ reported that harm was greater than benefit with aspirin in cardiovascular disease primary prevention, especially in the elderly population. Richman et al¹⁰ studied aspirin in primary prevention based on current evidence used by USPSTF. The USPSTF guidelines (2016)⁸ recommend low dose aspirin for adults aged 50-59 years with a $\geq 10\%$ 10-year risk of cardiovascular disease (CVD). For adults aged 60-69 years with a $\geq 10\%$ 10-year CVD risk, aspirin use depends on individual decision. No aspirin is recommended for adults aged 40-49 or ≥ 70 years. Adults ≥ 60 years may benefit from low dose aspirin, but adverse effects increase with age. Current guidelines support low dose aspirin in high-risk patients, especially adults in their 50s with CVD risk factors and who do not have bleeding risk factors.

Randomized Trials

The Canadian Cooperative Study Group conducted a multicenter, double-blinded, randomized clinical trial.¹¹ Patients were

included who had at least one cerebral or retinal ischemic episode in 3 months prior to study enrollment. Patients were randomized into four groups: (1) aspirin 325 mg plus placebo; (2) sulfinpyrazone 200 mg plus placebo; (3) both active medications; and (4) both placebo. Patients were evaluated at one month and every 3 months thereafter. During each interim visit a neurologic history was obtained from patients, and complete cardiovascular and neurologic examinations were conducted. There was no statistically significant interaction found between aspirin and sulfinpyrazone. As reported in this study, aspirin produced a 19% risk reduction ($P < 0.05$) in continuing ischemic events, stroke, and death; whereas, there was no risk reduction of these events in patients who received sulfinpyrazone. Formal analysis of this study showed that the aspirin benefit varied from center to center. From a total of 24 centers, 14 exhibited trends favoring aspirin use in reducing the occurrence of stroke or death, 5 centers exhibited no trends, and a reverse trend was exhibited in the other 5 centers. Formal analysis showed aspirin had no benefit in reducing death and stroke in women. However, aspirin significantly reduced the risk of stroke and death in men (RR 48%; $P < 0.05$).

The British Male Doctors¹² study was a randomized trial conducted in 5,139 healthy male doctors in the United Kingdom. Study subjects were randomized to either 500 mg aspirin daily or no aspirin. Only 70% of allocated subjects were taking aspirin by the end of 5 years. Gastrointestinal side effects were the most common reason for stopping aspirin. There were no significant differences in fatal or non-fatal myocardial infarction rates. Significantly ($P < 0.05$) reduced rates of cerebral transient ischemic attacks were reported. Surprisingly, a small and non-significant number of strokes were reported in the aspirin group. Vascular deaths (148/3429 vs 79/1710) were 6% lower, and non-vascular deaths (122/3429 vs 72/1710) were 15% lower in the aspirin group.

The Physicians' Health Study¹³ was a double blind, randomized study involving 22,071 physicians. Participants were divided into either an aspirin group or a placebo group. The average follow-up time of the study was 60.2 months. This study showed myocardial risk was 44% reduced in the aspirin group. An increased stroke risk was also noted in aspirin group, however, this was not statistically significant. There was no reduction in all cardiovascular mortality in the aspirin group. Detailed analysis showed that participants aged 50-years and older were the only group that had risk reduction of myocardial infarction, with greatest benefit in those with low cholesterol levels; however, there was significant benefit in all levels of cholesterol.

The Thrombosis Prevention Trial¹⁴ was a randomized clinical trial where study subjects were given aspirin and warfarin. A total of 5,499 men between 45–69 years of age at high risk of ischemic heart disease were enrolled. Study subjects were divided into four categories: (1) aspirin and warfarin; (2) aspirin and placebo warfarin; (3) warfarin and placebo aspirin; and (4) placebo aspirin and placebo warfarin. Aspirin's main effect was

a 20% reduction in ischemic heart disease (IHD) ($P=0.04$), mostly (32%) due to non-fatal events reduction ($P=0.04$). Warfarin's main effect was a 21% reduction in IHD ($P=0.02$), mostly (39%) due to non-fatal events reduction ($P=0.03$). IHD absolute reduction due to aspirin and warfarin were 2.3 and 2.6 per 1000 person-years, respectively. Both aspirin and warfarin reduced IHD by 34% ($P=0.006$) compared with both placebos. However, both active medication groups had increased hemorrhagic and fatal strokes. Also, dissecting and ruptured aneurysms occurred in 15 patients who were on warfarin compared to 3 in the remaining groups who were not on warfarin.

Hypertension is a risk factor for cardiovascular disease. The Hypertension Optimal Treatment randomized trial assessed the benefits of low dose aspirin and optimal diastolic blood pressure in hypertensive patients.¹⁵ This was a multicenter trial that included 18,790 patients between the ages of 50-80 years from 26 countries. All patients were hypertensive, with a diastolic blood pressure (DBP) between 100–115 mmHg. Patients were divided into two groups for aspirin 75 mg daily randomization and three groups for target DBP randomization (target DBP \leq 90

mmHg, \leq 85 mmHg, \leq 80 mmHg). Initially, felodipine 5 mg was given, later angiotensin converting enzyme inhibitors, beta blockers, and diuretics were added, and doses were up-titrated in a 5-step process. The incidence of cardiovascular events was lowest with mean DBP 82.6 mmHg; cardiovascular mortality was lowest at 86.5 mmHg. Aspirin reduced all myocardial infarction incidence by 36% ($P=0.002$) and major cardiovascular events by 15% ($P=0.03$), with no effect on stroke. The study concluded that small dose aspirin with blood pressure control reduced the risk of acute myocardial infarction without excess risk of cerebral bleeding.

The Japanese primary prevention project¹⁶ was another multicenter randomized trial. Study subjects were between 60–85 years-of-age and presented with diabetes, hypertension, and dyslipidemia. Patients were randomized into two groups— aspirin 100 mg daily or no aspirin. The 5-year primary outcomes were not significantly different between the two groups ($P=0.54$). The incidence of non-fatal myocardial infarction ($P=0.02$) and TIA ($P=0.04$) were significantly reduced in the aspirin group as compared to the no aspirin group. See Table 1 for outcomes of the above-mentioned randomized studies.

Table 1. Outcomes of Randomized Clinical Trials of Aspirin in Primary Prevention²⁷

Study Name (Number of patients / Duration)	Year	Age Group	Aspirin Dose	Outcome; Relative Risk (95% CI)				
				CV Events	Myocardial Infarction	Stroke	CV Mortality	All-Cause Mortality
BMD ¹² (5139 / 6 years)	1988	19-90	500 mg/ day	0.98 (0.80-1.20)	0.97 (0.66-1.42)	1.13 (0.72-1.78)	0.93 (0.70-1.23)	0.95 (0.85-1.06)
PHS ¹³ (22071 / 5.2 years)	1989	40-84	325 mg/ day	0.86 (0.71-0.96)	0.58 (0.47-0.71)	1.22 (0.93-1.59)	0.98 (0.72-1.38)	0.96 (0.79-1.15)
TPT ¹⁴ (5085 / 6.8 years)	1998	45-69	75 mg/ day	0.86 (0.72-1.04)	0.80 (0.64-0.99)	0.98 (0.65-1.47)	1.26 (0.93-1.69)	1.03 (0.80-1.32)
HOT ¹⁵ (18790 / 3.8 years)	1998	50-80	75 mg/ day	-----	-----	-----	-----	0.93 (0.79-1.09)
WHS ²⁶ (39876 / 10 year)	2005	\geq 45	100 mg alternate day	0.91 (0.80-1.03)	1.03 (0.84-1.25)	0.84 (0.70-1.01)	0.95 (0.74-1.22)	0.95 (0.85-1.06)
JPPP ¹⁶ (14658 / 5 year)	2014	60-85	100 mg/ day	0.94 (0.77-1.15)	0.53 (0.31-0.91)	1.00 (0.77-1.31)	1.02 (0.71-1.47)	0.98 (0.84-1.15)
ARRIVE ¹⁷ (12546 / 5year)	2018	\geq 55 M \geq 60 F	100 mg/ day	0.95 (0.79-1.15)	0.85 (0.69-1.11)	1.12 (0.80-1.55)	0.97 (0.62-1.52)	0.96 (0.81-1.13)
ASPREE ¹⁸ (19114 / 4.7year)	2018	65-73 \geq 74	65-100 mg/day	-----	-----	1.13 (0.66- 1.94)	0.82 (0.62-1.08)	1.14 (1.01-1.29)

BMD- British Male Doctor study; PHS- Physician Health Study; TPT- Thrombosis prevention trial; HOT- Hypertension Optimal Treatment study; WHS – Women Health Study; JPPP- Japanese Primary Prevention Project; ARRIVE-Aspirin to Reduce Risk of Initial Vascular Events study; ASPREE-Aspirin in Reducing Events in the Elderly study.

Most recently, the ARRIVE study¹⁷ was a multicenter, randomized, double blinded trial. Participants were men aged 55 years or more and women aged 60 years or more with moderate cardiovascular disease risk factors. Participants were randomly assigned to aspirin or placebo, then followed over 5 years. Aspirin did not lower all cardiovascular disease events (hazard ratio 0.95[0.79-1.15]), but there was a non-significant trend toward lower risk of myocardial infarction 0.85 (0.69-1.11) in the aspirin group compared to placebo group. Study findings were consistent with no clear benefit of aspirin, which may have also been related to the modest degree of underlying cardiovascular risk in participants and/or other recent changes in medical management and lifestyle modification.

In the ASPREE study,¹⁸ which enrolled nearly 20,000 people over age 70 in Australia and the United States, investigators found that the daily use of aspirin did not provide a benefit in regards to their primary end point of disability-free survival. In fact, they found higher all-cause mortality in those who received aspirin than those with placebo, although they urge caution in interpreting those results.

Zheng SL, et al¹⁹ conducted meta-analysis of 13 randomized trials, included 164,225 individuals. This study found that aspirin therapy associated with significant reduction in composite cardiovascular events compared to no aspirin group (hazard ratio [HR] 0.89, 95% credible interval 0.84-0.95; absolute risk reduction 0.38%, 95% CI 0.20-0.55; number needed to treat 265). Aspirin therapy was associated with increased major bleeding risk compared with no aspirin group (HR 1.43, 95% credible interval 1.30-1.56; absolute risk increase 0.47%, 95% CI 0.34-0.62; number needed to treat 210). The study concluded that aspirin use associated with lower cardiovascular events in individuals without cardiovascular disease and increased major bleeding risk.

Mahmoud AN, et al²⁰ conducted meta-analysis of 11 randomized studies to determine aspirin therapy in primary prevention of cardiovascular disease. Meta-analysis revealed that aspirin did not reduce incidence of all-cause mortality (risk ratio [RR] 0.98, 95% CI 0.93-1.02, $P=0.30$). Aspirin therapy was associated with major bleeding risk (RR 1.47, 95% CI 1.31-1.65, $P<0.0001$) and intracranial hemorrhage (RR 1.33, 95% CI 1.13-1.58, $P=0.001$). A similar finding was noted on all-cause mortality and major bleeding in diabetic and high cardiovascular risk patients (10 year risk > 7.5%). Aspirin was associated with reduced myocardial infarction incidence (RR 0.82, 95% CI 0.71-0.94, $P=0.006$). Sequential analysis of trial confirmed aspirin has no benefit for all - cause mortality up to a relative risk reduction 5%. The study concluded that aspirin was not associated with reduction in all - cause mortality in adults without known cardiovascular disease, and associated with increased major bleeding risk.

Aspirin for Primary Prevention in Diabetics

Diabetic patients have a 2–4 times increased risk for

cardiovascular disease, and more than two-thirds of diabetic patients die with heart disease. Diabetes plays a major role in calculating the 10-year cardiovascular risk. In diabetic patients, platelets demonstrate increased activity with exaggerated activation, adhesion, and aggregation. In addition, hyperglycemia itself acts as an oxidative stress, which further enhances the inflammatory process. Insulin deficiency and resistance increase intracellular calcium concentration, which leads to enhanced platelet activation and aggregation. Diabetes also causes endothelial dysfunction, thrombosis, and lipid-rich plaques. The degree of endothelial dysfunction depends on the duration of diabetes, and diabetes has also been shown to increase serum fibrinogen. Diabetic patients are prone to have a lipid-rich plaque with macrophage infiltration, which is more vulnerable to rupture. Aspirin inhibits thromboxane A2 production by irreversibly inhibiting COX1, thereby lowering platelet aggregation and COX2 at higher doses, leads to analgesic and antipyretic effect. Aspirin utilization in diabetics for primary prevention has been extensively studied, but remains controversial. Current guidelines (American Diabetic Association, American Heart Association, and American College of Cardiology Foundation) recommend low dose aspirin for diabetic patients with high atherosclerotic cardiovascular disease (ASCVD) risk scores (10-year risk >10%), who have low risk for gastrointestinal bleeding.²¹ Low dose aspirin is not recommended in diabetics with low ASCVD risk (10-year risk <5%). Low dose aspirin can be considered in diabetic patients with intermediate ASCVD risk scores (10-year risk 5%–10%) on an individualized basis.

The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes²² and the Prevention of Progression of Arterial Disease and Diabetes studies²³ were conducted solely in diabetic patients. Both were randomized, double-blinded controlled studies; there were no significant differences observed in ASCVD endpoints (ie, all atherosclerotic events, non-fatal myocardial infarction, and stroke).

Most recently, the ASCEND study²⁴ studied aspirin in primary prevention of cardiovascular events in diabetics and demonstrated a 12% lower risk of vascular events in the aspirin group compared to placebo, and the major bleeding risk was 29% higher. In contrast to other previous studies, this study group had a higher rate of cardio-protective treatments like statins and blood pressure medications.

Ripudaman, et al²⁵ studied the effect of aspirin on glucose metabolism in type 2 diabetes, and stated there was a significant improvement in fasting and postprandial blood glucose in patients with diabetes who were taking high dose aspirin. The effect could be due to increased peripheral insulin sensitivity, decreased hepatic glucose production, and decreased clearance of insulin. However, complications like major gastrointestinal bleeding were significantly high in patients receiving high-dose aspirin treatment.

Aspirin has some effect on preventing atherosclerosis in diabetic patients, but there is risk of vascular-related adverse effects. The treatment decision has to be made by physician and patient.

Gender-Specific Analysis of Aspirin for Primary Prevention

As is known, aspirin irreversibly inhibits COX 1, thereby reducing platelet aggregation. Women have reduced aspirin pharmacological effect compared to men, and in women, high aspirin resistance contributed to less cardiovascular benefits obtained compared to men. The Women's Health Study²⁶ is the largest trial to exclusively study aspirin for primary prevention of cardiovascular disease in women. This randomized study included women over age 45 who were given 100 mg aspirin every other day vs placebo. With low dose aspirin, there was no decrease in myocardial infarction or cardiovascular death noted, but there was a 17% reduction of stroke incidence over 10 years. Subgroup analysis showed that women aged 65 years and above who were taking low dose aspirin had a great reduction in myocardial infarction, major cardiovascular deaths, and ischemic strokes. A modest reduction of all cardiovascular diseases in women younger than 65 years-of-age with low dose aspirin was also reported, although the bleeding risk is higher.

Berger, et al²⁷ conducted a meta-analysis to determine if women get the same benefit as men with aspirin use. Meta-analysis data revealed that aspirin reduced myocardial infarction risk in men (RR 0.77; 95% CI 0.67-0.89), but not in women (RR 0.95; 95% CI 0.77-1.17). The analysis also showed that ischemic stroke risk was reduced in women taking aspirin (RR 0.75; 95% CI 0.60-0.94), but not in men (RR 1.06; 95% CI 0.85-1.32). There are limited data comparing aspirin use in women and men, and future studies are needed to better understand the role of gender differences in aspirin's effect.

Aspirin for Primary Prevention of Stroke

Meta-analysis of five randomized clinical trials revealed there was no significant effect on stroke (RR 1.08; 95% CI 0.95-1.24), but a decrease in myocardial infarction (RR 0.74; 95% CI 0.68-0.82). All participants in the clinical trials had major atherosclerotic risk factors (diabetes mellitus, hypertension, or advanced age).²⁸ Intracranial hemorrhage was increased in people taking high-dose aspirin for primary and secondary prevention, but no increase was observed with lower doses. A small increase in incidence of ischemic stroke was seen with aspirin therapy, but the overall increase did not reach statistical significance.

Aspirin has been reported to increase blood pressure (especially supine) and to counteract some antihypertensive medications. Hypertension itself is a strong risk factor for both ischemic and hemorrhagic stroke. Thrombogenic

properties are likely related to endothelial prostacyclin synthesis inhibition, especially with high doses. The effect of regular aspirin use for primary prevention of major vascular events was unknown in elderly people, as all randomized clinical trials to date have involved middle-aged people, who have higher chances of myocardial infarction than stroke. As discussed earlier, the incidence of hemorrhagic stroke increases with long-term and high-dose aspirin use.²⁸

Aspirin Dose in Primary Prevention of Cardiovascular Events

Aspirin dose less than 75 mg daily is more effective than higher doses because low dose doesn't have effect on prostacyclin, which is a platelet anti-aggregant and vasodilator and causes fewer gastrointestinal complications²⁹. Oral aspirin systemic bioavailability is necessary to prostacyclin synthesis inhibition by vascular endothelium, whereas thromboxane A2 synthesis inhibition by platelets occur in portal (pre-systemic) circulation³⁰. As per meta-analysis of randomized study,³¹ direct comparison of aspirin <75 mg daily and >75 mg daily has no significant difference on prevention of vascular event in high risk patients. Comparing aspirin with control, major extracranial bleeding risk was similar with all daily aspirin doses <325 mg (odds ratios 1.7 (95% confidence interval 0.8 - 3.3) for <75 mg; 1.5 (1.0 - 2.3) for 75-150 mg; and 1.4 (1.0 - 2.0) for 160-325 mg. Platelet function in diabetic patients is altered, however it is unclear, this may effect aspirin dose for cardioprotective outcomes in diabetic patient population.³²

Conclusion

With the significant benefit of aspirin in treating myocardial infarction and acute coronary syndromes¹¹ and its value in secondary prevention of cardiovascular events, it was logical to conclude it may benefit in primary prevention. In fact, earlier randomized studies showed this benefit. However, more recent studies, such as the ARRIVE trial¹⁷ and the ASPREE trial,¹⁸ failed to show such benefit. It is possible that the very low event rate contributed to that failure. Currently, the Western population follows a more healthy diet, striving to have better sugar control when diabetic, and physicians have a much lower target for management of low-density lipoprotein. These improvements, in addition to the significant advances in medical therapy, have led to lower rates of cardiovascular events. In fact, some studies admitted that the low event rate is indeed one of the limitations of such studies.

Recently, the American College of Cardiology and the American Heart Association published guidelines for aspirin use in primary prevention.³³ They also published data discouraging routine use of aspirin, particularly in patients with increased bleeding risk. The benefits of aspirin may be limited to patients between the ages of 40–70 years with significant risk factors for coronary artery diseases, as well as low risk of bleeding. A thoughtful discussion between the patients and their doctors should be conducted before beginning aspirin use.

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